National Clinical Guideline Centre

Draft for consultation

Cirrhosis

Assessment and management of cirrhosis

Clinical guideline

Appendices A – R

December 2015

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

The Royal College of Surgeons of England

Royal College of General Practitioners

Royal College of Nursing

NICE accredited

Funding
National Institute for Health and Care Excellence

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Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Cirrhosis: assessment and management of cirrhosis

1.1 Short title

Cirrhosis

2 The remit

The Department of Health has asked NICE to develop a clinical guideline on the 'assessment and management of cirrhosis'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Cirrhosis is condition that occurs as a response to liver damage. It is characterised at a cellular level by fibrosis and the distortion of the normal liver structure into abnormal nodules. It usually takes several years for liver damage to develop into cirrhosis but in some cases it may take an accelerated course over weeks.

b) Cirrhosis interferes with the normal functions of the liver, reducing its ability to produce proteins (reduced hepatic synthetic function). This can lead to problems such as coagulopathy (problems with blood clotting), low albumin and raised bilirubin.

c) The most common causes of cirrhosis include alcohol, chronic hepatitis C virus infection and non-alcoholic fatty liver disease. Less common causes include autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis or primary sclerosing cholangitis), genetic conditions, hepatitis B with or without hepatitis D, chronic

infection with hepatitis E virus in people who are immunosuppressed, secondary biliary cirrhosis, Budd–Chiari syndrome or veno-occlusive disease, prolonged exposure to certain chemicals or medications (such as amiodarone or methotrexate), sarcoidosis, chronic right-sided heart failure, and type IV glycogen storage disease.

d) At least 7000 new cases of cirrhosis were diagnosed each year between 1992 and 2001, based on an incidence study using the UK General Practice Research Database. The study estimated that the incidence of cirrhosis rose by 45% between 1992 and 2001.

e) In 2010 there were 5631 deaths in England recorded with an underlying diagnosis of cirrhosis of the liver. The British Society of Gastroenterology reported that mortality from cirrhosis in the UK increased from 6 per 100,000 population in 1993 to 12.7 per 100,000 population in 2000.

f) In patients admitted to hospital in England in 2012, the mortality rate was higher in patients admitted with liver disease (1 in 11 or 8.8 per cent) than in overall admissions (1 in 72 admissions or 1.4 per cent). Nearly half of liver disease admissions were for alcohol-related liver disease (47.7%), and approximately 1 in 8 of these resulted in a hospital death (12.3%). Men accounted for more than two-thirds of admissions for alcohol-related liver disease. Patients aged 50 to 69 had the greatest number of hospital deaths due to liver disease, but patients aged 70 or older had the highest mortality rate.

g) The NHS Atlas of Variation in Healthcare for People with Liver Disease revealed widespread geographical variation in the prevalence of risk factors for cirrhosis, such as hepatitis infection, obesity and alcohol abuse. Admission rates to hospital for end-stage liver disease due to chronic hepatitis C virus also showed widespread geographical variation, with the highest rates

found in central London and North West England. The North West region also had the highest rate of admissions for alcohol-related liver disease, but the North East region had the highest rate of admissions for all liver diseases.

h) The prevalence of cirrhosis varies according to level of deprivation; for both men and women the highest prevalence occurs in the most deprived quintile in England and lowest among the least deprived quintile. Consequently, the most deprived 20% of the population have significantly more admissions for cirrhosis than the rest of the population.

i) The aetiologies of cirrhosis in children and young people are generally different to those in adults (for example, biliary atresia), and the assessment (including the scoring systems for children for referral for transplantation) and management of these aetiologies will be different. However, it is acknowledged that although the guideline will be focused on adults, the recommendations may be useful to clinicians who are caring for young people who transition into this care pathway when they reach 16 years.

3.2 Current practice

a) Cirrhosis is often asymptomatic (40% of cases) and may be revealed by abnormal results from liver tests performed for other reasons or patients may present to their GPwith non-specific symptoms (for example, fatigue). People may also present with signs and symptoms of complications of cirrhosis such as portal hypertension (for example, ascites and variceal bleeding), increased risk of infection (for example, spontaneous bacterial peritonitis), decreased detoxification capacity (for example, hepatic encephalopathy) or hepatocellular carcinoma. This also impacts significantly on quality of life.

b) There are no standard criteria for identifying cirrhosis or referring a person with suspected cirrhosis from primary care for assessment

in secondary care. A study of referral practice in Liverpool PCT found that primary care practices had different criteria and standards for referral within the same PCT.

c) There is currently variation in practice across England and Wales for diagnostic tests for cirrhosis, for example, which liver tests are carried out and whether ultrasound is undertaken.

d) Liver biopsy, performed in secondary care, is the definitive diagnostic method for confirming cirrhosis. As well as revealing the extent of the fibrosis it helps determine the cause of the liver damage, and consequently may inform treatment options. The effectiveness, cost and patient acceptability of liver biopsy compared with non-invasive assessment of fibrosis are important factors to consider, and there is widespread variation in the use of non-invasive tests to assess liver fibrosis.

e) Guidelines are needed in primary care to standardise both the investigation of patients with suspected cirrhosis and the criteria for referral to secondary care in order to avoid delaying treatment.

f) Guidelines are needed in secondary care to standardise the methods used to diagnose cirrhosis and assess severity of liver dysfunction and also to standardise the investigation and treatment of complications of cirrhosis.

g) Guidelines are needed to standardise referral criteria to tertiary care for specialist liver treatments (for example, liver transplant assessment).

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults with cirrhosis that is suspected or confirmed when they are 16 years or older.

b) No patient subgroups have been identified as needing specific consideration.

4.1.2 Groups that will not be covered

a) People whose cirrhosis is diagnosed before the age of 16 years.

4.2 Setting

a) Primary and secondary NHS-commissioned care including referral to tertiary care.

4.3 Assessment and management

4.3.1 Key issues that will be covered

Assessment

a) Identification of people who may have cirrhosis.

b) Assessment of suspected cirrhosis including:

- Liver blood tests (for example, bilirubin).
- Non-invasive surrogate markers of cirrhosis (for example, transient elastography).
- Liver biopsy.

c) Tools to assess severity of cirrhosis (for example Child–Pugh score and Model for End-stage Liver Disease).

Management

d) Monitoring people with cirrhosis to detect complications early (for example, hepatocellular carcinoma).

e) Managing the complications of cirrhosis (for example, ascites, prevention of spontaneous bacterial peritonitis and hepatorenal syndrome)

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

f) Referral criteria for tertiary care (including criteria for referral for assessment for liver transplant).

4.3.2 Issues that will not be covered

a) Diagnosis, investigation and management of the underlying cause of cirrhosis.

b) Complications specific to the underlying cause of cirrhosis.

c) Liver transplantation (other than the criteria for referral for assessment for liver transplantation).

d) Management of hepatocellular carcinoma.

e) Management of variceal haemorrhage.

4.4 Main outcomes

a) Health-related quality of life.

b) Mortality (with or without later transplantation).

c) Adverse effects.

d) Length of hospital stay.

e) Re-admission rates.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these background review questions are draft versions and will be finalised with the Guideline Development Group.

4.5.1 Assessment

a) In whom should cirrhosis be suspected?

b) What is the usefulness of different tests in the diagnosis of cirrhosis?

c) What is the usefulness of different tools to assess the severity of cirrhosis?

4.5.2 Management

d) How should people with cirrhosis be monitored?

e) What are effective management strategies for complications related to cirrhosis?

f) What are the most important criteria for referring people with cirrhosis to tertiary care?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and

analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

The development of the guideline recommendations will begin in June 2014.

5 Related NICE guidance

5.1 Published guidance

- Subcutaneous implantation of a battery-operated catheter drainage system for managing refractory and recurrent ascites. NICE interventional procedure guidance 479 (2014).
- Hepatitis B and C – ways to promote and offer testing. NICE public health guidance 43 (2013).
- Hepatitis B (chronic). NICE clinical guideline 165 (2013).
- Acute upper gastrointestinal bleeding. NICE clinical guideline 141 (2012).
- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. NICE diagnostics guidance 5 (2012).
- Alcohol dependence and harmful alcohol use. NICE clinical guideline 115 (2011).
- Stent insertion for bleeding oesophageal varices. NICE interventional procedure guidance 392 (2011).
- Alcohol-use disorders: preventing harmful drinking. NICE public health guidance 24 (2010).
- Alcohol-use disorders: physical complications. NICE clinical guideline 100 (2010).

- Extracorporeal albumin dialysis for acute liver failure. NICE interventional procedure guidance 316 (2009).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Virtual Touch Quantification to diagnose and monitor liver fibrosis. NICE medical technology guidance. Publication expected February 2015.
- Suspected cancer. NICE clinical guideline. Publication expected May 2015.
- Liver disease (non-alcoholic). NICE clinical guideline. Publication date to be confirmed.
- Hepatitis C. NICE clinical guideline. Publication date to be confirmed.
- Rifaximin for the maintenance treatment of hepatic encephalopathy. NICE technology appraisal. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition.
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix B: Declarations of interest

The May 2007 version (as updated October 2008) of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

Iain Brew

Date	Item declared	Classification	Action taken
10/04/2014	At recruitment: GP with special interest in hepatitis C.	Personal specific non-financial	Declare and participate
	At recruitment: Contributor to the APPHG Report on Liver Disease 2014.	Personal specific non-financial	Declare and participate
	At recruitment: Has received honoraria, travel and accommodation expenses from Janssen for attending, speaking at and chairing meetings about treatment of hepatitis C.	Personal financial non-specific	Declare and participate
	At recruitment: Has received honoraria, travel and accommodation expenses from AbbVie for attending, speaking at and chairing meetings about treatment of hepatitis C.	Personal financial non-specific	Declare and participate
	At recruitment: I have received payments (£200 x 2) for articles on liver health published in the British Journal of Primary Care Nursing.	Personal financial non-specific	Declare and participate
11/07/2014	GDG1: Apologies received.	Nil	Nil
04/09/2014	GDG2: Payment for attending and chairing advisory boards for Janssen and AbbVie.	Personal financial non-specific	Declare and participate
17/10/2014	GDG3: Janssen paid for attendance at BASL in Newcastle (October 2014)	Personal financial non-specific	Declare and participate
26/11/2014	GDG4: No new DOI.	Nil	Nil
21/01/2015	GDG5: No new DOI.	Nil	Nil
18/02/2015	GDG6: Delivered a lecture on hepatitis C treatment in prisons for Gilead: honorarium payable.	Personal financial non-specific	Declare and participate
	GDG6: Conference and travel costs covered by Janssen for a hepatitis C meeting.	Personal financial non-specific	Declare and participate
26/03/2015	GDG7: No new DOI.	Nil	Nil
30/04/2015	GDG8: No new DOI.	Nil	Nil
25/06/2015	GDG9: AbbVie paying honorarium and travel costs 10 July meeting about hepatitis C treatments.	Personal financial non-specific	Declare and participate
29/07/2015	GDG10: Apologies received.	Nil	Nil
02/09/2015	GDG11: No new DOI.	Nil	Nil

David Fitzmaurice (co-optee)

Date	Item declared	Classification	Action taken
15/01/2015	None.	Nil	Nil
21/01/2015	GDG6: No new DOI.	Nil	Nil

Andrew Fowell

Date	Item declared	Classification	Action taken
21/04/2014	Recruitment: none declared.	Nil	Declare and participate
11/07/2014	GDG1: No new DOI.	Nil	Declare and participate
04/09/2014	GDG2: Received travel expenses from Janssen to attend a conference.	Personal financial non-specific	Declare and participate
04/09/2014	Secretary of the Wessex Gut Club (Gastroenterological society). Has responsibility for organising twice yearly meetings. All money paid is directly to the Gut Club. Meetings took place on the following dates and pharma company funding is outlined: November 2013: Roche, Janssen, AbbVie, Gilead, Ferring, Falk, Novartis, Vifor, Pentax July 2014: Janssen, Gilead, Falk, Tillots, Vifor, Ferring November 2014: dealt with organising programme of speakers only.	Non-personal financial non-specific	Declare and participate
		Roche: Non-personal financial specific	Declare and participate
17/10/2014	GDG3: No new DOI.	Nil	Nil
26/11/2014	GDG4: No new DOI.	Nil	Nil
21/01/2015	GDG5: No new DOI.	Nil	Nil
18/02/2015	GDG6: No new DOI.	Nil	Nil
26/03/2015	GDG7: Received travel and accommodation from Janssen to attend a conference in 2015.	Personal financial non-specific	Declare and participate
30/04/2015	GDG8: No new DOI.	Nil	Nil
25/06/2015	GDG9: No new DOI.	Nil	Nil
29/07/2015	GDG10: Organised speakers for the Wessex Gut Club meeting in July 2015.	Personal non-financial non-specific	Declare and participate
02/09/2015	GDG11: Organising speakers for the Wessex Gut Club meeting taking place in November 2015.	Personal non-financial non-specific	Declare and participate

Lynda Greenslade

Date	Item declared	Classification	Action taken
11/07/2014	GDG1: Norgine Advisory Board Member: 2/3 December 2013: accommodation and subsistence 8 April 2014: accommodation and subsistence Advisory Board calls: 22 and 29 June 2014	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
	GDG1: Norgine Educational Meeting Committee Member: telephone call 14 and 26 November 2013, 16 December 2013, 7 and 12 May 2014. One-off payment for being part of the education committee and a talk.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy

Date	Item declared	Classification	Action taken
	GDG1: Norgine-sponsored liver nurses meeting 6 and 7 June 2014: accommodation and subsistence. Payment received for chairing one session and giving one talk.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
	GDG1: Payment received from speaking at the (Norgine-sponsored) Royal College of Nursing congress: on 18 June 2014.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
	GDG1: Data on hepatic encephalopathy patients from Royal Free Foundation Trust given to advisory board meeting for real world data, for Norgine.	Personal non-financial specific	Withdraw from question relating to acute hepatic encephalopathy
	GDG1: Sponsored by Norgine to go to European Association for the Study of the Liver conference.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
04/09/2014	GDG2: Janssen paid for standard travel expenses to attend BASL Liver meeting.	Personal financial non-specific	Declare and participate
17/10/2014	GDG3: No new DOI.	Nil	Nil
26/11/2014	GDG4: Attended Norgine-sponsored Liver Nurses Educational Meeting on 21 and 22 November 2014. On the education board, chaired some sessions and gave a talk, Accommodation and subsistence provided.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
21/01/2015	GDG5: No new DOI.	Nil	Nil
18/02/2015	GDG6: No new DOI.	Nil	Nil
26/03/2015	GDG7: Funding for travel and accommodation received from Janssen to attend European Association for the Study of the Liver conference 2015.	Personal non-specific financial interest	Declare and participate
30/04/2015	GDG8: No new DOI.	Nil	Nil
25/06/2015	GDG9: Attended Norgine-sponsored liver nurses meeting 15 and 16 May 2015: accommodation and subsistence. Payment for chairing one session and giving one talk.	Personal financial non-specific	Declare and participate
29/07/2015	GDG10: No new DOI.	Nil	Nil
02/09/2015	GDG11: No new DOI.	Nil	Nil

Phillip Harrison (Chair)

Date	Item declared	Classification	Action taken
07/01/2014	None declared	Nil	Nil
11/07/2014	GDG1: No new DOI	Nil	Nil
04/09/2014	GDG2: No new DOI	Nil	Nil
17/10/2014	GDG3: No new DOI	Nil	Nil
26/11/2014	GDG4: No new DOI	Nil	Nil

Date	Item declared	Classification	Action taken
21/01/2015	GDG5: No new DOI	Nil	Nil
18/02/2015	GDG6: No new DOI	Nil	Nil
26/03/2015	GDG7: No new DOI	Nil	Nil
30/04/2015	GDG8: No new DOI	Nil	Nil
25/06/2015	GDG9: No new DOI	Nil	Nil
29/07/2015	GDG10: No new DOI	Nil	Nil
02/09/2015	GDG11: No new DOI	Nil	Nil

Brian Hogan

Date	Item declared	Classification	Action taken
11/07/2014	GDG1: A co-investigator on a National Multicentre UK Trial of Stents in the treatment of variceal haemorrhage (UKCRN 13392). This trial receives funding from the Stent Manufacturer (Ella-CS, Czech Republic) and from the NIHR (as an on-portfolio study the NHS support costs are met by NIHR). Participated in research on biomarkers of portal hypertension	Non-personal financial, non-specific Non-personal non-financial specific	Declare and participate Declare and participate
04/09/2014	GDG2: No new DOI	Nil	Nil
17/10/2014	GDG3: No new DOI	Nil	Nil
26/11/2014	GDG4: No new DOI	Nil	Nil
21/01/2015	GDG5: No new DOI	Nil	Nil
18/02/2015	GDG6: No new DOI	Nil	Nil
26/03/2015	GDG7: No new DOI	Nil	Nil
30/04/2015	GDG8: Apologies	Nil	Nil
25/06/2015	GDG9: No new DOI	Nil	Nil
29/07/2015	GDG10: No new DOI	Nil	Nil
02/09/2015	GDG11: No new DOI	Nil	Nil

Mark Hudson

Date	Item declared	Classification	Action taken
07/07/2014	At recruitment: Has advised Astellas on immunosuppression within the last year.	Personal financial non-specific	Declare and participate
	At recruitment: Has advised Novartis on immunosuppression within the last year.	Personal financial non-specific	Declare and participate
	At recruitment: Has advised Norgine on rifaximin within the last year.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
07/07/2014	At recruitment: I am the Co-Chief Investigator on the impact of rifaximin-α on the NHS Hospital Resource use associated with the management of patients with Hepatic Encephalopathy: A retrospective observational study (IMPRESS). The IMPRESS study is a multicentre CLRN Portfolio study funded by Norgine. The trial has been in development since April 2014. Has received no payment or personal financial gain from the IMPRESS study.	Personal non-financial specific	Withdraw from question relating to acute hepatic encephalopathy
11/07/2014	GDG1: No new DOI.	Nil	Nil
04/09/2014	GDG2: No new DOI.	Nil	Nil
17/10/2014	GDG3: Attended a Norgine advisory board on rifaximin. Received a payment on 27 October 2014 for attending a Norgine advisory board to discuss the natural history of hepatic encephalopathy.	Personal financial specific	Withdraw from question relating to acute hepatic encephalopathy
26/11/2014	GDG4: No new DOI.	Nil	Nil
21/01/2015	GDG5: No new DOI.	Nil	Nil
18/02/2015	GDG6: No new DOI.	Nil	Nil
26/03/2015	GDG7: No new DOI.	Nil	Nil
30/04/2015	GDG8: No new DOI.	Nil	Nil
25/06/2015	GDG9: Speaker for Norgine at a meeting (2 June) on hepatic encephalopathy. Chaired a session for Abbvie on 23 June relating to viral hepatitis.	Personal financial specific Personal financial specific	Declare and participate Declare and participate
29/07/2015	GDG10: Novartis provided travel support to attend International Liver Transplant Society meeting in	Personal financial non-specific	Declare and participate

Date	Item declared	Classification	Action taken
	Chicago from 7 to 11 July 2015.		
02/09/2015	GDG11: No new DOI	Nil	Nil

Phillip Johnson (co-optee)

Date	Item declared	Classification	Action taken
16/01/2015	At recruitment: One-off advisory board meetings: Astellas (13 February 2014) Boehringer-Ingelheim (17 October 2014).	Personal financial non-specific	Declare and participate (as a co-optee)
	At recruitment: funding received from Bayer Healthcare for 1-year support of research nurse/data manager from September 2014 to August 2015	Non-personal financial non-specific	Declare and participate (as a co-optee)
26/03/2015	GDG7: Travel expenses from Wako Life Sciences to attend an American Association for the Study of Liver Diseases meeting.	Personal financial specific	Declare and participate (as a co-optee)

Andrew Langford

Date	Item declared	Classification	Action taken
27/05/2014	At recruitment: In the last year, the British Liver Trust have received: funding from Roche for the development of case studies on "Confronting the silent epidemic: a critical review of hepatitis C management in the UK" a Hepatitis Awareness Leading Outcomes report (29 April 2013) funding from Astellas as support from 2013-2014 (15 May 2013) funding from Janssen for RCGP accreditation (2 August 2014) funding from Lundbeck for PR support funding from AbbVie as honoraria (panel) funding from Galderma as honoraria (NMSC) funding from Janssen as honoraria (EASL)	Non-personal financial non-specific	Declare and participate
11/07/2014	GDG1: Apologies received	Nil	Nil
04/09/2014	GDG2: British Liver Trust press release regarding rifaximin for hepatic encephalopathy	Non-personal non-financial specific	Declare and participate
17/10/2014	GDG3: No new DOI	Nil	Nil
26/11/2014	GDG4: Apologies received	Nil	Nil
21/01/2015	GDG5: No new DOI	Nil	Nil
18/02/2015	GDG6: Apologies received	Nil	Nil
26/03/2015	GDG7: No new DOI	Nil	Nil
30/04/201	GDG8: The British Liver Trust was gifted a Fibroscan	Non-personal	Withdraw

Date	Item declared	Classification	Action taken
5	machine by Norgine.	financial specific	from question relating to acute hepatic encephalopathy
25/06/2015	GDG9: No new DOI	Nil	Nil
29/07/2015	GDG10: No new DOI	Nil	Nil
02/09/2015	GDG11: No new DOI	Nil	Nil

Susan McRae

Date	Item declared	Classification	Action taken
01/07/2014	At recruitment: Employed by the Hepatitis C Trust, the UK HCV patient charity.	Personal non-financial	Declare and participate
11/07/2014	GDG1: No new DOI	Nil	Nil
04/09/2014	GDG2: No new DOI	Nil	Nil
17/10/2014	GDG3: No new DOI	Nil	Nil
26/11/2014	GDG4: No new DOI	Nil	Nil
21/01/2015	GDG5: No new DOI	Nil	Nil
18/02/2015	GDG6: No new DOI	Nil	Nil
26/03/2015	GDG7: No new DOI	Nil	Nil
30/04/2015	GDG8: No new DOI	Nil	Nil
25/06/2015	GDG9: No new DOI	Nil	Nil
29/07/2015	GDG10: Expenses paid for judging quality in care hepatitis C 2015 entries, organised by PMGroup with funding from Bristol-Myers Squibb and Gilead.	Personal financial non-specific	Declare and participate
02/09/2015	GDG11: No new DOI	Nil	Nil

Marsha Morgan

Date	Item declared	Classification	Action taken
27/06/2014	At recruitment: Has taken part in symposia both in the UK and abroad on aspects of alcohol dependence, alcohol-related liver disease, nutrition in chronic liver disease and hepatic encephalopathy.	Personal financial non-specific	Declare and participate
27/06/2014	At recruitment: A member of the Advisory board of the Institute of Alcohol Studies. Receive an annual stipend used to support research activities.	Personal financial non-specific	Declare and participate

Date	Item declared	Classification	Action taken
11/07/2014	GDG1: No new DOI.	Nil	Nil
04/09/2014	GDG2: No new DOI.	Nil	Nil
17/10/2014	GDG3: Author of Cochrane review currently in development on hepatic encephalopathy.	Personal non-financial specific	Declare and participate
26/11/2014	GDG4: No new DOI.	Nil	Nil
21/01/2015	GDG5: No new DOI.	Nil	Nil
18/02/2015	GDG6: No new DOI.	Nil	Nil
26/03/2015	GDG7: No new DOI.	Nil	Nil
30/04/2015	GDG8: No new DOI.	Nil	Nil
25/06/2015	GDG9: No new DOI.	Nil	Nil
29/07/2015	GDG10: Apologies received.	Nil	Nil
02/09/2015	GDG11: No new DOI.	Nil	Nil

Gerri Mortimore

Date	Item declared	Classification	Action taken
11/07/2014	GDG1: None declared	Nil	Nil
04/09/2014	GDG2: Apologies received	Nil	Nil
17/10/2014	GDG3: No new DOI	Nil	Nil
26/11/2014	GDG4: Apologies received	Nil	Nil
21/01/2015	GDG5: No new DOI	Nil	Nil
18/02/2015	GDG6: No new DOI	Nil	Nil
26/03/2015	GDG7: No new DOI	Nil	Nil
30/04/2015	GDG8: No new DOI	Nil	Nil
25/06/2015	GDG9: No new DOI	Nil	Nil
29/07/2015	GDG10: No new DOI	Nil	Nil
02/09/2015	GDG11: Apologies received	Nil	Nil

John O'Grady (co-optee)

Date	Item declared	Classification	Action taken
22/01/2015	At recruitment: None declared.	Nil	Nil
30/04/2015	GDG8: No new DOI.	Nil	Nil

Rachel Pryke (co-optee)

Date	Item declared	Classification	Action taken
19/01/2015	At recruitment: Speaker fee for attending RCGP Conference 2nd October 2014 in order to man a stand on bariatric surgery in conjunction with RCGP Nutrition Group and BOMSS, funded by Ethicon. The stand focuses on bariatric surgery care and post-surgical follow up.	Personal financial non-specific	Declare and participate (as a co-optee)
21/01/2015	GDG5: No new DOI.		

Valerie Ross

Date	Item declared	Classification	Action taken
03/07/2014	At recruitment: Has contributed to advisory boards for Janssen relating to the marketing of drugs for hepatitis C within the last 12 months.	Personal financial non-specific	Declare and participate
	At recruitment: Has contributed to advisory boards for Gilead relating to the marketing of drugs for hepatitis C within the last 12 months. Payment received including travel expenses.	Personal financial non-specific	Declare and participate
	At recruitment: Gave a presentation at a Bristol-Myers Squibb training day on 14 July 2014. Presented on background to the role and responsibilities of the pharmacist in the treatment of HCV and the managed entry of new therapies in this area.	Personal financial non-specific	Declare and participate
	At recruitment: Attended British Association for the Study of the Liver meeting in Newcastle on 15 to 17 September 2014. Janssen funded reduced conference attendance fee, travel, accommodation and subsistence.	Personal financial non-specific	Declare and participate
11/07/2014	GDG1: No new DOI.	Nil	Nil
04/09/2014	GDG2: No new DOI.	Nil	Nil
17/10/2014	GDG3: Apologies received.	Nil	Nil
26/11/2014	GDG4: No new DOI.	Nil	Nil
21/01/2015	GDG5: No new DOI.	Nil	Nil
18/02/2015	GDG6: No new DOI.	Nil	Nil
26/03/2015	GDG7: Funding for travel and accommodation received from Abbvie to attend European Association for the Study of the Liver conference in April 2015.	Personal financial non-specific	Declare and participate

Date	Item declared	Classification	Action taken
	GDG7: Attended an advisory board for AbbVie.	Personal financial non-specific	Declare and participate
30/04/2015	GDG8: No new DOI.	Nil	Nil
25/06/2015	GDG9: No new DOI.	Nil	Nil
29/07/2015	GDG10: Was a QiC Hepatitis Projects Judging panel member, sponsored by Gilead and Bristol-Myers Squibb on 14 July 2015.	Personal financial non-specific	Declare and participate
	GDG10: Was a presenter/facilitator at a Bristol-Myers Squibb sponsored nurse training day on 31 July 2015.	Personal financial non-specific	Declare and participate
02/09/2015	GDG11: No new DOI.	Nil	Nil

Roy Sherwood (co-optee)

Date	Item declared	Classification	Action taken
11/07/2014	At recruitment: None declared.	Nil	Nil
21/01/2015	GDG5: Receives a salary from the Pathology Department at King's College London which, as of 1 January 2015, is a private company (Viapath).	Personal financial specific	Declare and participate (as a co-optee)

NCGC team

GDG meeting	Declaration of interest	Classification	Action taken
11/07/2014	GDG1: In receipt of commissions.	N/A	N/A
04/09/2014	GDG2: No change to existing declarations.	N/A	N/A
17/10/2014	GDG3: No change to existing declarations.	N/A	N/A
26/11/2014	GDG4: No change to existing declarations.	N/A	N/A
21/01/2015	GDG5: No change to existing declarations.	N/A	N/A
18/02/2015	GDG6: No change to existing declarations.	N/A	N/A
	GDG6: No change to existing declarations.	N/A	N/A
26/03/2015	GDG7: No change to existing declarations.	N/A	N/A
30/04/2015	GDG8: No change to existing declarations.	N/A	N/A
25/06/2015	GDG9: No change to existing declarations.	N/A	N/A
29/07/2015	GDG10: No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
02/09/2015	GDG11: No change to existing declarations.	N/A	N/A

NIHR team

GDG meeting	Declaration of interest	Classification	Action taken
11/07/2014	GDG1: No change to existing declarations.	N/A	N/A
04/09/2014	GDG2: No change to existing declarations.	N/A	N/A
17/10/2014	GDG3: No change to existing declarations.	N/A	N/A
26/11/2014	GDG4: No change to existing declarations.	N/A	N/A
21/01/2015	GDG5: No change to existing declarations.	N/A	N/A
18/02/2015	GDG6: No change to existing declarations.	N/A	N/A
	GDG6: No change to existing declarations.	N/A	N/A
26/03/2015	GDG7: No change to existing declarations.	N/A	N/A
30/04/2015	GDG8: No change to existing declarations.	N/A	N/A
25/06/2015	GDG9: No change to existing declarations.	N/A	N/A
29/07/2015	GDG10: No change to existing declarations.	N/A	N/A
02/09/2015	GDG11: No change to existing declarations.	N/A	N/A

Appendix C: Clinical review protocols

C.1 Risk factors and risk assessment tools

C.1.1 Risk factors

Table 1: Review protocol: Risk factors

Component	Description
Review question	What are the risk factors that indicate the populations at specific risk for cirrhosis?
Objectives	To estimate the prognostic value of different risk factors to predict the future development of cirrhosis and to facilitate the decision to test for cirrhosis in primary care (that is, those at higher risk of developing cirrhosis in the future should be considered for testing for cirrhosis)
Population	Adults and young people who are 16 years or older
Presence or absence of prognostic variable	Obesity (BMI ≥30, or a lower BMI for people of Asian family origin) Alcohol misuse Viral hepatitis B Viral hepatitis C Type 2 diabetes
Outcomes	**Critical outcomes:** Cirrhosis: time-to-event. If time-to-event data is not available, categorical data will be used (that is, the relative risk of developing cirrhosis at different time points).
Study design	Prospective and retrospective cohort Systematic reviews of the above
Exclusions	Studies not taking into account all the essential confounding factors at analysis (in multivariate analysis) or design stage. Studies not taking into account all the confounding factors will be considered if no other evidence is available. Studies with univariate analyses if studies with multivariable analysis are available. Studies that do not have at least 10 events per covariate in the multivariate analysis will be downgraded for risk of bias. If sufficient evidence is available, these studies will be excluded.
How the information will be searched	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only. No date restriction will be applied.
Key confounders	The following are key confounders for each risk factor. Studies must have taken these confounders into consideration, either by adjusting for in the multivariate analysis or accounting for at design stage (for example excluding people with one of the other risk factors) or describing baseline characteristics between these groups. Obesity (BMI ≥30, BMI >25 for people of an Asian family origin): age, ethnicity, treatments for obesity (weight loss or surgery), all of the other risk factors. Alcohol misuse: gender, age, ethnicity, level and pattern of alcohol misuse, all of the other risk factors. Viral hepatitis B: gender, age, ethnicity, treatment for hepatitis B, all of the other risk factors.

Component	Description
	Viral hepatitis C: gender, age, ethnicity, treatment for hepatitis C, all of the other risk factors. Type 2 diabetes: gender, age, ethnicity, treatment for type 2 diabetes, all of the other risk factors.
The review strategy	Meta-analysis may be considered, if appropriate. If no other study designs are available, case-control studies will be considered. We will consider whether the severity/level of the prognostic variable (that is, BMI level, level of alcohol consumed, severity of type 2 diabetes) influences the development of cirrhosis, if available in the literature.

C.1.2 Risk tools

Table 2: Review protocol: Risk tools

Component	Description
Review question	Are there any validated risk tools that indicate the populations at specific risk for cirrhosis?
Objectives	To assess the discriminative ability and calibration of the risk factor tools in prediction of future risk of cirrhosis
Population	Adults and young people who are 16 years or older Strata: male/female
Risks stratification tools	Any validated risk factor tools
Reference standard / target condition	Development of cirrhosis (confirmed on liver biopsy)
Outcomes (in terms of discrimination/ calibration)	**Critical outcomes:** ROC area under the curve (of each risk tool for each outcome)/concordance c-statistic. Sensitivity, specificity, predictive values. Predicted risk, observed risk/calibration plot (reproduced with author permissions) (that is, predicted x-year mean risk % verses Kaplan-Meier x-year event rate). Narrative of agreement between observed and predicted risk and whether underestimation/overestimation of predicted risk). Other outcomes: D statistics, R2 statistic and Brier score.
Study design	Cohort (preferably prospective)
How the information will be searched	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. No date restriction will be applied.
The review strategy	Meta-analysis may be considered, if appropriate

C.2 Diagnostic tests

Table 3: Review protocol: Blood fibrosis test

Component	Description
Review question	In people with suspected (or under investigation for) cirrhosis, what is the most accurate blood fibrosis test to identify whether the condition is present (as indicated by the reference standard, liver biopsy)? ***First line approach to review RCT test and treat studies. Patients randomised to 1 test (with appropriate treatment for a positive result) versus another test (with appropriate treatment for a positive result) and look at patient outcomes.*** ***Patient outcomes for test-and-treat studies*** ***Survival (time-to-event) or mortality at 5 years (dichotomous)*** ***Health-related quality of life (continuous)*** ***Incidence of a decompensating event: ascites, variceal bleeding, HCC, HRS (dichotomous)*** ***Adverse effects of testing (dichotomous)*** ***Referral to secondary or tertiary care (dichotomous)*** ***Need for liver transplant (dichotomous)*** ***Second-line approach to review diagnostic accuracy studies of each test compared to the reference standard, liver biopsy. Diagnostic accuracy studies will be reviewed unless RCT test-and-treat studies are available for all index tests.***
Study design	RCTs (for test-and-treat) Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Exclusions: Case control studies
Population	Adults and young people >16 years with suspected (or under investigation for) cirrhosis. ***Stratify studies based on the underlying cause.*** • Alcohol misuse disorders • Hepatitis C • Non-alcoholic fatty liver disease • People with multiple aetiologies • PBC or PSC (reported separately) Studies including mixed aetiologies which do not provide results subgrouped by aetiology will be excluded from the review. Exclusions: • Patients under 16 years old • General population or patients not suspected to have cirrhosis (not thought to be at risk population and without signs or symptoms) • Current diagnosis of cirrhosis (hepatic decompensation compatible with cirrhosis, encephalopathy, variceal bleeding, ascites) • Patients with Hepatitis B
Setting	Primary and secondary care
Index test	Blood fibrosis tests: • FibroTest *for all aetiologies* (haptoglobin, α2M, Apo A1, γGT, Bilirubin, age, sex)

	• Enhanced liver fibrosis (ELF) (PIIINP, hyaluronic acid, TIMP-1) Note: ELF has changed since inception and newer test excludes age as an additional variable). Validated in HCV and some metabolic liver diseases. • APRI (aspartate aminotransferase (AST) /platelet ratio index) • FIB4 (platelets, ALT, AST) • AST/ALT ratio *Only include tests that have been validated in an independent validation cohort for the aetiology*
Reference standard / target condition	Cirrhosis diagnosed by liver biopsy using one of the following scoring systems: • Knodell score (F4) • Ishak fibrosis score (F5 or F6) • METAVIR (F4) • For NAFLD populations only, specific fibrosis scoring systems defined Kleiner 2005 and Brunt 2001 references Liver biopsy should be at least 6 portal tracts or a length of 15mm or more. Studies which do not specify this requirement will be excluded, unless no studies with this reference standard are identified (for each aetiology strata). A biopsy less than 25mm or 10 portal tracts will reduce the accuracy of the reference standard test and the quality of evidence will be downgraded. *Exclusions* • Studies that used scoring systems other than METAVIR, Ishak and Knodell scores for diagnosis of cirrhosis or using different cut-off values to those specified above to indicate a positive test result. • Liver biopsy length or number of portal tracts not stated or less than 15mm and 6 portal tracts
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** • ROC curve or area under curve (including DINA adjusted AUC) ***The GDG set the critical measure for decision making as the sensitivity. The GDG set a level of 95% as an acceptable level for the sensitivity of the test (this level will be used to assess imprecision).***
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.
Review Strategy	Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity : • People who are drinking alcohol or have ceased but previously drank alcohol at harmful levels (for the alcohol strata) (>80% with people still drinking; <80%) Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). • Extract data on the number of valid test readings for use in assessing the methodological quality Synthesis of data

	• Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods. If limited evidence is available for each aetiology we will, in order of preference: - Consider evidence from conference abstracts and contact the authors - Consider extrapolating evidence from another aetiology strata if evidence is available - Consider evidence from studies reporting the accuracy in mixed aetiologies

Table 4: Review protocol: Non-invasive imaging

Component	Description
Review question	In people with suspected (or under investigation for) cirrhosis, what is the most accurate non-invasive imaging test (transient elastography (fibroscan or ARFI); ultrasound or MR elastography) to identify whether cirrhosis is present (as indicated by the reference standard, liver biopsy)?
Objectives	***First line approach to review RCT test and treat studies. Patients randomised to one test (with appropriate treatment for a positive result) versus another test (with appropriate treatment for a positive result) and look at patient outcomes.*** ***Patient outcomes for test-and-treat studies*** ***Survival (time-to-event) or mortality at 5 years (dichotomous)*** ***Health-related quality of life (continuous)*** ***Incidence of a decompensating event: ascites, variceal bleeding, HCC, HRS (dichotomous)*** ***Adverse effects of testing (dichotomous)*** ***Referral to secondary or tertiary care (dichotomous)*** ***Need for liver transplant (dichotomous)*** ***Second-line approach to review diagnostic accuracy studies of each test compared to the reference standard, liver biopsy. Diagnostic accuracy studies will be reviewed unless RCT test-and-treat studies are available for all index tests.***
Study design	RCTs (for test-and-treat) Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Exclusions: Case control studies
Population / Target condition	Adults and young people >16 years with suspected (or under investigation for) cirrhosis. ***Stratify studies based on the underlying cause.*** • Alcohol misuse conditions • Hepatitis C • Non-alcoholic fatty liver disease • People with multiple aetiologies • PBC or PSC (reported separately) Studies including mixed aetiologies which do not provide results subgrouped by aetiology will be excluded from the review. Exclusions: • Patients under 16 years old

	• General population or patients not suspected to have cirrhosis (not thought to be at risk population and without signs or symptoms) • Current diagnosis of cirrhosis (hepatic decompensation compatible with cirrhosis, encephalopathy, variceal bleeding, ascites) • Patients with Hepatitis B
Setting	Primary and secondary care
Index test	Transient elastography Acoustic radiation force impulse (ARFI) imaging Point shear wave elastography (pSWE) Ultrasound MR elastography ***The index test should be carried out according to the manufacturer's guidelines on performance standards (for example in the percentage of the transient elastography scan that needs to be successful for a valid scan).*** Exclusions Index tests using ultrasound and liver microbubble transit time
Reference standard (could be more than 1)	Cirrhosis diagnosed by liver biopsy using 1 of the following scoring systems: • Knodell score (F4) • Ishak fibrosis score (F5 or F6) • METAVIR (F4) • For NAFLD populations only, specific fibrosis scoring systems defined Kleiner 2005 and Brunt 2001 references Liver biopsy should be at least 6 portal tracts or a length of 15mm or more. Studies which do not specify this requirement will be excluded, unless no studies with this reference standard are identified (for each aetiology strata). A biopsy less than 25mm or 10 portal tracts will reduce the accuracy of the reference standard test and the quality of evidence will be downgraded. *Exclusions* • Studies that used scoring systems other than METAVIR, Ishak and Knodell scores for diagnosis of cirrhosis or using different cut-off values to those specified above to indicate a positive test result. • Liver biopsy length or number of portal tracts not stated or less than 15mm and 6 portal tracts
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** • ROC curve or area under curve (including DINA adjusted AUC) ***The GDG set the critical measure for decision making as the sensitivity. The GDG set a level of 95% as an acceptable level for the sensitivity of the test (this level will be used to assess imprecision).***
Other exclusions	Case-control studies
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.

Review Strategy	Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity : • Active drinkers and people who have ceased drinking (for the alcohol strata) (>80% with people still drinking; <80%) Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). • Extract data on the number of valid test readings for use in assessing the methodological quality Synthesis of data Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods. If limited evidence is available for each aetiology we will, in order of preference: • Consider evidence from conference abstracts and contact the authors • Consider extrapolating evidence from another aetiology strata if evidence is available • Consider evidence from studies reporting the accuracy in mixed aetiologies

Table 5: Review protocol: Blood fibrosis test versus individual blood test

Component	Description
Review question	In people with suspected (or under investigation for) cirrhosis, is a blood fibrosis test more accurate compared to an individual blood test to identify whether the condition is present (as indicated by the reference standard, liver biopsy)? ***First line approach to review RCT test and treat studies. Patients randomised to 1 test (with appropriate treatment for a positive result) versus another test (with appropriate treatment for a positive result) and look at patient outcomes.*** ***Patient outcomes for test-and-treat studies*** ***Survival (time-to-event) or mortality at 5 years (dichotomous)*** ***Health-related quality of life (continuous)*** ***Incidence of a decompensating event: ascites, variceal bleeding, HCC, HRS (dichotomous)*** ***Adverse effects of testing (dichotomous)*** ***Referral to secondary or tertiary care (dichotomous)*** ***Need for liver transplant (dichotomous)*** ***Second-line approach to review diagnostic accuracy studies of each test compared to the reference standard, liver biopsy. Diagnostic accuracy studies will be reviewed unless RCT test-and-treat studies are available for all index tests.***
Study design	RCTs (test-and-treat) Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Exclusions: Case control studies
Population	Adults and young people >16 years with suspected (or under investigation for) cirrhosis.

	Stratify studies based on the underlying cause. • Alcohol misuse disorders • Hepatitis C • Non-alcoholic fatty liver disease • People with multiple aetiologies • PBC or PSC (reported separately) Studies including mixed aetiologies which do not provide results subgrouped by aetiology will be excluded from the review. Exclusions: • Patients under 16 years old • General population or patients not suspected to have cirrhosis (not thought to be at risk population and without signs or symptoms) • Current diagnosis of cirrhosis (hepatic decompensation compatible with cirrhosis, encephalopathy, variceal bleeding, ascites) • Patients with Hepatitis B
Setting	Primary and secondary care
Index test	*See Q4 for fibrosis tests* Individual blood tests: • Albumin • Platelets • Prothrombin Time (INR) • AST • ALT • Bilirubin • γGT (alcohol/ cholestasis)
Reference standard / target condition	Cirrhosis diagnosed by liver biopsy using 1 of the following scoring systems: • Knodell score (F4) • Ishak fibrosis score (F5 or F6) • METAVIR (F4) • For NAFLD populations only, specific fibrosis scoring systems defined Kleiner 2005 and Brunt 2001 references Liver biopsy should be at least 6 portal tracts or a length of 15mm or more. Studies which do not specify this requirement will be excluded, unless no studies with this reference standard are identified (for each aetiology strata). A biopsy less than 25mm or 10 portal tracts will reduce the accuracy of the reference standard test and the quality of evidence will be downgraded. *Exclusions* • Studies that used scoring systems other than METAVIR, Ishak and Knodell scores for diagnosis of cirrhosis or using different cut-off values to those specified above to indicate a positive test result. • Liver biopsy length or number of portal tracts not stated or less than 15mm and 6 portal tracts
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity

	Important outcomes: • ROC curve or area under curve (including DINA adjusted AUC) ***The GDG set the critical measure for decision making as the sensitivity. The GDG set a level of 95% as an acceptable level for the sensitivity of the test (this level will be used to assess imprecision).***
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.
Review Strategy	Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity : • Active drinkers and people who have ceased drinking (for the alcohol strata) (>80% with people still drinking; <80%) Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). • Extract data on the number of valid test readings for use in assessing the methodological quality Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods. If limited evidence is available for each aetiology we will, in order of preference: • Consider evidence from conference abstracts and contact the authors • Consider extrapolating evidence from another aetiology strata if evidence is available • Consider evidence from studies reporting the accuracy in mixed aetiologies

Table 6: Review protocol: Non-invasive tests versus blood fibrosis test

Component	Description
Review question	In people with suspected (or under investigation for) cirrhosis, is a combination of 2 non-invasive tests more accurate compared to a blood fibrosis test alone or an imaging test alone to identify whether cirrhosis is present (as indicated by the reference standard, liver biopsy)?
Objectives	***First line approach to review RCT test and treat studies. Patients randomised to 1 test (with appropriate treatment for a positive result) versus another test (with appropriate treatment for a positive result) and look at patient outcomes.*** ***Patient outcomes for test-and-treat studies*** ***Survival (time-to-event) or mortality at 5 years (dichotomous)*** ***Health-related quality of life (continuous)*** ***Incidence of a decompensating event: ascites, variceal bleeding, HCC, HRS (dichotomous)*** ***Adverse effects of testing (dichotomous)*** ***Referral to secondary or tertiary care (dichotomous)*** ***Need for liver transplant (dichotomous)*** ***Second-line approach to review diagnostic accuracy studies of each test compared to the reference standard, liver biopsy. Diagnostic accuracy studies will be reviewed***

	unless RCT test-and-treat studies are available for all index tests.
Study design	RCTs (for test-and-treat) Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Exclusions: Case control studies
Population / Target condition	Adults and young people >16 years with suspected (or under investigation for) cirrhosis. ***Stratify studies based on the underlying cause.*** • Alcohol misuse conditions (narratively report the duration of abstinence before the test) • Hepatitis C • Non-alcoholic fatty liver disease • People with multiple aetiologies • PBC or PSC (reported separately) Studies including mixed aetiologies which do not provide results subgrouped by aetiology will be excluded from the review. Exclusions: • Patients under 16 years old • General population or patients not suspected to have cirrhosis (not thought to be at risk population and without signs or symptoms) • Current diagnosis of cirrhosis (hepatic decompensation compatible with cirrhosis, encephalopathy, variceal bleeding, ascites) • Patients with Hepatitis B
Setting	Primary and secondary care
Index test	Individual blood fibrosis test versus Individual imaging test versus diagnosis made on the basis of a combination of 2 non-invasive tests (a blood fibrosis test and an imaging test; 2 imaging tests; or 2 blood fibrosis tests) *Only include blood fibrosis tests that have been validated in an independent validation cohort for the aetiology* ***The index test should be carried out according to the manufacturer's guidelines on performance standards (for example in the percentage of the transient elastography scan that needs to be successful for a valid scan).***
Reference standard (could be more than 1)	Cirrhosis diagnosed by liver biopsy using 1 of the following scoring systems: • Knodell score (F4) • Ishak fibrosis score (F5 or F6) • METAVIR (F4) • For NAFLD populations only, specific fibrosis scoring systems defined Kleiner 2005 and Brunt 2001 references Liver biopsy should be at least 6 portal tracts or a length of 15mm or more. Studies which do not specify this requirement will be excluded, unless no studies with

	this reference standard are identified (for each aetiology strata). A biopsy less than 25mm or 10 portal tracts will reduce the accuracy of the reference standard test and the quality of evidence will be downgraded. *Exclusions* • Studies that used scoring systems other than METAVIR, Ishak and Knodell scores for diagnosis of cirrhosis or using different cut-off values to those specified above to indicate a positive test result. • Liver biopsy length or number of portal tracts not stated or less than 15mm and 6 portal tracts
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** • ROC curve or area under curve (including DINA adjusted AUC) ***The GDG set the critical measure for decision making as the sensitivity. The GDG set a level of 95% as an acceptable level for the sensitivity of the test (this level will be used to assess imprecision).***
Other exclusions	Case-control studies
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.
Review Strategy	Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity : • Active drinkers and people who have ceased drinking (for the alcohol strata) (>80% with people still drinking; <80%) Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). • Extract data on the number of valid test readings for use in assessing the methodological quality • Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods. If limited evidence is available for each aetiology we will, in order of preference: • Consider evidence from conference abstracts and contact the authors • Consider extrapolating evidence from another aetiology strata if evidence is available • Consider evidence from studies reporting the accuracy in mixed aetiologies

C.3 Severity risk tools

Table 7: Review protocol: Severity risk tools

Component	Description
Review question	Which risk assessment tool is the most accurate and cost-effective for predicting the risk of future morbidity and mortality in people with compensated cirrhosis?

Component	Description
	When (at what severity score on the risk assessment tool) should people with cirrhosis be referred to specialist care?
Objectives	This review focuses on validation studies. To find the most accurate severity risk tool by assessing the discriminative ability (for example AUC) and calibration of the tools. To determine a threshold for low and high risk groups, that determines high risk people who should be referred to specialist care, based on: • the predicted risk of the outcome at each score • the sensitivity and specificity at given cut-off thresholds; for example, a lower threshold would mean additional cost of referral in people that will not have the event (high number of false positives, lower specificity), whereas a higher threshold would mean people who will have the event will not be referred (high number of false negatives, low sensitivity)
Population	Adults and young people >16 years with compensated cirrhosis (no prior decompensating event) Exclusions: • People with decompensating cirrhosis (prior decompensating event) • Prognosis of outcomes after transplant in patients with end-stage liver disease undergoing transplant. • Prognosis of outcomes after TIPS in patients undergoing TIPS
Risks stratification tools	• Model for end stage liver disease (MELD) • Child-Pugh (Child-Turcotte-Pugh) • UK model for end stage liver disease (UKELD) • Transient elastography (transient elastography) Modified risk tools by the addition of the following risk factors: • Hepatovenous portal pressure gradient (HVPG) • Na (for example MELD-Na) • Delta-MELD • MELD-EEG • Transient elastography • Nutrition
Event	• Survival • A decompensating event (hepatic encephalopathy; ascites; spontaneous bacterial peritonitis [SBP]; variceal bleeding; hepatorenal syndrome [HRS]; jaundice) or hepatocellular carcinoma (HCC) For both outcomes: report separately at different timepoints reported by study (minimum 3 months)
Outcomes (in terms of discriminatio n/calibration)	ROC area under the curve (of each risk tool for each outcome)/concordance c-statistic Sensitivity, specificity, predictive values Predicted risk, observed risk/calibration plot (reproduced with author permissions) (that is, predicted x-year mean risk % verses Kaplan-Meier x-year event rate). Narrative of agreement between observed and predicted risk and whether underestimation/overestimation of predicted risk) Other outcomes: D statistics, R2 statistic and Brier score
Study design	Cohort (prospective or retrospective). Only include external validation studies (not the development/derivation or internal validation studies).
How the	The databases to be searched are Medline, Embase, The Cochrane Library.

Component	Description
information will be searched	Studies will be restricted to English language only. No date restriction will be applied.
The review strategy	Meta-analysis may be considered, if appropriate. If no external validation studies are available, then include internal validation studies but as long as the patients are different (spatially or temporally).

C.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Table 8: Review protocol: surveillance for the early detection of hepatocellular carcinoma (HCC)

Review question	When and how frequently should surveillance testing be offered for the early detection of hepatocellular carcinoma (HCC) in people with cirrhosis?
Population	Adults and young people (16 and over) with confirmed cirrhosis, without HCC at the start of surveillance, or with a history of HCC prior to surveillance. Population strata (that will not be combined in analysis): None Exclusions: • People without cirrhosis (exclude studies recruiting >15% of people without cirrhosis, that is with other stages of fibrosis or risk factors for HCC) • People whose cirrhosis is diagnosed before 16 years old • People with hepatitis B (exclude studies with mixed aetiologies and >15% of people with hepatitis B) • HCC at the start of surveillance or a history of HCC prior to surveillance

Intervention	Intervention:
	• No surveillance
	• Surveillance with ultrasound, with or without serum AFP assay:
	  ○ yearly
	  ○ 6-monthly
	  ○ 3-monthly
	Exclusions:
	Studies that evaluate one-time screening instead of surveillance

Comparison	No surveillance versus surveillance Different frequencies of surveillance
Outcomes	**Critical outcomes:** • Transplant-free survival (time-to-event) or mortality at 5 years • Health-related quality of life **Important outcomes:** • HCC occurrence • Lesion of HCC less than or equal to 3 cm, greater than 3 cm • Number of lesions (if multiple lesions) • Liver cancer staging (according to Barcelona Clinic Liver Cancer [BCLC] system)

	• Liver transplant
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.
Study design	RCTs, systematic reviews of RCTs, observational studies, systematic reviews of observational studies.
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Subgrouping will occur if there is statistical heterogeneity in meta-analysis results. Subgroups include: • Subgroup by aetiology (different risks of HCC depending on the underlying cause) • Severity of underlying liver disease: Child-Pugh A or B versus Child-Pugh C • Treatment/prior treatment for underlying condition versus not on treatment (for example, if the hepatitis C virus has been treated or not) Minimally important differences – none identified If no evidence is identified from RCT studies, evidence will be considered from observational studies, to investigate the predictive ability of surveillance at different frequencies or no surveillance on patient outcomes, using multivariable analysis adjusting for other confounders. Confounding factors (must be taken into account at analysis or design stage): • Age • Severity of cirrhosis • Aetiology of the liver disease: hepatitis C versus other non-viral causes of cirrhosis • Co-existing morbidities • Progression of liver disease, treatment of underlying liver disease (for example, abstinence from alcohol or antiviral therapy) Exclusions: Studies not taking into account all the essential confounding factors at analysis (in multivariate analysis) or design stage will be excluded. Studies not taking into account all the confounding factors will be considered if no other evidence is available for each comparison. Studies with univariate analyses will be excluded. Studies with univariate analysis will be considered if studies with multivariable analysis are not available for each comparison. Evidence from studies in people with cirrhosis and a proportion of people with HBV >15% will only be considered if there is no evidence identified using the criteria above.

C.5 Surveillance for the detection of varices

Table 9: Review protocol: surveillance for the detection of varices

Review question	How frequently should surveillance testing using endoscopy be offered for the detection of oesophageal varices and isolated gastric varices in people with cirrhosis?
Population	Adults and young people (16 and over) with confirmed cirrhosis, without varices and who have not already been started on primary prophylactic therapy for the prevention of variceal bleeding. Population strata (that will not be combined in analysis):

	Severity of the underlying liver disease: • Child-Pugh A • Child-Pugh B and C Exclusions: • People whose cirrhosis is diagnosed before 16 years old • Oesophageal or gastric varices already present, or on primary prophylaxis for the prevention of variceal bleeding or taking beta-blockers
Intervention	Intervention: endoscopy at: • Baseline only • Yearly • Every 2 years • Every 3 years
Comparison	Comparison: endoscopy at: • Baseline only • Yearly • Every 2 years • Every 3 years Exclusions: Surveillance endoscopy versus no surveillance endoscopy
Outcomes	**Critical outcomes:** • Survival (time-to-event) or mortality at 5 years • Free from variceal bleeding (time-to-event) or variceal bleeding at 5 years • Health-related quality of life **Important outcomes:** • Free from varices (time-to-event) • Occurrence of moderate or large varices • Size of varices • Number receiving prophylactic treatment (beta-blockers or EVL)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only.
Study design	RCTs, systematic reviews of RCTs, observational studies, systematic reviews of observational studies
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Subgrouping will occur if there is statistical heterogeneity in meta-analysis results. Subgroups include: • Primary biliary cirrhosis and primary sclerosing cholangitis versus other aetiologies • Alcohol-related cirrhosis versus non-alcohol related cirrhosis • Presence of portal hypertension: hepatic venous pressure gradient (HVPG) of <10 mmHg versus HVPG of ≥10 mmHg • Treatment/prior treatment for underlying condition versus not on treatment Minimally important differences – none identified. If no evidence is identified from RCT studies, evidence will be considered from observational studies to investigate the predictive ability of surveillance at different frequencies on patient

	outcomes, using multivariable analysis adjusting for other confounders. Confounding factors (must be taken into account at analysis or design stage): • Age • Severity of cirrhosis • Aetiology of the liver disease • Portal hypertension • Co-existing morbidities • Progression of liver disease, treatment of underlying liver disease (for example, abstinence from alcohol or antiviral therapy)

C.6 Prophylaxis of variceal haemorrhage

Table 10: Review protocol: primary prevention of bleeding in people with oesophageal varices due to cirrhosis

Review questions	**What is the clinical- and cost-effectiveness of non-selective beta-blockers for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis?** **What is the clinical- and cost-effectiveness of endoscopic band ligation for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis?** **What is the clinical- and cost-effectiveness of non-selective beta-blockers compared with endoscopic band ligation for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis?**
Objectives	To determine whether non-selective beta-blockers, endoscopic band ligation, or placebo or no intervention is more effective for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis
Review population	Adults and young people (16 years and over) with endoscopically verified oesophageal varices that have never bled, with cirrhosis as the underlying cause.
Interventions and comparators: generic/class; specific/drug	Oral non-selective beta-blockers; Carvedilol Oral non-selective beta-blockers; Propranolol Band ligation; Conventional Band ligation; Multiband Placebo No intervention Comparisons: Oral non-selective beta-blockers versus placebo or no intervention Band ligation versus no intervention Oral non-selective beta-blockers versus band ligation Exclusions: Nadolol (not licenced or widely used in the UK for this indication)
Outcomes	**Critical** • Health-related quality of life at end of study (continuous) • Survival (with or without transplant) at end of study (time to event)

	• Free from primary variceal bleeding at end of study (time to event) **Important** • Hospital admission at end of study (dichotomous) • Hospital length of stay at end of study (continuous) • Primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study (dichotomous) • Bleeding related mortality at end of study (dichotomous) • Adverse events: fatigue at end of study (dichotomous)
Study design	Systematic review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	People with current or previous variceal bleeding/variceal haemorrhage/upper gastrointestinal bleeding (as determined by endoscopy) People without cirrhosis who have another cause of varices People with gastric varices
Population stratification	Size of varices (small) Size of varices (medium or large)
Reasons for stratification	Effectiveness of beta-blockers and band ligation expected to be different in people with small varices compared to people with medium or large varices.
Other stratifications	Drugs will be combined within the same drug class irrespective of dose or duration of intervention.
Subgroup analyses if there is heterogeneity	• Severity of underlying liver disease at the time of intervention (measured by Child-Pugh score) (Child-Pugh score A; Child-Pugh score B or C); intervention expected to be less effective in people with more severe cirrhosis • Age of patient (65 years and under; over 65 years); increased age may reduce effectiveness of intervention
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: no date restriction Language: studies will be restricted to English language only

C.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Table 11: Review protocol: Prevention of bacterial infections in people with confirmed cirrhosis and upper gastrointestinal bleeding

Review question	**What is the most clinically- and cost-effective prophylactic antibiotic for the primary prevention of bacterial infections in people with cirrhosis and upper gastrointestinal bleeding?**
Guideline condition and its definition	Cirrhosis
Objectives	To determine the most effective antibiotic for primary prevention of bacterial infections in people with cirrhosis and upper gastrointestinal bleeding
Review population	People with cirrhosis and upper gastrointestinal bleeding Adults and young people (16 years and over)
Interventions and	IV: Penicillin (beta-lactams); Amoxicillin

comparators: generic/class; specific/drug (All interventions will be compared with each other)	IV: Penicillin (beta-lactams); Co-Amoxiclav (Amoxicillin and clavulanic acid [Augmentin]) IV: Penicillin (beta-lactams); Ampicillin IV: Penicillin (beta-lactams); Tazocin IV: Cephalotin (beta-lactams); Cephalotin IV: 3rd generation Cephalosporins (beta-lactams); Cefotaxime IV: 3rd generation Cephalosporins (beta-lactams); Ceftazidime IV: 3rd generation Cephalosporins (beta-lactams); Ceftriaxone IV: Aminoglycoside; Gentamicin IV: Aminoglycoside; Tobramycin IV: Aminoglycoside; Amikacin IV: Quinolones; Ciprofloxacin IV: Quinolones; Pefloxacin IV: Quinolones; Ofloxacin IV: Quinolones; Floxacin IV: Carbopenums; Meropenum IV: Carbopenums; Ertapenem IV: Carbopenums; Impenem IV: Glycopeptide; Vancomycin IV: Glycylcycline; Tigecycline Oral: Quinolones; Ciprofloxacin Oral: Quinolones; Norfloxacin Oral: Quinolones; Pefloxacin Oral: Quinolones; Ofloxacin Oral: Quinolones; Floxacin Oral: Quinolones; Levofloxacin Oral: Quinolones; Moxifloxacin Oral: Penicillin; Amoxycilin Oral: Penicillin; Co-amoxiclav [Augmentin] Oral: Penicillin; Phenoxymethylpenicillin (Penicillin V) Oral: Sulfonamides Trimethoprim Oral: Sulfonamides Trimethoprim/Sulphamethoxazole [Septrin] Oral: Sulfonamides; Co-trimoxazole Oral: 3rd generation Cephalosporin; Cefalexin Oral: Clarythromycin Oral: Erythromycin Oral: Colistin Oral: Clindamycin Oral: Doxycycline Oral: Azithromycin Oral: Metronidazole Combinations; Ceftriaxone (IV) and norfloxacin (oral) (any other combinations of the above)
Comparisons	IV versus oral IV versus IV Oral versus oral Any combinations of drugs above (that is, IV + oral combination versus monotherapy) Exclusions: Placebo/no treatment
Outcomes	Critical outcomes • Occurrence of bacterial infections at end of study (dichotomous) • Quality of life at end of study (continuous) • All-cause mortality (time to event) Important outcomes

	• Renal failure at end of study (dichotomous) • Length of hospital stay at end of study (continuous) • Re-admission rate at end of study (continuous) • Antibiotic complications (for example Clostridium difficile, diarrhoea) (no minimally important differences identified)
Study design	Systematic review of RCTs RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	• Bleeding from non-cirrhotic portal hypertension (that is portal vein thrombosis) • People with nephrotic syndrome • People whose cirrhosis is diagnosed before 16 years of age • Other routes of administration other than that specified above • Placebo as a comparator • Conference abstracts
Subgroup analyses if there is heterogeneity	• Severity of the underlying liver disease (Child Pugh A (score 5, 6) - normal decompensation; Child Pugh B (score 7,8,9) - moderate decompensation; Child Pugh C (score 10-15) - decompensated liver disease; MELD categories; Child Pugh mixed categories); Degree of underlying liver decompensation at time of haemorrhage may reflect on effectiveness of antibiotics. • Different modes of administration (IV administration; IV, then oral administration; Oral; Other; IV and oral); Must give IV at first due to oral bleeding but can then switch to oral antibiotics. They may not be as effective.
Search criteria	Databases: Medline, Embase, The Cochrane Library. Date limits for search: from 2010 onwards (date of Cochrane review search) Language: English language only Systematic review and RCT search filters will be applied.
Review strategy (further details)	A meta-analysis will be conducted on RCTs with appropriate outcome data. If no RCT evidence is identified in full-text publications, conference abstracts will be considered.

C.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 12: Review protocol: TIPS versus LVP

Review question	**What is the clinical- and cost-effectiveness of transjugular intrahepatic portosystemic shunt (TIPS) compared with large-volume paracentesis (LVP) with albumin in the management of diuretic-resistant ascites due to cirrhosis?**
Guideline condition	Cirrhosis
Objectives	To determine whether TIPS or LVP is more effective in the management of diuretic-resistant ascites due to cirrhosis
Review population	Adults and young people (16 years and over) with confirmed cirrhosis and diuretic-resistant (or refractory) ascites Exclude:

	• Patients whose cirrhosis is diagnosed before 16 years old • Patients with ascites from causes other than cirrhosis (that is, peritoneum malignancy, heart failure, tuberculosis, pancreatitis, nephrotic syndrome, other causes)
Interventions and comparators: (All interventions will be compared with each other, unless otherwise stated)	TIPS LVP with albumin infusion (includes sequential LVP) Note: TIPS interventions will be considered alone or followed by diuretic treatment. TIPS using either coated or uncoated stents will be considered. Data will be extracted on any concomitant diuretic therapies and the details of the TIPS intervention (for example diameter). Exclusions: • LVP without albumin infusion • No intervention • Placebo
Outcomes	**Critical outcomes:** • Re-accumulation of ascites at end of study (dichotomous) • Health-related quality of life at end of study (continuous) • Transplant free survival at 12 months (time to event) **Important outcomes:** • Spontaneous bacterial peritonitis at end of study (dichotomous) • Renal failure at end of study (dichotomous) • Hepatic encephalopathy at end of study (dichotomous) • Length of stay at end of study (continuous) • Re-admission rate at end of study (dichotomous)
Study design	Systematic review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	None
Subgroup analyses if there is heterogeneity	• Severity of underlying liver disease at the time of intervention (measured by MELD) (MELD score <15; MELD score ≥ 15); TIPS intervention expected to be less effective in people with more severe cirrhosis • Age of patient (65 years and under; over 65 years); increased age may reduce effectiveness of TIPS intervention • Current or past encephalopathy (current encephalopathy; past encephalopathy; no encephalopathy); current or past encephalopathy may reduce the effectiveness of TIPS • Type of TIPS stent (coated stents; uncoated stents); TIPS intervention expected to be more effective with interventions using coated stents
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: no date restriction Language: studies will be restricted to English language only

C.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 13: Review protocol: SBP prevention in people with cirrhosis and ascites

Review question	What is the clinical- and cost-effectiveness of antibiotics compared with placebo for the primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites?
Guideline condition and its definition	Cirrhosis
Objectives	To estimate the clinical effectiveness of prophylactic oral antibiotics for the primary prevention of SBP in patients with confirmed cirrhosis and ascites
Review population	Patients with cirrhosis and ascites
	Adults and young people (16 years and over)
Interventions and comparators:	Oral: quinolones: ciprofloxacin Oral: quinolones: norfloxacin Oral: quinolones: pefloxacin Oral: quinolones: ofloxacin Oral: quinolones: floxacin Oral: penicillin: amoxycillin Oral: penicillin: co-amoxiclav Oral: sulfonamides: co-trimoxazole (trimethoprim+sulphamethoxazole) Oral: third generation cephalosporin: cefalexin Placebo No intervention **Comparisons:** Any oral antibiotic (mono-therapy; all classes of antibiotics pooled together) versus placebo/no intervention
Outcomes	**Critical:** • Occurrence of SBP at end of study (dichotomous) • All-cause mortality (time to event) • Quality of life at end of study (continuous) **Important:** • Incidence of resistant organisms at end of study (dichotomous) • Renal failure at end of study (dichotomous) • Liver failure at end of study (dichotomous) • Length of hospital stay at end of study (continuous) • Re-admission rate at end of study (dichotomous)
Study design	Systematic review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	None
Other exclusions	People with nephrotic syndrome People whose cirrhosis is diagnosed before 16 years of age People with previous SBP; studies which included more than 15% of patients who had previously had SBP People with variceal bleeding

Subgroup analyses if there is heterogeneity	• Severity of the underlying liver disease (Child Pugh 9 or less; Child Pugh >9). Severity of underlying liver disease may reflect on effectiveness of antibiotics. • Risk of SBP (High risk: ascitic protein level <15 g/litre (1.5 g/dl); Low risk: ascitic protein level ≥15 g/litre (1.5g/dl)); Those at higher risk of SBP are more likely to have the outcome and may be more likely to see an effect of antibiotics • Antibiotic class (Penicillins; Quinolones; 3rd generation cephalosporins; Sulfonamides); Different antibiotic classes may have different effectiveness.
Search criteria	Databases: Medline, Embase, The Cochrane Library. Date limits for search: from 2010 onwards (date of Cochrane review search) Language: English language only Systematic review and RCT search filters will be applied.

C.10 Volume replacers in hepatorenal syndrome

Table 14: Volume replacers in hepatorenal syndrome

Review question	**Which is the most clinically and cost-effective volume replacer for patients with hepatorenal syndrome due to cirrhosis who are also receiving vasoactive drugs?**
Objectives	To estimate the clinical effectiveness and cost-effectiveness of volume replacers in the management of patients with hepatorenal syndrome due to cirrhosis who are also receiving vasoactive drugs
Population	• Adults and young people (16 and over) with confirmed cirrhosis and hepatorenal syndrome . Hepatorenal syndrome is defined as reversible renal dysfunction occurring in patients with cirrhosis (with a serum creatinine 133 micromol/litre and an absence of other identifiable causes of renal failure). • People who are also receiving vasoconstrictors (vasopressin, ornipressin, terlipressin, octreotide, midodrine, noradrenaline, norepinephrine, dopamine). Population strata (that will not be combined in analysis): No population strata (type I and type II hepatorenal syndrome will be grouped together in the analysis) Exclusions • People whose cirrhosis is diagnosed before 16 years old • Renal failure due to hypovolaemia as defined by sustained improvement of renal function (creatinine decreasing to <133 micromol/litre) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day • Renal failure due to current or recent treatment with nephrotoxic drugs • Renal failure due to parenchymal renal disease • People receiving vaptans
Intervention	IV albumin IV crystalloids (Ringer's lactate solution, 0.9% sodium chloride (saline), Hartmann's solution, dextrose) IV polygel, plasma or colloid expanders (group all polygel, plasma or colloid expanders together, for example haemocel, gelofusion/gelofusine, dextran, manitol, voluven)
Comparisons	IV albumin versus IV crystalloids IV albumin versus polygel, plasma or colloid expanders IV crystalloids versus polygel, plasma or colloid expanders

	Interested in the effect of the volume replacer, therefore the vasoconstrictor type and dose should be the same within both arms of the study.
Outcomes	**Critical outcomes:** Survival (time-to-event) or mortality at 3 months Health-related quality of life (continuous) Reversal of hepatorenal syndrome or improved renal function (dichotomous – as defined by the study) at 3 months (reduction of serum creatinine below 133 micromol/litre, creatinine clearance, renal function returning to functioning kidneys without the requirement for drugs) **Important outcomes:** Time to discharge from hospital (time to event) Re-admission to hospital (dichotomous) Adverse events of volume replacement (infection) Adverse events of volume replacement (heart failure)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.
Study designs	RCTs Systematic reviews
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data. Subgrouping will occur if there is statistical heterogeneity in meta-analysis results. Subgroups include: • Length of time in established hepatorenal syndrome (less than 24 hours versus more than 24 hours) • Aetiology of liver injury (alcohol-related versus non-alcohol related) • Albumin (high dose >40 g/day versus low dose <40 g/day) • Severity of the underlying liver disease/degree of liver decompensation at the time of hepatorenal syndrome ○ Child-Pugh B (score 7, 8, 9) /moderate decompensation ○ Child-Pugh C (score 10–15) /severe decompensation liver disease Minimally important differences – none identified. If no RCT evidence is identified in full-text publications, conference abstracts will be considered.
Exclusion	Crossover studies, observational studies

C.11 Management of an episode of acute hepatic encephalopathy

Table 15: Review protocol: acute hepatic encephalopathy

Review question	What is the most clinically and cost-effective intervention for the first-line treatment of an episode of acute hepatic encephalopathy in people with cirrhosis?
Objectives	To investigate the most clinically and cost-effective intervention for the first line treatment of an episode of acute encephalopathy. A network meta-analysis (NMA) will be considered.
Population	Adults and young people (16 and over) with confirmed cirrhosis, presenting at their GP or emergency care with an episode of acute hepatic encephalopathy . • Only patients in whom hepatic encephalopathy is associated with cirrhosis

	• hepatic encephalopathy is diagnosed based on clinical observation of a change in mental state associated with known chronic liver disease/cirrhosis based on either biopsy or relevant clinical tests and imaging, with the exclusion of other causes of confusion. • Acute hepatic encephalopathy stages 1, 2, 3 and 4 (West Haven Criteria) will be included. **Population strata (that will not be combined in analysis):** None Exclusions • People whose cirrhosis is diagnosed before 16 years old • People with minimal hepatic encephalopathy (sometimes called latent or subclinical) • People with chronic hepatic encephalopathy (if acute is not stated in the research paper, there is no definition for when acute hepatic encephalopathy becomes chronic. Inclusion for acute hepatic encephalopathy should be based on the first line treatment on admission with acute symptoms) • Primary or secondary prevention of hepatic encephalopathy • Patients in whom hepatic encephalopathy is caused by acute liver failure (may be described as fulminant hepatic failure, sub-acute liver failure) • Patients with another underlying cause of confusion/impaired mental state (for example heart failure, hyponatraemia, renal failure, hypoglycaemia)
Intervention	• Non-absorbable disaccharides (combined within drug class): o lactulose (including different routes of administration, for example enema) o lactitol • Oral non-absorbable antibiotics (with or without sorbitol) (individual drug level, not combined within drug class): o aminoglycosides (neomycin) o rifaximin o vancomycin • Other oral antibiotics (metronidazole) • Phosphate enemas (combined within drug class) • Polyethylene gycol electrolyte solution, PEG 3350 • Amino acids (IV or oral): o l-ornithine-l-aspartate (LOLA) o branch chain amino acids (combined within drug class) • IV flumazenil • Oral probiotics (combined within drug class) • Sodium benzoate • Oral zinc • MARS • Combination therapy (any combinations of the above) • Placebo/no treatment <u>Exclusions:</u> Second-line treatment Dopaminergic agonists (used for chronic hepatic encephalopathy treatment) Liver dialysis Mannitol enema (not widely used in the UK) Paromomycin (not licenced in the UK) Lactitol versus lactulose studies (as non-absorbable disaccharides will be combined within drug class)
Comparisons	Any head to head comparison (combination or mono therapy)

	Any intervention versus placebo/no treatment **Duration of treatment up to2 weeks (exclude studies with duration of treatment >2 weeks as this will not be treatment of the acute episode)** **Note:** Drugs will be combined within drug class as defined above Doses as per standard doses in the BNF Different doses and durations of treatment will be combined
Outcomes	**Critical outcomes:** • Survival (time-to-event) • No improvement in hepatic encephalopathy (time to event outcome or dichotomous if time to event not reported; improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) • Health-related quality of life (continuous) **Important outcomes:** • Time to discharge from hospital (time to event) • Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) *Note: If performing a NMA, one network will be performed per outcome so limit to 2 critical outcomes (survival and 'no improvement in hepatic encephalopathy' outcomes). For other outcomes, direct pairwise comparisons will be presented.*
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.
Study designs	RCTs and systematic reviews of RCTs Exclusions: Observational studies Crossover studies
Review strategy	A meta-analysis will be conducted on RCTs with appropriate outcome data Sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Subgroups include: • Grade of acute hepatic encephalopathy (grade 1-2 versus grade 3-4): people with grade 4 hepatic encephalopathy are not able to take oral drugs so the intervention is expected to be less effective • Severity of the underlying liver disease (Child-Pugh A versus Child-Pugh B/C): interventions expected to be more effective in people with less severe underlying liver disease. Minimally important differences – none identified. If no RCT evidence is identified in full-text publications, conference abstracts will be considered.

Appendix D: Health economic review protocol

Table 16: Health economic review protocol

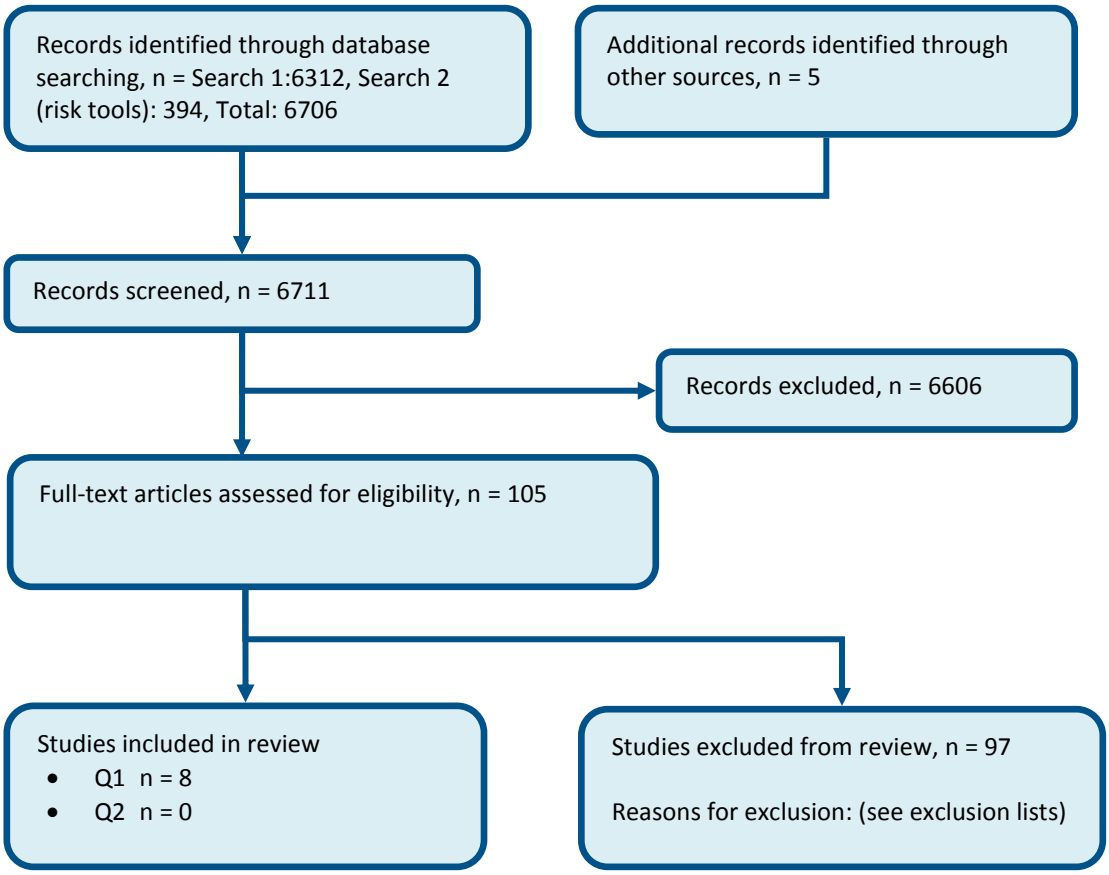
Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 1999, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[625] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France,

	Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 1999 or later but that depend on unit costs and resource data entirely or predominantly from before 1999 will be rated as 'Not applicable'. • Studies published before 1999 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix E: Clinical article selection

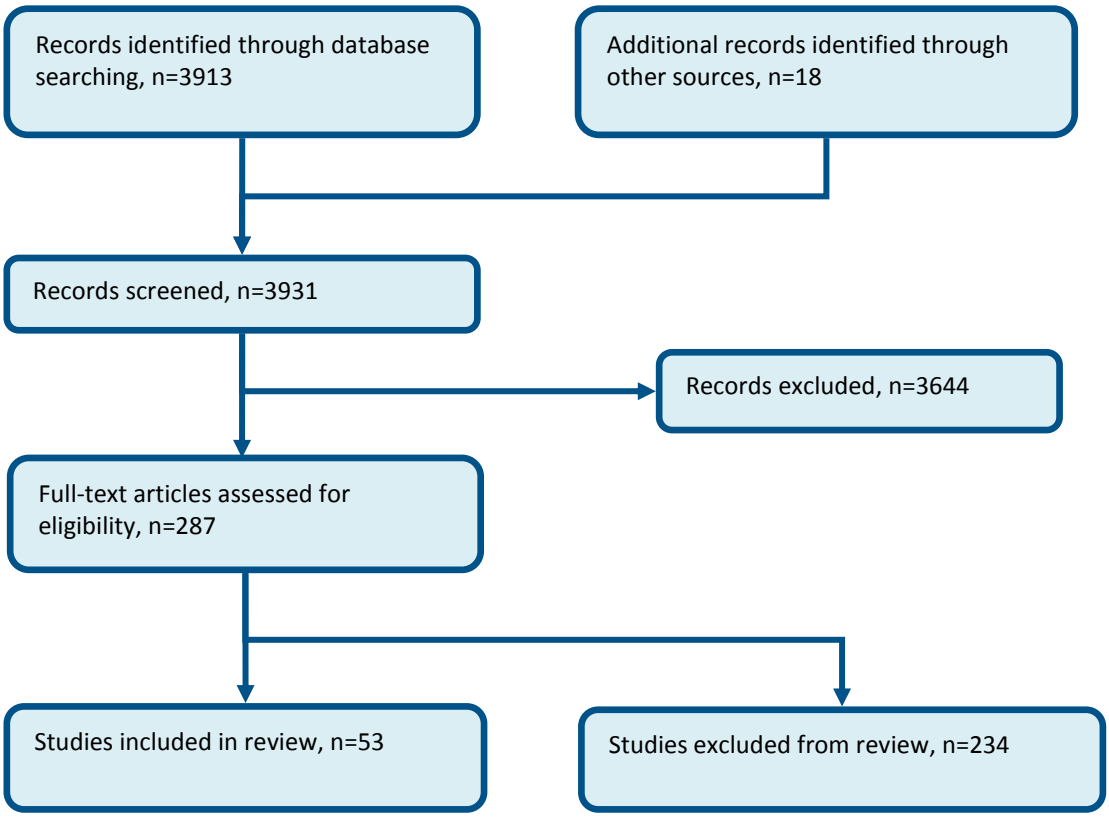
E.1 Risk factors and risk assessment tools

Figure 1: Flow diagram of clinical article selection for review question 1 (risk factors) and 2 (risk tools)



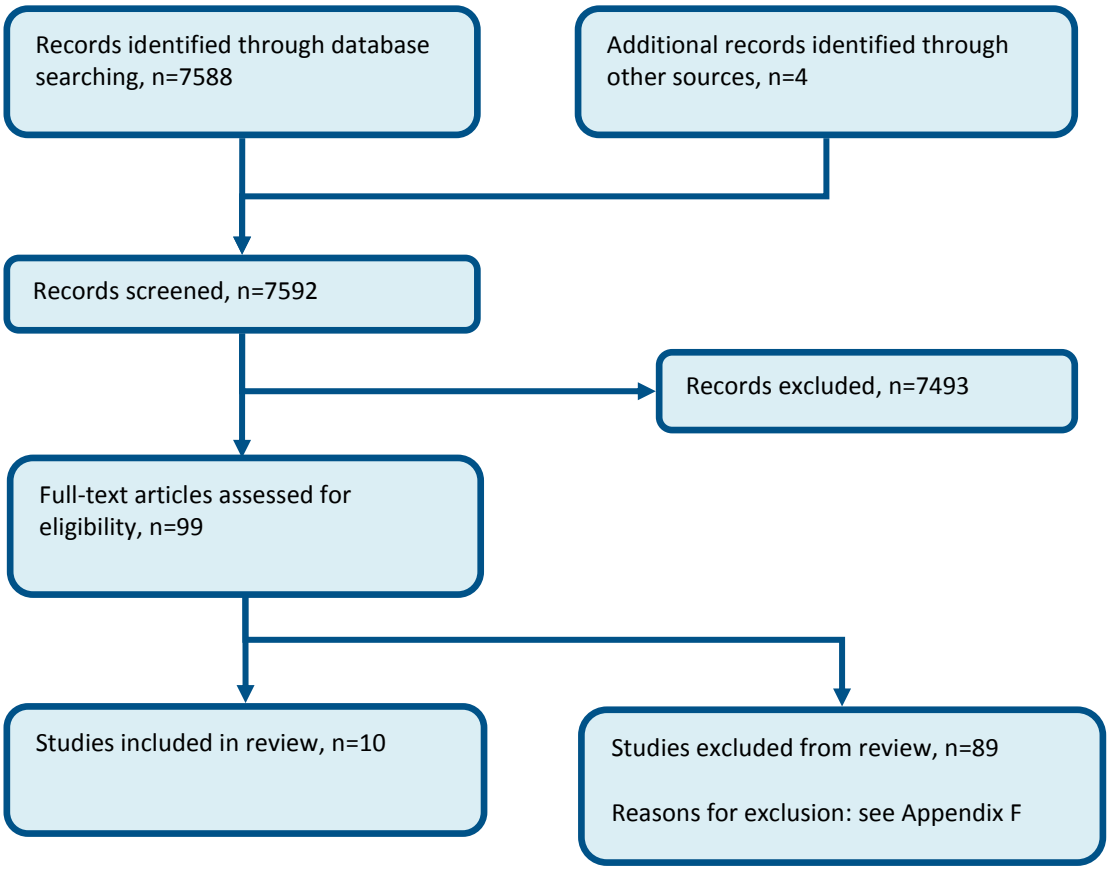
E.2 Diagnostic tests

Figure 2: Flow chart of clinical article selection for the review of diagnostic tests



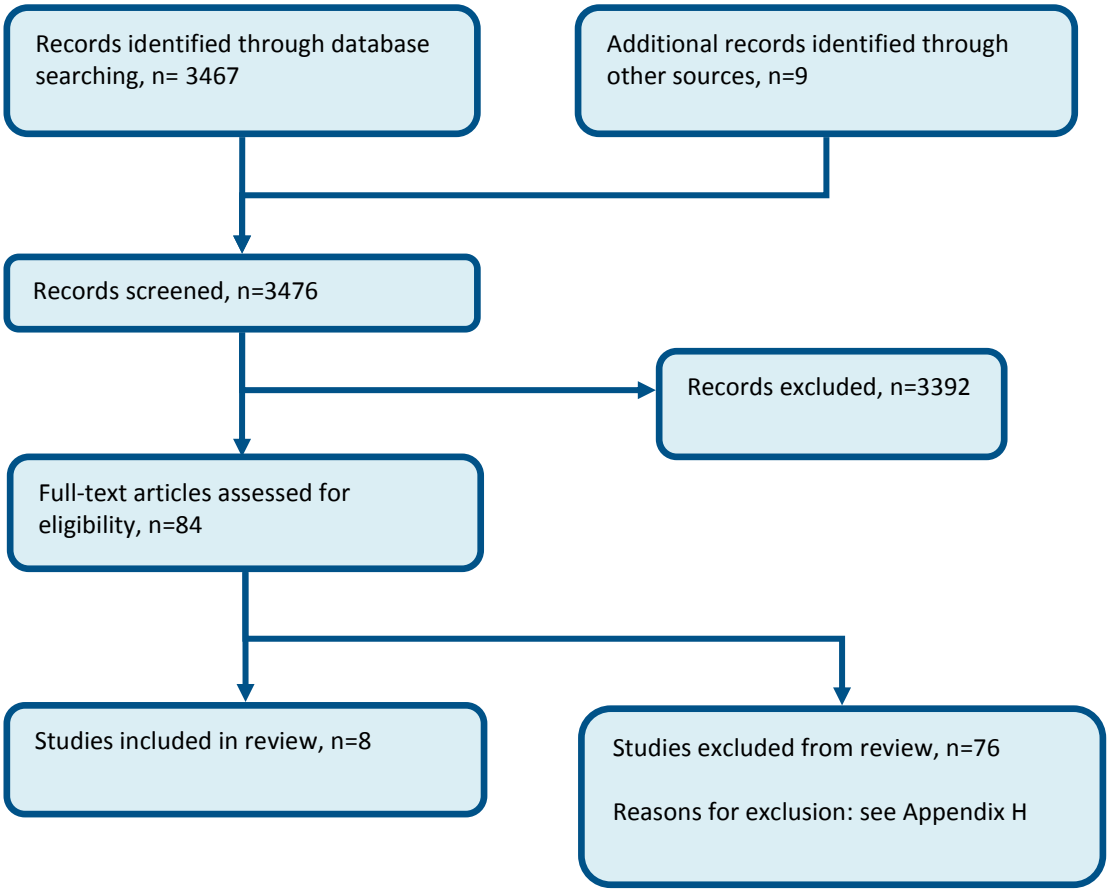
E.3 Severity risk tools

Figure 3: Flow chart of clinical article selection for the review of severity risk tools



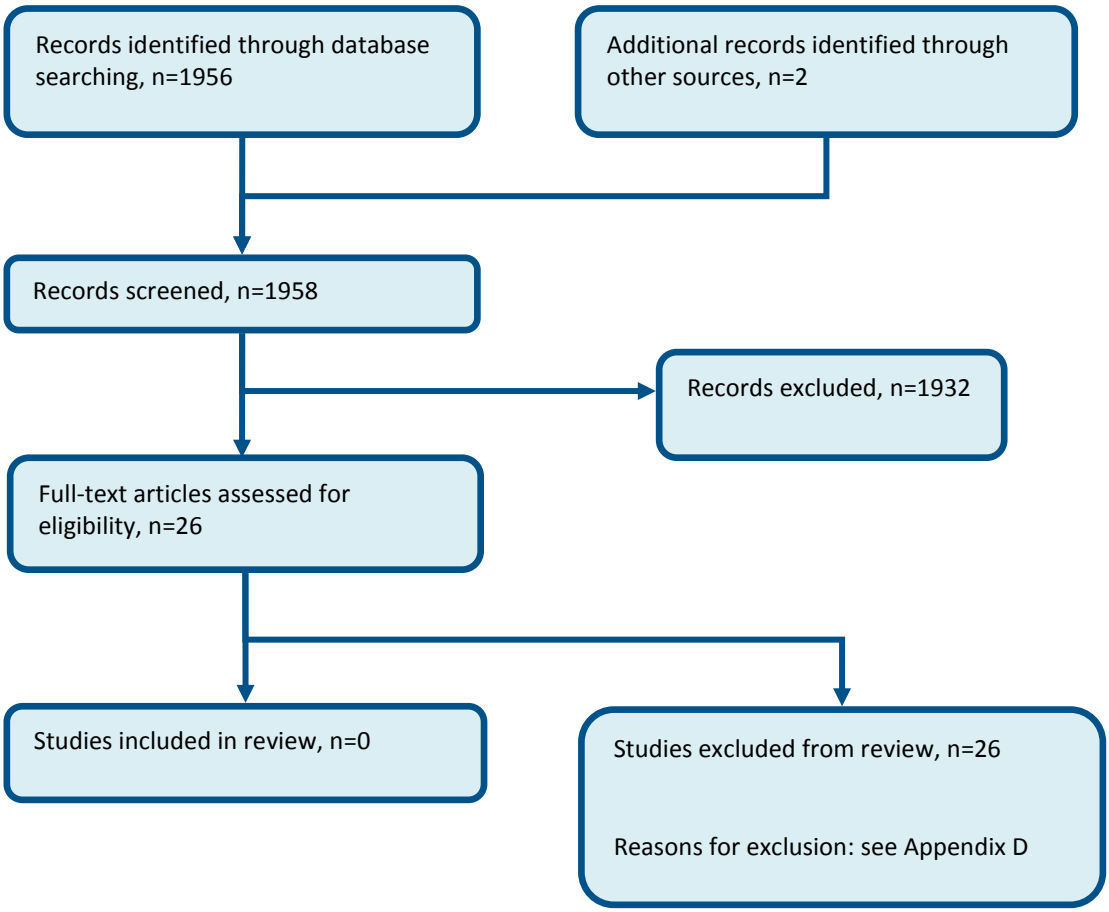
E.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Figure 4: Flow chart of clinical article selection for the review of surveillance for the early detection of HCC



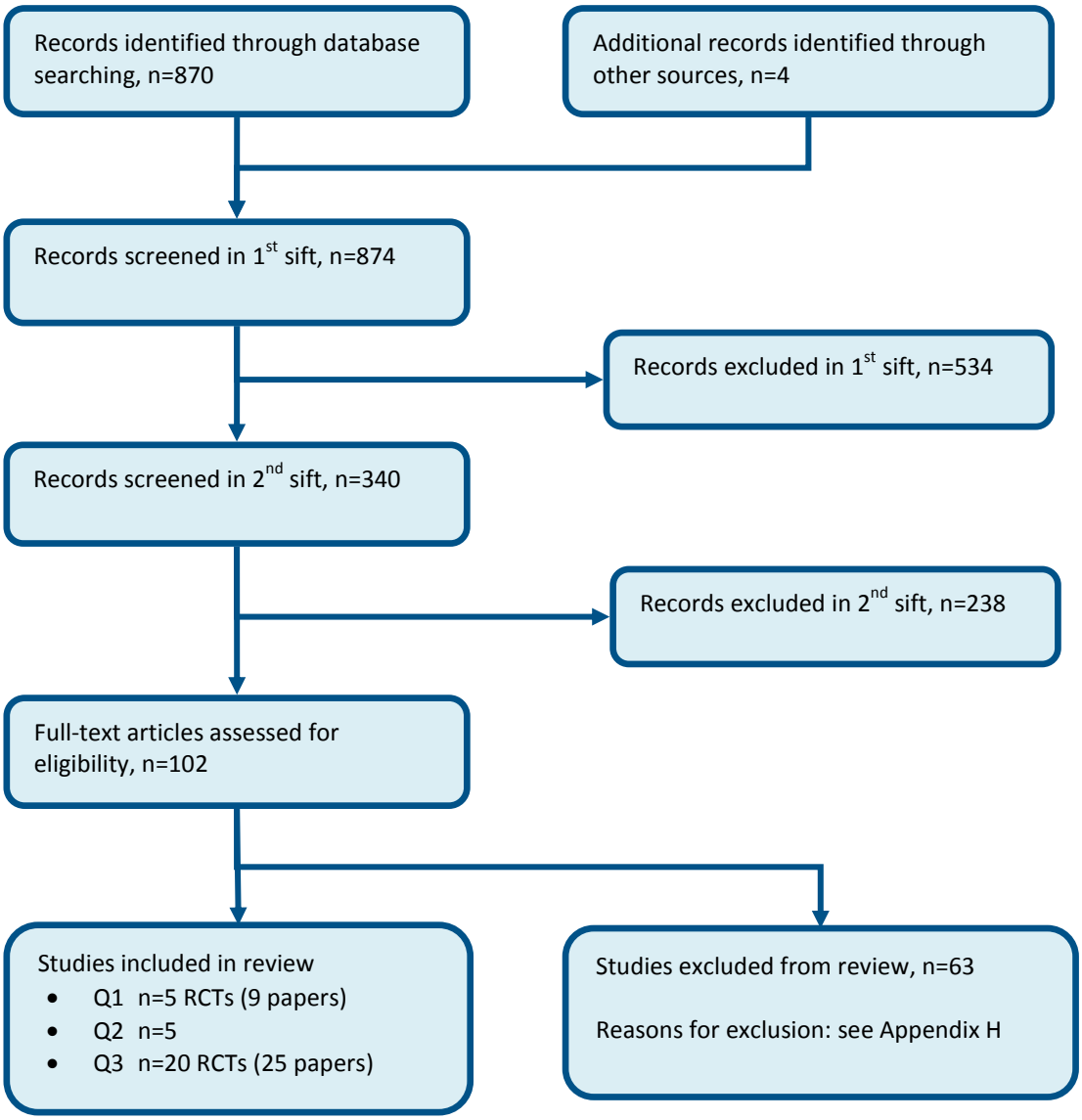
E.5 Surveillance for the detection of varices

Figure 5: Flow chart of clinical article selection for the review of surveillance for the detection of varices



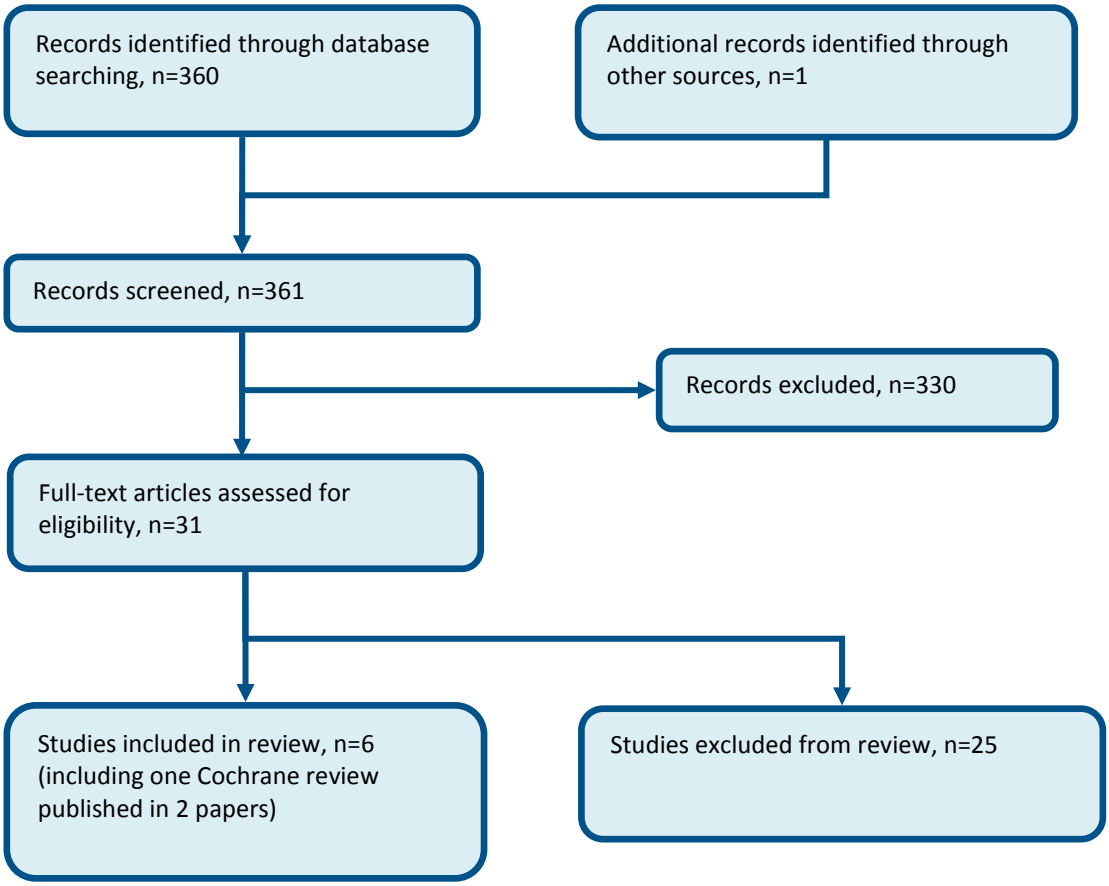
E.6 Prophylaxis of variceal haemorrhage

Figure 6: Flow chart of clinical article selection for the review of primary prevention of bleeding in people with oesophageal varices due to cirrhosis



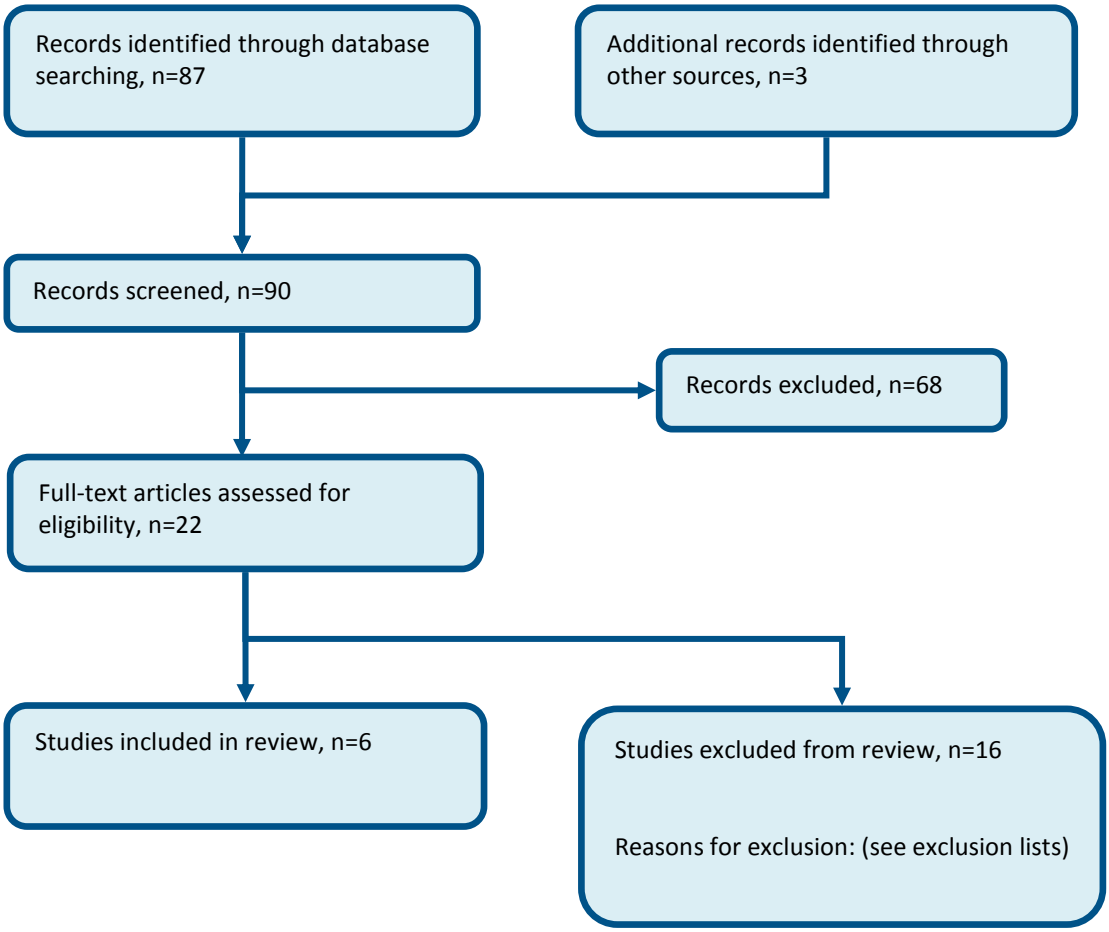
E.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Figure 7: Flow chart of clinical article selection for the review of primary prevention of bacterial infections in people with cirrhosis and upper gastrointestinal bleeding



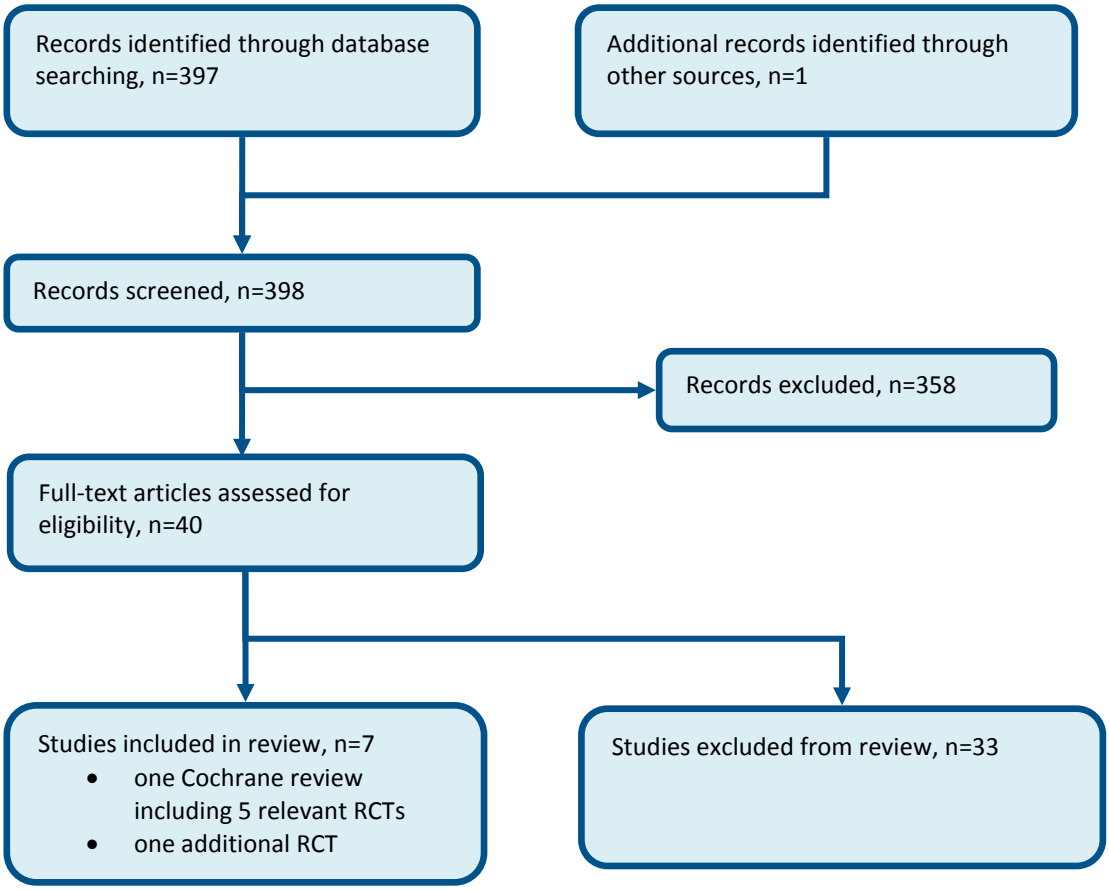
E.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Figure 8: Flow chart of clinical article selection for the review of TIPS versus LVP



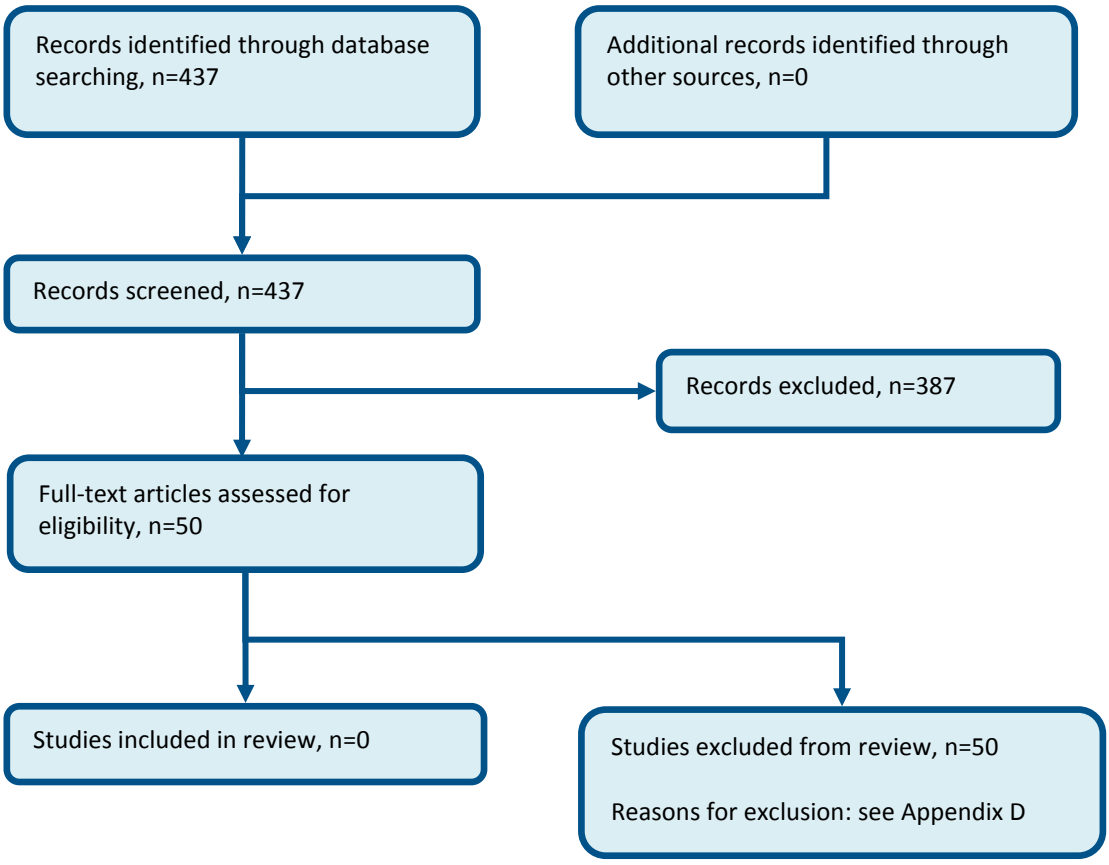
E.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Figure 9: Flow chart of clinical article selection for the review of SBP prevention in people with cirrhosis and ascites



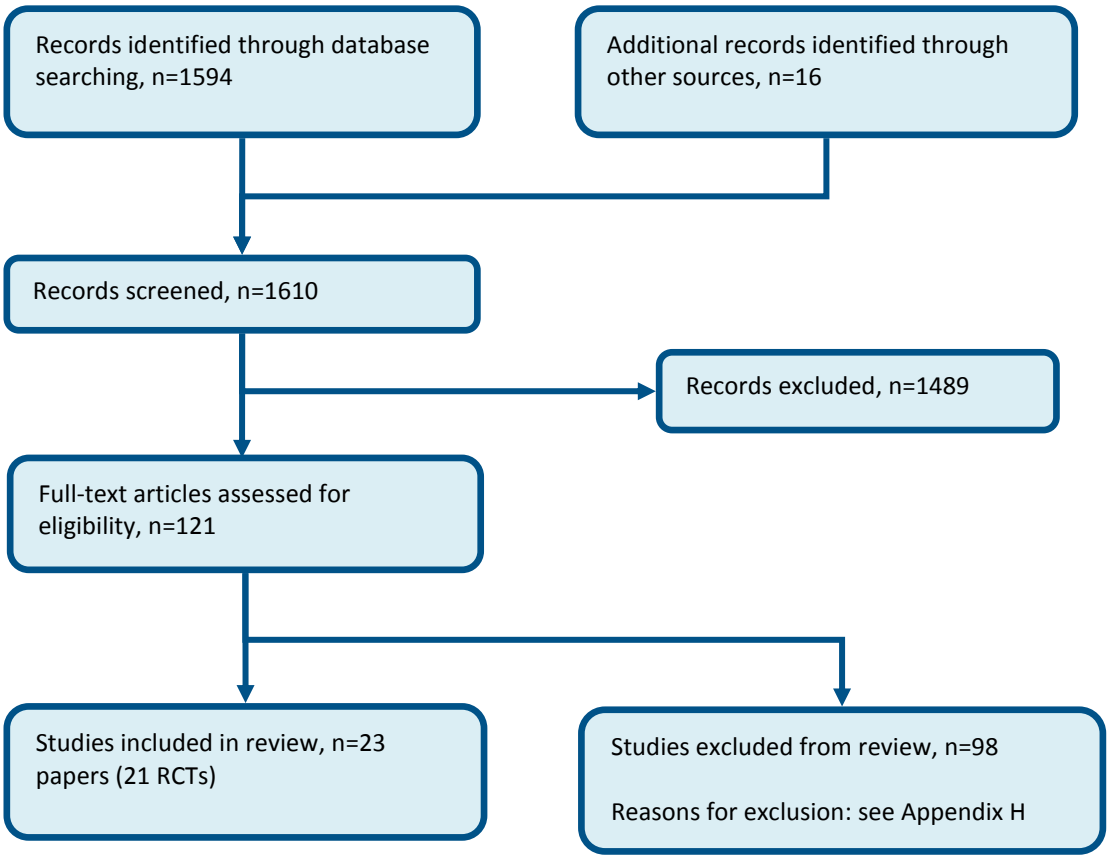
E.10 Volume replacers in hepatorenal syndrome

Figure 10: Flow chart of clinical article selection for the review of volume replacers in the treatment of hepatorenal syndrome



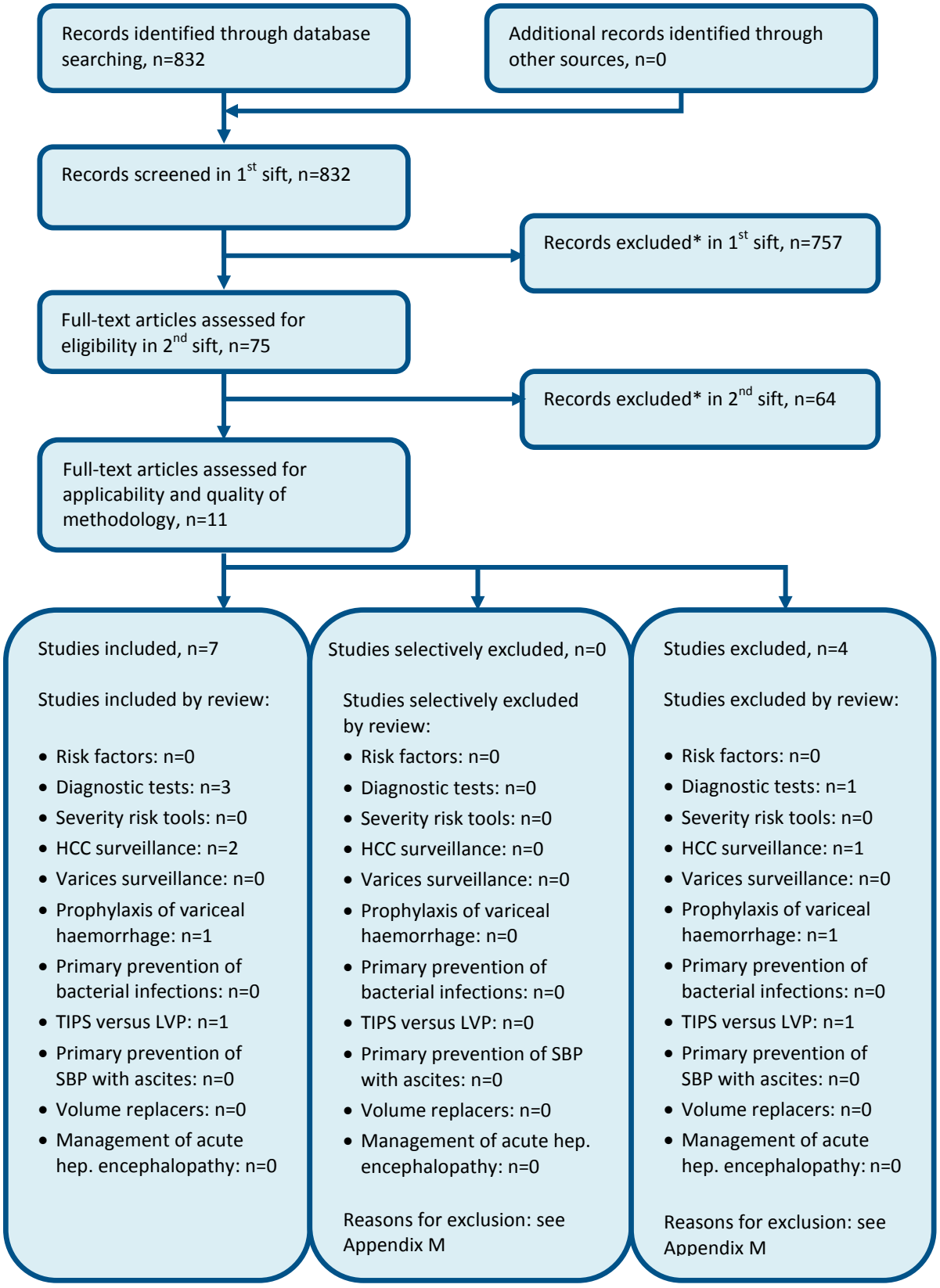
E.11 Management of an episode of acute hepatic encephalopathy

Figure 11: Flow chart of clinical article selection for the review of acute hepatic encephalopathy



Appendix F: Health economic article selection

Figure 12: Flow chart of economic article selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Literature search strategies

G.1 Contents

Search strategies used for the cirrhosis guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2012.[625] All searches were run up to **24th August 2015** unless stated otherwise. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. We do not

routinely search for electronic, ahead of print or 'online early' publications. Where possible searches were limited to retrieve material published in English.

Table 17: Database date parameters

Database	Dates searched
Medline	1946 – 24 August 2015
Embase	1980 – 24 August 2015
The Cochrane Library	Cochrane Reviews to 2015 Issue 8 of 12 CENTRAL to 2015 Issue 7 of 12 DARE, HTA and NHSEED to 2015 Issue 2 of 4

Searches for the **clinical reviews** were run in Medline (OVID) and Embase (OVID) except the risk tools question (G.4.2) which was run in Medline only. Additional searches were run in the Cochrane Library, see Table 18.

Table 18: Databases searched

Question	Question number	Databases
Diagnostic tests	G.4.3	Medline, Embase, Cochrane Library
Surveillance for the early detection of hepatocellular carcinoma (HCC)	G.4.5	Medline, Embase, Cochrane Library
Surveillance for the detection of varices	G.4.6	Medline, Embase, Cochrane Library
Management of an episode of acute hepatic encephalopathy	G.4.11	Medline, Embase, Cochrane Library
Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding	G.4.8	Medline, Embase, Cochrane Library
Prophylaxis of variceal haemorrhage	G.4.7	Medline, Embase, Cochrane Library
Risk assessment tools	G.4.2	Medline
Risk factors	G.4.1	Medline, Embase
Severity risk tools	G.4.4	Medline, Embase
TIPS versus LVP for ascites	G.4.9	Medline, Embase, Cochrane Library
Volume replacers in hepatorenal syndrome	G.4.10	Medline, Embase, Cochrane Library

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA databases were hosted by the Centre for Research and Dissemination (CRD). The Health Economic Evaluation Database (HEED) ceased production in 2014 with access ceasing in January 2015. For the final dates of HEED searches, please see individual economic questions.

For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in CRD and HEED were constructed using population terms only.

G.2 Population search strategies

G.2.1 Standard cirrhosis population

The standard population was not used in questions G.4.2, G.4.5, G.4.7, G.4.9, G.4.10, G.4.11, G.5.2 and G.5.2.

Medline search terms

1.	exp liver cirrhosis/
2.	fibrosis/ and liver/
3.	(((liver* or hepat*) adj5 fibro*) or cirrho*).ti,ab.
4.	or/1-3

Embase search terms

1.	exp liver cirrhosis/
2.	fibrosis/ and liver/
3.	(((liver* or hepat*) adj5 fibro*) or cirrho*).ti,ab.
4.	or/1-3

Cochrane search terms

#1.	[mh "liver cirrhosis"]
#2.	(cirrho* or ((liver or hepat*) near/5 fibro*)):ti,ab
#3.	{or #1-#2}

G.3 Study filter search terms

G.3.1 Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

G.3.2 Randomised controlled trials (RCT) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

G.3.3 Observational studies (OBS) search terms

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

G.3.4 Prognostic studies (PROG) search terms

Medline search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and logistic models/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
9.	roc curve/
10.	or/1-9

Embase search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and statistical model/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.

9.	receiver operating characteristic/
10.	or/1-9

G.3.5 Diagnostic accuracy studies (DIAG) search terms

medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(roc curve* or auc).ti,ab.
8.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(roc curve* or auc).ti,ab.
7.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

G.3.6 Health economics (HE) search terms

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.

13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.3.7 Quality of life (QOL) search terms

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/
2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

G.3.8 Economic modelling (MOD) search terms

Medline search terms

1.	exp models, economic/
2.	*models, theoretical/
3.	*models, organizational/
4.	markov chains/
5.	monte carlo method/
6.	exp decision theory/
7.	(markov* or monte carlo).ti,ab.
8.	econom* model*.ti,ab.
9.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
10.	or/1-9

Embase search terms

1.	statistical model/
2.	exp economic aspect/
3.	1 and 2
4.	*theoretical model/
5.	*nonbiological model/
6.	stochastic model/
7.	decision theory/
8.	decision tree/

9.	monte carlo method/
10.	(markov* or monte carlo).ti,ab.
11.	econom* model*.ti,ab.
12.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
13.	or/3-12

G.3.9 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.

16.	or/8-15

G.4 Searches for specific questions

G.4.1 Risk factors

- What are the risk factors that indicate the populations at specific risk for cirrhosis?

Medline search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	exp *diabetes mellitus, type 2/
5.	(diabet* adj2 (type 2 or type2 or type ii or type two)).ti.
6.	(dm2 or t2d*).ti.
7.	(diabet* adj2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)).ti.
8.	exp *obesity/
9.	exp *overweight/
10.	(obesity or obese).ti.
11.	(overweight or over-weight or over weight or overeating or over eating or over-eating).ti.
12.	*body mass index/
13.	(body mass index or bmi).ti.
14.	*hepatitis b/ or *hepatitis c/
15.	(hepatitis adj (b or c)).ti.
16.	(drinker* or (drink* adj2 use*) or ((alcohol* or drink*) adj5 (abstinen* or abstain* or abus* or addict* or attenuat* or binge* or crav* or dependen* or detox* or disease* or disorder* or excessiv* or harm* or hazard* or heavy or high risk or intoxicat* or misus* or overdos* or (over adj dos*) or problem* or rehab* or reliance or reliant or relaps* or withdraw*))).ti.
17.	exp *alcohol-related disorders/
18.	alcoholi*.ti.
19.	or/4-18
20.	exp risk/
21.	prevalence/
22.	incidence/
23.	(risk* or prevalence* or incidence* or predict* or associat*).ti.
24.	or/20-23
25.	Study filters SR (G.3.1) or OBS (G.3.3) or PROG (G.3.4)
26.	3 and 19 and (24 or 25)
27.	limit 26 to English language
	See **Table 17** for date parameters

Embase search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	exp *non insulin dependent diabetes mellitus/
5.	(diabet* adj2 (type 2 or type2 or type ii or type two)).ti.

6.	(dm2 or t2d*).ti.
7.	(diabet* adj2 (noninsulin or non insulin or slow-onset or slow onset or adult-onset or adult onset)).ti.
8.	exp *obesity/
9.	(obesity or obese).ti.
10.	(overweight or over-weight or over weight or overeating or over eating or over-eating).ti.
11.	*body mass/
12.	(body mass index or bmi).ti.
13.	*hepatitis b/ or *hepatitis c/
14.	(hepatitis adj (b or c)).ti.
15.	(drinker* or (drink* adj2 use*) or ((alcohol* or drink*) adj5 (abstinen* or abstain* or abus* or addict* or attenuat* or binge* or crav* or dependen* or detox* or disease* or disorder* or excessiv* or harm* or hazard* or heavy or high risk or intoxicat* or misus* or overdos* or (over adj dos*) or problem* or rehab* or reliance or reliant or relaps* or withdraw*))).ti.
16.	*alcoholism/
17.	alcoholi*.ti.
18.	or/4-17
19.	exp *risk/
20.	*prevalence/
21.	*incidence/
22.	(risk* or prevalence* or incidence* or predict* or associat*).ti,ab.
23.	or/19-22
24.	Study filters SR (A.3.1) or OBS (A.3.3) or PROG (A.3.4)
25.	3 and 18 and (23 or 24)
26.	limit 25 to English language
	See **Table 17** for date parameters

G.4.2 Risk assessment tools

- Are there any validated risk tools that indicate the populations at specific risk for cirrhosis?

Medline search terms

1.	(cirrho* adj5 (risk* adj3 (score* or stratif* or assess* or calculat* or engine* or equation* or algorithm* or chart* or table* or predict* or function*))).ti,ab.
2.	(cirrho* adj5 ((decision or predict* or assess* or screen* or score* or scoring or stratif* or prognos* or logistic*) adj3 (tool* or rule* or instrument*1 or index* or test* or technique* or analys* or model*))).ti,ab.
3.	1 or 2
4.	animals/ not humans/
5.	animals, laboratory/
6.	exp animal experiment/
7.	exp animal model/
8.	exp rodentia/
9.	(rat or rats or mouse or mice).ti.
10.	or/4-9
11.	3 not 10
12.	limit 11 to English language
	See **Table 17** for date parameters

G.4.3 Diagnostic tests

Searches for the following four questions were run as one search:

- In people with suspected (or under investigation for) cirrhosis:

  a) What is the most accurate blood fibrosis test to identify whether cirrhosis is present?

  b) What is the most accurate non-invasive imaging test to identify whether cirrhosis is present?

  c) Is the most accurate blood fibrosis test more accurate compared to an individual blood test to identify whether cirrhosis is present?

  d) Is a combination of 2 non-invasive tests more accurate compared to a blood fibrosis test alone or an imaging test alone to identify whether cirrhosis is present?

Medline search terms

1.	Standard population (G.2.1)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	exp diagnostic tests, routine/
5.	((blood or liver) adj2 test*).ti,ab.
6.	'enhanced liver fibrosis'.ti,ab.
7.	(fibrotest* or fibrosis test*).ti,ab.
8.	elasticity imaging techniques/ or exp ultrasonography, doppler/
9.	((transient or magnetic or mr) adj3 elastogra*).ti,ab.
10.	fibroscan.ti,ab.
11.	(acoustic radiation force impulse or arfi).ti,ab.
12.	(ultrasound* or ultrason* or sonograph* or echograph*).ti,ab.
13.	ultrasonography/
14.	((shear or wave) adj4 (elastogr* or imag*)).ti,ab.
15.	or/4-14
16.	Study filters SR (G.3.1) or RCT (G.3.2) or DIAG (G.3.5)
17.	3 and 15 and 16
18.	limit 17 to English language
	See **Table 17** for date parameters

Embase search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	diagnostic test/
5.	((blood or liver) adj2 test*).ti,ab.
6.	'enhanced liver fibrosis'.ti,ab.
7.	(fibrotest* or fibrosis test*).ti,ab.
8.	*echography/ or *doppler echography/ or *elastography/
9.	((transient or magnetic or mr) adj3 elastogra*).ti,ab.
10.	fibroscan.ti,ab.
11.	(acoustic radiation force impulse or arfi).ti,ab.
12.	((shear or wave) adj4 (elastogr* or imag*)).ti,ab.

13.	or/4-12
14.	Study filters SR (G.3.1) or RCT (G.3.2) or DIAG (G.3.5)
15.	3 and 13 and 14
16.	limit 15 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	Standard population (G.2)
#2.	MeSH descriptor: [diagnostic tests, routine] explode all trees
#3.	((blood or liver) near/2 test*):ti,ab
#4.	enhanced liver fibrosis:ti,ab
#5.	(fibrotest* or fibrosis test*):ti,ab
#6.	MeSH descriptor: [elasticity imaging techniques] explode all trees
#7.	MeSH descriptor: [ultrasonography, doppler] explode all trees
#8.	MeSH descriptor: [ultrasonography] this term only
#9.	((transient or magnetic or mr) near/3 elastogra*):ti,ab
#10.	fibroscan:ti,ab
#11.	(acoustic radiation force impulse or arfi):ti,ab
#12.	(ultrasound* or ultrason* or sonograph* or echograph*):ti,ab
#13.	((shear or wave) near/4 (elastogr* or imag*)):ti,ab
#14.	{or #2-#13}
#15.	#1 and #14
	See **Table 17** for date parameters

G.4.4 Severity risk tools

Searches for the following two questions were run as one search:

- Which risk assessment tool is the most accurate and cost-effective for predicting the risk of morbidity and mortality in people with compensated cirrhosis?
- When (at what severity score on the risk assessment tool) should people with cirrhosis be referred to specialist care?

Medline search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	(child pugh or childpugh or child na or childna or meld or ukeld).ti,ab.
5.	(child turcotte or childturcotte).ti,ab.
6.	model for end stage liver disease.ti,ab.
7.	model for endstage liver disease.ti,ab.
8.	or/4-7
9.	elasticity imaging techniques/
10.	((transient or magnetic or mr) adj3 elastogra*).ti,ab.
11.	fibroscan.ti,ab.
12.	or/9-11
13.	8 or 12
14.	Study filters OBS (G.3.3) or PROG (G.3.4)

15.	3 and 13 and 14
16.	limit 15 to English language
	See **Table 17** for date parameters

Embase search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	*child pugh score/
5.	(child pugh or childpugh or child na or childna or meld or ukeld).ti,ab.
6.	(child turcotte or childturcotte).ti,ab.
7.	*model for end stage liver disease score/
8.	model for end stage liver disease.ti,ab.
9.	model for endstage liver disease.ti,ab.
10.	or/4-9
11.	*elastography/
12.	((transient or magnetic or mr) adj3 elastogra*).ti,ab.
13.	fibroscan.ti,ab.
14.	or/11-13
15.	10 or 14
16.	Study filters OBS (G.3.3) or PROG (G.3.4)
17.	3 and 15 and 16
18.	limit 17 to English language
	See **Table 17** for date parameters

G.4.5 Surveillance for the early detection of hepatocellular carcinoma (HCC)

- When and how frequently should surveillance testing be offered for the early detection of hepatocellular carcinoma in people with cirrhosis?

Medline search terms

1.	carcinoma, hepatocellular/
2.	liver neoplasms/
3.	((hepatocellular or liver or hepatic or hepato) adj2 (cancer or carcinoma* or neoplasm*)).ti,ab.
4.	(hepatoma* or hepatocarcinoma* or hcc).ti,ab.
5.	or/1-4
6.	exp early diagnosis/
7.	surveillance.ti,ab,hw.
8.	screen*.ti,ab.
9.	(early and (detect* or diagnos* or stage*)).ti,ab.
10.	or/6-9
11.	5 and 10
12.	Excluded study designs and publication types (G.3.9)
13.	11 not 12
14.	Study filters SR (G.3.1) or RCT (G.3.2) or OBS (G.3.3)
15.	13 and 14
16.	limit 15 to English language

	See **Table 17** for date parameters

Embase search terms

1.	liver cell carcinoma/
2.	liver carcinoma/
3.	liver cancer/
4.	(hepatoma* or hepatocarcinoma* or hcc).ti,ab.
5.	((hepatocellular or liver or hepatic or hepato) adj2 (cancer or carcinoma* or neoplasm*)).ti,ab.
6.	or/1-5
7.	early diagnosis/
8.	surveillance.ti,ab,hw.
9.	screen*.ti,ab.
10.	(early and (detect* or diagnos* or stage*)).ti,ab.
11.	or/7-10
12.	6 and 11
13.	Excluded study designs and publication types (G.3.9)
14.	12 not 13
15.	Study filters SR (G.3.1) or RCT (G.3.2) or OBS (G.3.3)
16.	14 and 15
17.	limit 16 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	MeSH descriptor: [carcinoma, hepatocellular] explode all trees
#2.	MeSH descriptor: [liver neoplasms] explode all trees
#3.	(hepatoma* or hepatocarcinoma* or hcc):ti,ab
#4.	((hepatocellular or liver or hepatic or hepato) near/2 (cancer or carcinoma* or neoplasm*)):ti,ab
#5.	{or #1-#4}
#6.	MeSH descriptor: [early diagnosis] explode all trees
#7.	(surveillance or screen*):ti,ab
#8.	(early and (detect* or diagnos* or stage*)):ti,ab
#9.	{or #6-#8}
#10.	#5 and #9
	See **Table 17** for date parameters

G.4.6 Surveillance for the detection of varices

- How frequently should surveillance testing using endoscopy be offered for the detection of oesophageal varices and isolated gastric varices in people with cirrhosis?

Medline search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	endoscopy, gastrointestinal/ or capsule endoscopy/ or double-balloon enteroscopy/ or duodenoscopy/ or esophagoscopy/ or gastroscopy/
5.	((gi or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or

	duod* or oesoph* or esophag*) adj3 endoscop*).ti,ab.
6.	(ogd or egd or ugie or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*).ti,ab.
7.	or/4-6
8.	"esophageal and gastric varices"/
9.	((gi or stomach* or gastric or gastrointest* or gastro-intest* or duod* or oesoph* or esophag*) adj3 (varic* or varix*)).ti,ab.
10.	(detect* or diag* or surveillance* or test* or imag* or assess*).ti,ab.
11.	8 or 9
12.	10 and 11
13.	7 or 12
14.	Study filters SR (G.3.1) or RCT (G.3.2) or OBS (G.3.3)
15.	3 and 13 and 14
16.	limit 15 to English language
	See **Table 17** for date parameters

Embase search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	*gastrointestinal endoscopy/ or *esophagoscopy/ or *duodenoscopy/ or *gastroscopy/ or *capsule endoscopy/ or *double-balloon enteroscopy/
5.	((gi or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) adj3 endoscop*).ti,ab.
6.	(ogd or egd or ugie or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*).ti,ab.
7.	or/4-6
8.	*stomach varices/
9.	*esophagus varices/
10.	((gi or stomach* or gastric or gastrointest* or gastro-intest* or duod* or oesoph* or esophag*) adj3 (varic* or varix*)).ti,ab.
11.	or/8-10
12.	(detect* or diag* or surveillance* or test* or imag* or assess*).ti,ab.
13.	11 and 12
14.	7 or 13
15.	Study filters SR (G.3.1) or RCT (G.3.2) or OBS (G.3.3)
16.	3 and 14 and 15
17.	limit 16 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	Standard population (G.2)
#2.	MeSH descriptor: [esophagoscopy] this term only
#3.	MeSH descriptor: [endoscopy, gastrointestinal] this term only
#4.	MeSH descriptor: [duodenoscopy] this term only
#5.	MeSH descriptor: [gastroscopy] this term only
#6.	MeSH descriptor: [capsule endoscopy] this term only

#7.	MeSH descriptor: [double-balloon enteroscopy] this term only
#8.	((gi or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) near/3 endoscop*):ti,ab
#9.	(ogd or egd or ugie or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*):ti,ab
#10.	{or #2-#9}
#11.	MeSH descriptor: [esophageal and gastric varices] this term only
#12.	((gi or stomach* or gastric or gastrointest* or gastro-intest* or duod* or oesoph* or esophag*) near/3 (varic* or varix*)):ti,ab
#13.	(detect* or diag* or surveillance* or test* or imag* or assess*):ti,ab
#14.	#11 or #12
#15.	#13 and #14
#16.	#10 or #15
#17.	#1 and #16
	See **Table 17** for date parameters

G.4.7 Prophylaxis of variceal haemorrhage

Searches for the following three questions were run as one search:

- What is the clinical- and cost- effectiveness of non-selective beta-blockers for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis?
- What is the clinical- and cost- effectiveness of endoscopic band ligation for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis?
- What is the clinical- and cost- effectiveness of non-selective beta-blockers compared with endoscopic band ligation for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis?

Medline search terms

1.	"esophageal and gastric varices"/
2.	((oesophag* or esophag*) adj3 (varic* or varix)).ti,ab.
3.	((varix or varic*) adj2 bleed* adj3 (prevent* or prophyla*)).ti,ab.
4.	or/1-3
5.	adrenergic beta-antagonists/
6.	propranolol/
7.	nadolol/
8.	(carvedilol or propranolol or bedranol or inderal or syprol or nadolol or corgard or solgol).ti,ab.
9.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
10.	or/5-9
11.	ligation/
12.	(ligat* or (endoscop* adj2 therap*) or ebl or evl or band* or multiband*).ti,ab.
13.	or/11-12
14.	10 or 13
15.	4 and 14
16.	Excluded study designs and publication types (G.3.9)
17.	15 not 16
18.	Study filters SR (G.3.1) or RCT (G.3.2)
19.	17 and 18

20.	limit 19 to English language
	See **Table 17** for date parameters

Embase search terms

1.	exp esophagus varices/
2.	((oesophag* or esophag*) adj3 (varic* or varix)).ti,ab.
3.	((varix or varic*) adj2 bleed* adj3 (prevent* or prophyla*)).ti,ab.
4.	or/1-3
5.	*beta adrenergic receptor blocking agent/
6.	*propranolol/
7.	*carvedilol/
8.	*nadolol/
9.	(carvedilol or propranolol or bedranol or inderal or syprol or nadolol or corgard or solgol).ti,ab.
10.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
11.	or/5-10
12.	exp *ligation/
13.	*endoscopic therapy/
14.	(ligat* or (endoscop* adj2 therap*) or ebl or evl or band* or multiband*).ti,ab.
15.	or/12-14
16.	11 or 15
17.	4 and 16
18.	Excluded study designs and publication types (G.3.9)
19.	17 not 18
20.	Study filters SR (G.3.1) or RCT (G.3.2)
21.	19 and 20
22.	Limit 21 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	[mh ^"esophageal and gastric varices"]
#2.	((oesophag* or esophag*) near/3 (varic* or varix)):ti,ab
#3.	((varix or varic*) near/2 bleed* near/3 (prevent* or prophyla*)):ti,ab
#4.	#1 or #2 or #3
#5.	[mh ^"adrenergic beta-antagonists"]
#6.	[mh ^propranolol]
#7.	[mh ^nadolol]
#8.	(carvedilol or propranolol or bedranol or inderal or syprol or nadolol or corgard or solgol):ti,ab
#9.	((beta or b) near/3 (block* or antagonist*)):ti,ab
#10.	{or #5-#9}
#11.	[mh ^ligation]
#12.	(ligat* or (endoscop* near/2 therap*) or ebl or evl or band* or multiband*):ti,ab
#13.	#11 or #12
#14.	#10 or #13
#15.	#4 and #14
	See **Table 17** for date parameters

G.4.8 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Searches for the following two questions were run as one search:

- What is the most clinically and cost-effective prophylactic antibiotic for the primary prevention of bacterial infections in people with cirrhosis and upper gastrointestinal bleeding?
- What is the clinical and cost-effectiveness of antibiotics compared with placebo for the primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites?

Medline search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	exp antibacterial agents/
5.	antibiotic*.ti,ab.
6.	(anti-bacterial* or antibacterial*).ti,ab.
7.	(anti-microbial* or antimicrobial*).ti,ab.
8.	(anti-mycobacterial* or antimycobacterial*).ti,ab.
9.	(bacteriocid* or bactericid*).ti,ab.
10.	exp antibiotic prophylaxis/
11.	or/4-10
12.	Study filters SR (G.3.1) or RCT (G.3.2)
13.	3 and 11 and 12
14.	Limit 13 to English language
	See **Table 17** for date parameters

Embase search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	exp *antibiotic agent/
5.	*antibiotic prophylaxis/
6.	antibiotic*.ti,ab.
7.	(anti-bacterial* or antibacterial*).ti,ab.
8.	(anti-microbial* or antimicrobial*).ti,ab.
9.	(anti-mycobacterial* or antimycobacterial*).ti,ab.
10.	(bacteriocid* or bactericid*).ti,ab.
11.	or/4-10
12.	Study filters SR (G.3.1) or RCT (G.3.2)
13.	3 and 11 and 12
14.	Limit 13 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	Standard population (G.2)
#2.	MeSH descriptor: [antibiotic prophylaxis] explode all trees
#3.	MeSH descriptor: [anti-bacterial agents] explode all trees
#4.	(antibiotic* or anti-bacterial* or antibacterial* or anti-microbial* or antimicrobial* or anti-

	mycobacterial* or antimycobacterial* or bacteriocid* or bactericid*):ti,ab,kw
#5.	{or #2-#4}
#6.	#1 and #5
	See **Table 17** for date parameters

G.4.9 TIPS versus LVP for ascites

- What is the clinical and cost-effectiveness of transjugular intrahepatic portosystemic shunt (TIPS) compared with large-volume paracentesis (LVP) with albumin in the management of diuretic-resistant ascites due to cirrhosis?

Medline search terms

1.	ascites/
2.	ascit*.ti,ab.
3.	or/1-2
4.	Excluded study designs and publication types (G.3.9)
5.	3 not 4
6.	portasystemic shunt, transjugular intrahepatic/
7.	peritoneovenous shunt/
8.	((transjugular intrahepatic adj2 port?systemic adj2 (stent* or shunt*)) or tips* or port?systemic anastomosis).ti,ab.
9.	or/6-8
10.	paracentesis/
11.	(paracentes* or lvp).ti,ab.
12.	or/10-11
13.	9 and 12
14.	Study filters SR (A.3.1) or RCT (A.3.2)
15.	5 and 13 and 14
16.	Limit 15 to English language
	See **Table 17** for date parameters

Embase search terms

1.	exp ascites/
2.	ascit*.ti,ab.
3.	or/1-2
4.	Excluded study designs and publication types (G.3.9)
5.	3 not 4
6.	transjugular intrahepatic portosystemic shunt/
7.	peritoneum vein shunt/
8.	((transjugular intrahepatic adj2 port?systemic adj2 (stent* or shunt*)) or tips* or port?systemic anastomosis).ti,ab.
9.	or/6-8
10.	paracentesis/
11.	(paracentes* or lvp).ti,ab.
12.	or/10-11
13.	9 and 12
14.	Study filters SR (A.3.1) or RCT (A.3.2)
15.	5 and 13 and 14

16.	Limit 15 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	[mh ^ascites]
#2.	ascit*:ti,ab
#3.	#1 or #2
#4.	[mh ^"portasystemic shunt, transjugular intrahepatic"]
#5.	[mh ^"peritoneovenous shunt"]
#6.	((transjugular intrahepatic near/2 (portosystemic or portasystemic or porto-systemic or porta-systemicemic) near/2 (stent* or shunt*)) or tips* or ((portosystemic or portasystemic or porto-systemic or porta-systemic) next anastomosis)):ti,ab
#7.	#4 or #5 or #6
#8.	[mh ^paracentesis]
#9.	(paracentes* or lvp):ti,ab
#10.	#8 or #9
#11.	#7 and #10
#12.	#3 and #11
	See **Table 17** for date parameters

G.4.10 Volume replacers in hepatorenal syndrome

- Which is the most clinically and cost-effective volume replacer for patients with hepatorenal syndrome due to cirrhosis who are also receiving vasoactive drugs?

Medline search terms

1.	hepatorenal syndrome/
2.	hepatorenal.ti,ab.
3.	((bile or cholemic) adj nephrosis).ti,ab.
4.	((flint or heyd or urohepatic) adj (syndrome* or disease*)).ti,ab.
5.	hepato-renal.ti,ab.
6.	(type adj2 hrs).ti,ab.
7.	or/1-6
8.	Excluded study designs and publication types (G.3.9)
9.	7 not 8
10.	Study filters SR (A.3.1) or RCT (A.3.2)
11.	9 and 10
12.	Limit 11 to English language
	See **Table 17** for date parameters

Embase search terms

1.	*hepatorenal syndrome/
2.	hepatorenal.ti,ab.
3.	((bile or cholemic) adj nephrosis).ti,ab.
4.	((flint or heyd or urohepatic) adj (syndrome* or disease*)).ti,ab.
5.	hepato-renal.ti,ab.
6.	(type adj2 hrs).ti,ab.
7.	or/1-6

8.	Excluded study designs and publication types (G.3.9)
9.	7 not 8
10.	Study filters SR (A.3.1) or RCT (A.3.2)
11.	9 and 10
12.	Limit 11 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	MeSH descriptor: [hepatorenal syndrome] explode all trees
#2.	hepatorenal:ti,ab
#3.	((bile or cholemic) next nephrosis):ti,ab
#4.	((flint or heyd or urohepatic) next (syndrome* or disease*)):ti,ab
#5.	hepato-renal:ti,ab
#6.	(type near/2 hrs):ti,ab
#7.	#1 or #2 or #3 or #4 or #5 or #6
	See **Table 17** for date parameters

G.4.11 Management of an episode of acute hepatic encephalopathy

- What is the most clinically and cost-effective intervention for the first-line treatment of an episode of acute hepatic encephalopathy in people with cirrhosis?

Medline & Embase search terms

1.	hepatic encephalopathy/
2.	((portalsytemic or portal systemic or portosystemic or porto systemic) adj1 encephalopath*).ti,ab.
3.	hepatic encephalopath*.ti,ab.
4.	((hepatic or hepaticum) adj1 coma*).ti,ab.
5.	or/1-4
6.	Excluded study designs and publication types (G.3.9)
7.	5 not 6
8.	Study filters SR (A.3.1) or RCT (A.3.2)
9.	7 and 8
10.	Limit 9 to English language
	See **Table 17** for date parameters

Cochrane search terms

#1.	MeSH descriptor: [hepatic encephalopathy] explode all trees
#2.	((portalsytemic or portal systemic or portosystemic or porto systemic) near/1 encephalopath*):ti,ab
#3.	hepatic encephalopath*:ti,ab
#4.	((hepatic or hepaticum) near/1 coma*):ti,ab
#5.	{or #1-#4}
	See **Table 17** for date parameters

G.5 Health economics search

G.5.1 Health economic reviews

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Medline & Embase search terms

1.	Standard population (G.2)
2.	Excluded study designs and publication types (G.3.9)
3.	1 not 2
4.	Study filter HE (G.3.6)
5.	3 and 4
6.	Limit 5 to English language
	Date parameters: 2013 – 24 August 2015

CRD search terms

#1.	MeSH descriptor liver cirrhosis explode all trees in NHSEED,HTA
#2.	MeSH descriptor fibrosis in NHSEED,HTA
#3.	MeSH descriptor liver in NHSEED,HTA
#4.	#2 and #3
#5.	((((liver* or hepat*) adj5 fibro*) or cirrho*)) in NHSEED, HTA
#6.	#1 or #4 or #5
#7.	MeSH descriptor ascites explode all trees in NHSEED,HTA
#8.	(ascit*) in NHSEED, HTA
#9.	#6 or #7 or #8
	Date parameters: Inception to 24 August 2015

HEED search terms

1.	ax=cirrho*
2.	ax=liver* or hepat*
3.	ax=fibro*
4.	cs=2 and 3
5.	ax=ascit*
6.	cs=1 or 4 or 5
	Date parameters: Inception to 12 June 2014

G.5.2 Quality of life reviews

Quality of life searches were conducted in Medline and Embase only. The populations for cirrhosis and NAFLD were combined for this search.

Medline search terms

1.	fatty liver/
2.	non-alcoholic fatty liver disease/
3.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
4.	(nafl* or nash).ti,ab.
5.	or/1-4
6.	Excluded study designs and publication types (**Error! Reference source not found.**)

7.	5 not 6
8.	Study filter QOL (G.3.7)
9.	7 and 8
10.	Limit 9 to English language & date parameters: 1946 to 27 August 2015
11.	exp liver cirrhosis/
12.	fibrosis/ and liver/
13.	(((liver* or hepat*) adj5 fibro*) or cirrho*).ti,ab.
14.	or/11-13
15.	ascites/
16.	ascit*.ti,ab.
17.	or/15-16
18.	14 or 17
19.	18 not 6
20.	19 and 8
21.	Limit 20 to English language & date parameters: 1946 to 13 June 2014
22.	10 or 21

Embase search terms

1.	nonalcoholic fatty liver/
2.	(((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
3.	(nafl* or nash).ti,ab.
4.	or/1-3
5.	Excluded study designs and publication types (**Error! Reference source not found.**)
6.	4 not 5
7.	Study filter QOL (A.3.7)
8.	6 and 7
9.	Limit 8 to English language & date parameters: 1980 to 27 August 2015
10.	exp liver cirrhosis/
11.	fibrosis/ and liver/
12.	(((liver* or hepat*) adj5 fibro*) or cirrho*).ti,ab.
13.	or/10-12
14.	exp *ascites/
15.	ascit*.ti,ab.
16.	or/15-15
17.	13 or 16
18.	17 not 5
19.	18 and 7
20.	Limit 20 to English language & date parameters: 1946 to 13 June 2014
21.	9 or 20

G.5.3 Economic modelling

Economic modelling searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA

Medline search terms

1.	exp *liver diseases/
2.	(liver* or hepat* or steatohepat* or cirrho*).ti.
3.	or/1-2
4.	Excluded study designs and publication types (G.3.9)
5.	3 not 4
6.	Study filter MOD (G.3.8)
7.	5 and 6
8.	Limit 7 to English language
	Date parameters: 1946 to 27 August 2015

Embase search terms

1.	exp *liver disease/
2.	(liver* or hepat* or steatohepat* or cirrho*).ti.
3.	or/1-2
4.	Excluded study designs and publication types (A.3.8)
5.	3 not 4
6.	Study filter MOD (G.3.8)
7.	5 and 6
8.	Limit 7 to English language
	Date parameters: 1980 to 27 August 2015

CRD search terms

#1.	MeSH descriptor liver diseases explode all trees in NHSEED,HTA
#2.	(liver* or hepat* or steatohepat* or cirrho*):ti in NHSEED, HTA
#3.	#1 or #2
#4.	MeSH descriptor models, economic explode all trees in NHSEED,HTA
#5.	MeSH descriptor models, theoretical in NHSEED,HTA
#6.	MeSH descriptor models, organizational in NHSEED,HTA
#7.	MeSH descriptor markov chains in NHSEED,HTA
#8.	MeSH descriptor monte carlo method in NHSEED,HTA
#9.	MeSH descriptor decision theory explode all trees in NHSEED,HTA
#10.	(markov* or monte carlo) OR (econom* model*) in NHSEED, HTA
#11.	((decision* adj2 (tree* or analy* or model*))) in NHSEED, HTA
#12.	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13.	#3 and #12
	Date parameters: Inception to 27 August 2015

HEED search terms

1.	ti=liver* or hepat* or steatohepat* or cirrho*
2.	ax=model* or markov or monte carlo
3.	cs=1 and 2
	Date parameters: Inception to 27 August 2014

G.6 References

Appendix H: Clinical evidence tables

H.1 Risk factors and risk assessment tools

H.1.1 Risk factors

Reference	ASKGAARD 2015[50]
Study type and analysis	Prospective. Multivariate analyses (Cox proportional hazards model).
Number of participants and characteristics	**Total n=55,917** **Men n=27,178** Lifetime abstainers 63 Current abstainers 350 <1 drinking days/week 2,946 1 drinking days/week 2,401 2–4 drinking days/week 9,165 5–6 drinking days/week 4,495 7 drinking days/week 7,276 **Women n=29,875** Lifetime abstainers 265 Current abstainers 370 <1 drinking days/week 7,682 1 drinking days/week 4,345 2–4 drinking days/week 9,481 5–6 drinking days/week 3,147 7 drinking days/week 3,931

Reference	ASKGAARD 2015[50]
	Data were used from a Danish prospective cohort study originally designed to investigate associations between diet and other lifestyle exposures and cancer in middle-aged individuals. From December 1993 to May 1997, 160,725 Danish women and men aged 50 to 64 years were invited to participate in the Diet, Cancer and Health study. Eligible cohort members were born in Denmark and not previously diagnosed with cancer. In all, 27,178 men and 29,875 women participated in the study (response rate 35%). For the present study of drinking pattern and risk of alcoholic cirrhosis, the authors excluded subjects diagnosed with alcoholic cirrhosis before baseline (n=86). Also excluded were subjects with missing information on alcohol amount (n=105), smoking (n=27), education (n=27), and waist circumference (n=50), and participants who reported conflicting answers on alcohol amount and frequency (n=236) or smoking status and tobacco use (n=7). At baseline, participants were asked to recall the average amount per week of specific types of alcohol they consumed when they were 20–29, 30–39, 40–49, and 50–59 years old and the number of drinking days per week over the years.
Prognostic variable(s)	Alcohol use (categorical: lifetime abstainers, current abstainers, and five categories of drinkers with up to 7 drinking days per week): on the basis of questionnaire items about alcohol use at initial examination
Confounders	• age • sex • length of education • waist circumference • smoking
Outcomes and effect sizes	Participants were observed from baseline until diagnosis of alcoholic cirrhosis (n=342), migration (n=337), loss to follow-up (n=2), death from other causes (n=8,132), or 31st December 2011 (end of follow-up), whichever came first. Information on liver cirrhosis was obtained from the National Patient Register and the Danish Register of Causes of Death. The former was established in 1977 and contains data on all somatic hospital admissions and, since 1995, data on outpatient contacts as well. The Danish register of Deaths contains information on all causes of death in Denmark. In both registries, diagnoses are recorded according to the 8th and 10th international classification of diseases (codes for alcoholic cirrhosis, ICD-8: 571.0 and ICD-10: K70.3, and codes for unspecified cirrhosis, ICD-8: 571.9, 456.0, 785.3 and ICD-10: 185.0, 185.9, K74.6, R18.9), and the validity is considered to be high. The data on vital status and migration were obtained from the Danish Civil Registration system. For the hazard ratios of developing alcoholic cirrhosis, the reference group for alcohol use was 2–4 drinking days per week. Multivariate analysis used the Cox proportional hazards model (CI) adjusted for the above mentioned confounders. **Men who received diagnosis of alcoholic cirrhosis n=257**

Reference	ASKGAARD 2015[50]
	Drinking alcohol at baseline: Lifetime abstainers n=0 N/A Current abstainers n=7 HR 10.0 (4.32; 23.0) <1 drinking days/week n=14 HR 1.34 (0.67; 2.67) 1 drinking days/week n=8 HR 1.30 (0.59; 2.87) 2–4 drinking days/week n=27 HR 1.00 = REFERENCE GROUP 5–6 drinking days/week n=30 HR 1.43 (0.84; 2.43) 7 drinking days/week n=171 HR 3.65 (2.39; 5.55) **Women who received diagnosis of alcoholic cirrhosis n=85** Drinking alcohol at baseline: Lifetime abstainers n=0 N/A Current abstainers n=2 HR 4.03 (0.91; 17.8) <1 drinking days/week n=16 HR 1.45 (0.71; 2.96) 1 drinking days/week n=5 HR 0.81 (0.29; 2.24) 2–4 drinking days/week n=15 HR 1.00 = REFERENCE GROUP 5–6 drinking days/week n=17 HR 2.30 (1.14; 4.67) 7 drinking days/week n=30 HR 1.73 (0.85; 3.52)

Reference	BECKER 2002[73]
Study type and analysis	Prospective cohort. Multiplicative Poisson regression models, assuming constant intensity within each 10 year interval.
Number of participants and characteristics	Subjects from several cohort studies: Copenhagen County Centre of Preventative Medicine: 1897 (n=234), 1914 (n=924) and 1936 (n=1,105) birth cohorts. World Health Organisation Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) I (n=3,769) MONICA II (n=1,396) and MONICA III (n=1,985), the Copenhagen City Heart Study (n=17,960) and the Copenhagen Male Study (n=3,257). Total number of

Reference	BECKER 2002[73]
	participants = 30,630. Mean age at first examination was 52 years (range 21–93). Male/female: 16,295/14,335 Events at follow up (death or discharge with alcoholic induced cirrhosis) Total alcohol intake (drinks/week) <1 n=6,119 26 1–7 n=11,460 35 8–21 n=8,918 75 22–35 n=2,481 58 >35 n=1,652 98 Individuals abstaining because of drug treatment for an alcohol related problem (n=7) were excluded.
Prognostic variable(s)	1. Alcohol intake: Copenhagen City Heart Study and Copenhagen County Centre of Preventative Medicine asked about their average number of weekly drinks of wine, beer and spirits. Copenhagen Male study asked about their average number of weekly drinks of wine, beer and spirits on week days and weekend days (these were added for consistency with above 2 studies). A Danish standard drink contains 12 g of alcohol. 2. BMI
Confounders	1. Prognostic variable: alcohol intake • age • smoking habits (never, ex-smokers, current 1–14 g/day, current 15–24 g/day and current >24 g/day), • number of years of school education (less than 8 years, 8–11 years, 12 or more years). • BMI (20 or less, 20–25, 25–30, more than 30). • percentage wine of total alcohol intake. 2. prognostic variable: BMI variables included in the analysis not reported but methods report than significant variables were included in the model. The number of current smokers was higher among those who later developed alcohol-induced liver cirrhosis. No differences in school education were observed. BMI>32 was more prevalent among those who developed cirrhosis than in the total sample.
Outcomes and effect sizes	End points in analysis were death or discharge with alcohol-induced cirrhosis (ICD-8 code 571.09). 292 individuals (80 women and 212 men) developed alcohol-induced cirrhosis, corresponding to an incidence rate of 0.07% per year. 26 individuals who developed alcohol-induced cirrhosis were non-drinkers. Data were analyzed by means of multiplicative Poisson regression models, assuming constant intensity within each 10-year age interval. Results given as rate ratios or relative risks. A dose-dependent increase in relative risk for developing alcohol-induced cirrhosis with increasing alcohol intake was observed among women, and a J-shaped relationship among men.

Reference	BECKER 2002[73]
	Alcohol results for men: Total alcohol intake (drinks/week) <1 RR=7.76 (3.35–18.0) 1–7 RR=1 (reference) 8–21 RR=2.34 (1.18–4.62) 22–35 RR=10.4 (5.4–19.9) >35 RR=20.4 (10.8–38.8) Alcohol results for women: Total alcohol intake (drinks/week) <1 RR=1.32 (0.51–3.38) 1–7 RR=1.19 (0.54–2.59) 8–21 RR=5.33 (2.63–10.8) 22–35 RR=10.8 (4.28–27.1) >35 RR=14.1 (4.45–44.6) BMI results: <20 RR=2.2 (1.3–3.9) 20–24 RR=1 (reference) >30 RR=2.2 (1.5-3.4)

Reference	BLACKWELDER 1980[92]
Study type and analysis	Prospective retrospective cohort
Number of participants and characteristics	n=8,008 (analysed as continuous therefore numbers in each risk factor category not reported) Honolulu Heart Study is a prospective study of coronary heart disease and stroke among men of Japanese descent in Hawaii, born between 1900 and 1919 and residing on the island of Oahu in 1965. Subsequent deaths among men in the cohort were identified through surveillance of death certificates and obituary columns. Based on the Eighth Revision of the International Classification of Diseases, an underlying cause, independent of the one appearing on the death certificate, was assigned to most deaths at a conference of heart study physicians: all available evidence, including heart study examination findings and autopsy information, was considered in assigning this cause.

Reference	BLACKWELDER 1980[92]
	Follow-up 8 years
Prognostic variable(s)	Alcohol consumption: usual intake was estimated from answers to questions on usual consumption of beer, wine, and liquor (ml per day of ethanol). A second source of information collected was a 24-hour dietary recall interview.
Confounders	• age • cigarettes smoked per day • systolic blood pressure • serum cholesterol • relative weight
Outcomes and effect sizes	Event: death due to cirrhosis 16 deaths due to cirrhosis. Level of usual alcohol intake (ml/day) 0 6 events 1–10 1 event 11–30 2 events 31+ 7 events Standardised coefficient from multivariate analysis of the association of alcohol intake with death from cirrhosis of the liver: 0.341 (t=3.11, estimated coefficient divided by its standard-error, p<0.01)

Reference	FUCHS 1995[308]
Study type and analysis	Prospective cohort. Proportional-hazards model to adjust for multiple risk factors simultaneously.
Number of participants and characteristics	n=85,709 Average alcohol intake (g/day) Events at follow-up (death due to cirrhosis of the liver) 0 n=25,535 12 0.1–1.4 n=11,304 1 1.5–4.9 n=18,406 5

Reference	FUCHS 1995[308]
	5.0–14.9 n=17,783 10 15.0–29.9 n=8106 9 ≥30 n=4521 15 The Nurses' Health Study. 85,709 women, 34 to 59 years of age and without a history of myocardial infarction, angina, stroke, or cancer, who completed a dietary questionnaire in 1980. Because the group of women who now abstain from alcohol may include former heavy drinkers and women who stopped drinking because of illness, we excluded from our primary analysis 2957 women who reported no alcohol intake in 1980 but had greatly decreased their alcohol intake in the previous 10 years. 12 year follow-up period
Prognostic variable(s)	Alcohol consumption: asked to report their average frequency of consumption of specified foods and beverages during the previous 12 months, on three occasions. Questions about the consumption of beer, wine, and spirits were included as separate items. Total alcohol intake was the sum of the values for all three beverages; a 12 oz (360 ml) can or bottle of beer was assumed to contain 13.2 g of alcohol, a 4 oz (120 ml) glass of wine 10.8 g, and a standard drink of spirits 15.1 g.
Confounders	• age (in five-year categories) • smoking status (participants were grouped into those who never smoked, those who had formerly smoked, and those who smoked less than 15, 15 to 24, and more than 24 cigarettes per day) • body-mass index (in quintiles) • regular aspirin use (≥2 days per week) • regular vigorous exercise (≥1 day per week) • high plasma cholesterol level (yes or no) • diabetes (yes or no) • hypertension (yes or no) • myocardial infarction in a parent at 60 years of age (yes or no) • past or present oral-contraceptive use (yes or no) • menopausal status • past or present postmenopausal hormone use (yes or no) • energy-adjusted intake of dietary fibre and saturated fat (in quintiles).

Reference	FUCHS 1995[308]
	For each woman, person-years of follow-up were counted from the date of return of the 1980 questionnaire to 31 May 1992 or, for those who died, until the date of death. Because the focus was on mortality, and because people tend to reduce alcohol consumption markedly or to discontinue consumption after a major illness is diagnosed, levels of alcohol intake reported after 1980 were not taken into consideration in the primary analysis. For all other covariates, person-years of follow-up were assigned according to the risk-factor status reported on the most recently completed questionnaire.
Outcomes and effect sizes	Endpoint: death due to cirrhosis of the liver (made systematic searches of the vital records of the states and the National Death Index to discover deaths among women who did not respond during each questionnaire cycle. A physician, blinded to data on alcohol consumption and other risk factors, reviewed death certificates and medical records to classify the cause of death according to the International Classification of Diseases, Eighth Revision ICD-8). Total 52 deaths from cirrhosis of the liver. Average alcohol intake (g/day): relative risk from multivariate analysis. Primary analysis used incidence rates with person-years of follow-up as the denominators. Calculated relative risk as the incidence of death among women with a given alcohol intake divided by the corresponding rate among women who did not consume alcohol. Used proportional hazards model to adjust for multiple risk factors simultaneously. 0 1.0 0.1–1.4 0.21 (0.027–1.59) 1.5–4.9 0.69 (0.24–1.98) 5.0–14.9 1.27 (0.54–3.01) 15.0–29.9 1.86 (0.76–4.59) ≥30 2.55 (1.06–6.11)

Reference	IOANNOU 2003[426]
Study type and analysis	Prospective cohort.
Number of participants and characteristics	Baseline data were collected from 1971–1974 as part of the first National Health and Nutrition Examination Survey (NHANES I) and included interviews, physical examinations, and laboratory investigations on 14,407 participants aged 25–74 years in the United States. The NHANES I participants were subsequently followed up in 1982–1984, 1986, 1987, and finally in 1992 as part of the NHANES Epidemiologic Follow-up Study (NHEFS).

Reference	IOANNOU 2003[426]
	Excluded participants who might have already had chronic liver disease or cirrhosis at the time of entry into the study (1227 participants who reported a history of jaundice; were found to have hepatomegaly or splenomegaly on physical examination; or had a serum albumin level less than 3 g/dl) Excluded 565 participants who either died or had a diagnosis of liver cirrhosis in their hospitalization records within the first 5 years after entry into the study (to reduce the possible effects of subclinical liver disease on BMI and fat distribution. Excluded 604 participants with missing information for any one of the variables (BMI, age, alcohol consumption, sex, race, educational attainment, household income, and geographic location in the United States). Final analysis n=11,465. Male/female: 4439/7026. Mean follow-up time of 12.9 years Normal weight: n=5752; overweight: n=3774; obese: n=1939
Prognostic variable(s)	BMI: calculated at entry into the study. BMI categorized participants into normal-weight (BMI <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), and obese categories (BMI ≥30 kg/m^2)
Confounders	• Age (modelled as a continuous variable) • alcohol consumption over the previous 12 months (modelled as a dummy variable with categories: none [which included consuming alcohol <2–3 times per year], >0 to 1 drink/day, >1 to 2 drinks/day, and >2 drinks/day, • sex • race (Caucasian, non-Caucasian) • education (high school graduate or not) • household income (modelled as a continuous-categoric variable in $1000 intervals) • geographic location in the United States (modelled as a dummy variable with categories: Northeast, Midwest, South, and West). Models with and without adjusting for serum cholesterol level or the presence of self-reported diabetes mellitus were used to investigate whether obesity is associated with cirrhosis over and above any effect that is mediated through diabetes mellitus and hypercholesterolemia, which are risk factors for non-alcoholic steatohepatitis.
Outcomes and effect sizes	Death or hospitalisation caused by cirrhosis Specially trained NHANES I Epidemiologic Follow-up Study personnel used all available hospital records to assign the principal diagnosis as “the condition established after study to be chiefly responsible for occasioning the admission of the patient to the health care facility.” Causes of

Reference	IOANNOU 2003[426]

death were abstracted from the death certificates. Death or hospitalization caused by cirrhosis was defined by one of the following International Classification of Diseases, Ninth Revision diagnoses, recorded either on the death certificate or as the principal diagnosis of hospitalization: 571.2 (alcohol induced cirrhosis), 571.5 (cirrhosis without mention of alcohol), 571.6 (biliary cirrhosis), 456.0 (oesophageal varices with bleeding), 456.1 (oesophageal varices, no mention of bleeding), 572.2 (hepatic coma), 572.3 (portal hypertension), 572.4 (hepatorenal syndrome), and 155.0 (primary liver cancer).

The Cox proportional-hazards model was used to determine the hazard ratio comparing obese or overweight persons with normal-weight persons with respect to the risk for cirrhosis-related death or hospitalization, after adjusting for confounders. The date 5 years after the measurement of the BMI was used as time 0 in the model because the analysis was restricted to participants who remained alive and without a diagnosis of cirrhosis for at least 5 years after entry into the study.

Adjusting for diabetes:

Obese versus normal weight: adjusted hazard ratio 1.65 (95% CI 0.9–3.1)

Overweight versus normal weight: adjusted hazard ratio 1.08 (95% CI 0.6–1.9)

Not adjusting for diabetes:

Obese versus normal weight: adjusted hazard ratio 1.69 (95% CI 1.0–3.0)

Overweight versus normal weight: adjusted hazard ratio 1.16 (95% CI 0.7–1.9)

The associations between BMI category and cirrhosis related death or hospitalization were not appreciably different between men and women, between Caucasians and non-Caucasians, or between persons with serum iron saturation above or below 45% (data not shown).

	Reported alcohol consumption		
BMI category (adjusted HRs)	**None**	**Up to 0.3 drinks/day**	**>0.3 drinks/day**
Overweight (versus normal)	1.93 (0.7–5.3)	1.31 (0.4–4.2)	0.97 (0.5–1.8)
Obese (versus normal)	4.10 (1.4–11.4)	2.48 (0.7–8.4)	0.80 (0.3–2.1)

Adjusting for serum cholesterol level had almost no effect on the association between BMI category and death or hospitalization owing to cirrhosis. There was little difference in the rates of death or hospitalization caused by cirrhosis by geographic region, diabetes mellitus status, or serum cholesterol level.

Reference	KLATSKY 1992[479]
Study type and analysis	Prospective. Multivariate analyses (Cox proportional hazards model).
Number of participants and characteristics	n=128,934 Never 15,498 Past drinker 4,194 <1 drink/month 27,417 >1/month, <1/day 47,895 1–2/day 23,408 3–5/day 8,518 26/day 2,004 128,934 persons who underwent health examinations at the Oakland and San Francisco facilities of the Kaiser Permanente Medical Care Program, a prepaid health plan, from January 1978 to December 1985. The study population comprised 79.8% of all persons who underwent the health examination during the years of data collection. The remaining 20.2% included persons who were examined during absences of the research clerk, persons who declined, and those who failed to supply required inclusion data.
Prognostic variable(s)	Alcohol use (categorical: never-drinkers, ex-drinkers, and five categories of drinkers up to six drinks per day or more): on the basis of questionnaire items about alcohol use at initial examination
Confounders	• age • sex • race • education • BMI • marital status • upper gastrointestinal history • smoking • coffee and tea consumption
Outcomes and effect sizes	Hospitalisation or death due to cirrhosis. Hospitalisations at Northern California Kaiser Permanente facilities were ascertained through December 1988 or until subjects left the health plan. Hospitalisation for cirrhosis was detected by computer search for a primary discharge diagnosis of International Classification of Diseases, Adapted, Eighth Revision (ICDA-8), code 571. Primary death certificate diagnoses of cirrhosis were classified by ICD-9 codes as alcoholic (ICD-9 codes 571.0-571.3) or as non-alcoholic (ICD-9 codes 571.4-571.9).

Reference	KLATSKY 1992[479]
	For non-alcoholic cirrhosis, the reference group for alcohol use was lifelong non-drinkers. For alcoholic cirrhosis, there were too few non-drinkers to use this category as the reference, so the reference group for alcohol use also included persons who reported current consumption of less than one drink per day. Multivariate analysis used the Cox proportional hazards model. Outcome was described as 'relative risk'. Hospitalisation for alcoholic cirrhosis n=59 Drinks/day Reference RR 1.0 Ex-drinkers RR 5.4 1–2 RR 7.7 3–5 RR 18.2 ≥6 RR 33.1 Hospitalisation for non-alcoholic cirrhosis n=30 Drinks/day Reference RR 1.0 Ex-drinkers RR 1.2 1–2 RR 0.8 3–5 RR (analysis not performed because of the small number of cases) ≥6 RR 0.8 Death from alcoholic cirrhosis n=40 Drinks/day Reference RR 1.0 Ex-drinkers RR 17.1 1–2 RR 7.8 3–5 RR 21.6 ≥6 RR 83.4 Death from non-alcoholic cirrhosis n=32

Reference	KLATSKY 1992[479]
	Drinks/day Reference RR 1.0 Ex-drinkers RR 16.3 1–2 RR 7.0 3–5 RR 6.4 ≥6 RR 23.6

Reference	LIU 2010A[526]
Study type and analysis	Prospective cohort (Million Women study). Cox regression models.
Number of participants and characteristics	Total n=1,230,662 Events = 1811 (first cirrhosis-related hospital admission or death) BMI <22.5 n=237,619 414 22.5 to <25 n=331,480 402 25 to <27.5 n=266,795 343 27.5 to <30 n=173,498 236 30 to <35 n=156,733 283 ≥35 n=64,537 133 Participants were excluded if they reported having had any type of liver disease or had a diagnosis of cancer (except non-melanomatous skin cancer) before recruitment or if their BMI was unknown. Mean age at recruitment was 56 years. Mean BMI was 27.6. 77% reported drinking alcohol and among these the mean reported alcohol consumption was 54 g/week. Women were recruited through NHS breast screening centres in England and Scotland 1996–2001.
Prognostic variable(s)	BMI
Confounders	Data adjusted for: • age • region of recruitment (10 regions) • socioeconomic status (in fifths according to the deprivation index, a score based on residential address that takes into account employment,

Reference	LIU 2010A[526]
	household overcrowding, home and care ownership) • alcohol consumption (none [never or past], consumption of <30, 30 to <70, 70 to <150, and >150 g/week) • smoking (never, past, current 1–9 cigarettes per day, current 10–19 cigarettes per day, and ≥20 cigarettes per day) • strenuous physical activity (once a week or less, more than once a week). The proportion of women in the upper socioeconomic group decreased with increasing BMI. The proportion of women reporting drinking any alcohol and the amount they drank decreased with increasing BMI. The proportion of women who were current smokers and the proportion who reported doing strenuous physical activity more than once per week also decreased with increasing BMI. The proportion who reported being treated for diabetes also increased with increasing BMI.
Outcomes and effect sizes	Outcome: hospital admission with cirrhosis or death from cirrhosis (women were classified as having a hospital admission with liver cirrhosis or death from liver cirrhosis if during follow up they had a hospital record or death registration with an ICD10 code of K70, K73 or K74). Average length of follow up 6.2 years. Used Cox regression models to analyse data. And outcome described as 'relative risk' BMI category <22.5 RR=1.36 (1.23–1.5) 22.5 to <25 RR=1.00 (0.91–1.10) 25 to <27.5 RR=1.05 (0.94–1.17) 27.5 to <30 RR=1.11 (0.97–1.26) 30 to <35 RR=1.49(1.33–1.68) ≥35 RR=1.77(1.49–2.10) Among the women with a BMI of 22.5 and above (women with a BMI below 22.5 excluded from this analysis as could not exclude the possibility that previous illness contributed to weight loss): Per 5 unit increase in BMI 1.28 (1.119–1.38) (that is, the estimated increase in the risk of cirrhosis was 28% (95% CI 195 to 38%) for every 5 unit increase in BMI).

	Reported alcohol consumption				
BMI category	**<70g/week**	**70 to <150 g/week**	**≥150 g/week**	**No diabetes**	**Diabetes**
22.5 to <25	1.00 (0.85–1.17)(reference)	1.59 (1.31–1.92)	3.44 (2.7–4.37)	1.00 (0.9–1.11)(reference)	4.29 (2.74–6.73)
25 to <30	0.96 (0.84–1.1)	1.83 (1.56–2.16)	3.82 (3.09–4.72)	1.05 (0.96–1.15)	4.37 (3.3–5.78)
≥30	1.35 (1.15–1.59)	2.31 (1.81–2.94)	6.53 (4.98–8.55)	1.38 (1.24–1.54)	5.94 (4.83–7.31)

Reference	LIU 2010A[526]
	Above data are relative risks (95% floated confidence interval) adjusted for age, region, socioeconomic status, physical activity and alcohol and smoking as appropriate.

Reference	SCHULT 2011[785]
Study type and analysis	Prospective cohort. Logistic regression.
Number of participants and characteristics	792 subjects from a longitudinal cohort study conducted in Gothenburg, during a 40 year study period. In 1963 all men born in 1913 on those days which were even multiples of 3 and still alive at the age of 50 were invited to participate in a longitudinal population study. None of the participants had cirrhosis at inclusion. Cirrhosis was classified as patients with a diagnosis of 571,00-99, 571A-X and K70.2-3, K71.7, K74.0-6 on The Swedish Hospital Discharge Register based on compulsory reports on diagnoses for all hospitalised patients in Sweden (using the Swedish version of the International Classification of Diseases).
Prognostic variable(s)	1. Alcohol abuse I (individuals who have sought help for alcohol addiction, been arrested for drunkenness or had been provided with institutional care by social authorities) 2. Alcohol abuse II (self-reported as having alcohol problems and/or daily alcohol consumption). 3. BMI
Confounders	BMI, triglycerides, 2 definitions of alcohol abuse
Outcomes and effect sizes	Endpoint: patients who were hospitalised and/or died with a diagnosis of liver cirrhosis. 14 patients developed cirrhosis (established histopathologically in 11 and 3 had typical radiological findings with clinical complications). 'Model 1' results (Alcohol abuse 1 definition): BMI OR 1.27 (1.09–1.48) Alcohol abuse 0.71 (0.17–2.92) 'Model 2' results (alcohol abuse 2 definition) BMI OR 1.26 (1.08–1.47)

Reference	SCHULT 2011[785]
	Alcohol abuse OR 1.55 (0.36–6.78)

H.1.2 Risk tools

No relevant clinical studies were identified.

H.2 Diagnostic tests

Study	Arena 2008[47]
Study type	Prospective cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=161 consecutive patients, 11 excluded due to liver biopsy length, final analysis n=150). Recruitment between 1 September 2006 and 1 July 2007
Countries and Settings	Italy. University Hospital.
Funding	Academic or government (grants from the Italian Ministry of Education, Universities and Research, the University of Florence and the Italian Liver Foundation and Instituto de Salud Carlos III, Spain).
Age, gender, ethnicity	Age, mean (SD): 50.6 (12.5), range 21-70 years; Male/female: 92/58; Ethnicity: not reported; ALT (U/l): not reported
Patient characteristics	Population: HCV-related chronic liver disease referred for the histopathological assessment of disease progression. Inclusion: levels of ALT >1.5-fold the upper normal limit either persistently or intermittently, and detectable HCV RNA. Exclusion: BMI ≥30; presence of ascites at clinical or ultrasound examination; presence of HCC or previous/current decompensation of the disease; co-infection with HIV or HBV; use of IV drugs, previous or current alcohol abuse or the use of hepatotoxic drugs, genetic liver disease, autoimmune hepatitis, vascular diseases of the liver, biliary tract disorders, ongoing or recent (within 1 year) therapy with antiviral agents, cardiac failure, age <18 or >70 years and pregnancy,
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan, Echosens, France), optimal cut-off threshold calculated (14.8kPa): operator was a staff physician (AU) who had previously performed determinations in patients with CLD. Considered representative measurements of the median value of 10 successful acquisitions with a success rate of at least 60%, and with an IQR over a median ratio lower than 30%.
Reference standard	Liver biopsy (METAVIR F4): performed on the right lobe of the liver with a 16 G semiautomatic modified Menghini needle system (BIOMOL; Hospital Service, Aprilia, Italy) under local anaesthesia and ultrasound guidance. Only samples with a length >25 mm and including at least 11 complete portal tracts were considered adequate (average 33(0.7)mm and 15(3) portal

Study	Arena 2008[47]
	tracts). Sections of liver tissue, 5 mm thick, were stained with haematoxylin & eosin and Masson trichrome, and were examined by an experienced pathologist.
Time between index test and reference standard	Same day
Target condition	Cirrhosis
Prevalence of cirrhosis according to reference standard	29/150 (19.33%)

Results: Fibroscan

AUC (90% CI): 0.98 (0.95-0.99)

Optimal cut-off threshold (if calculated): 14.8kPa

Threshold: 14.8kPa (optimal)

Sensitivity: 94

Specificity: 92

Positive predictive value (PPV): 73

Negative predictive value (NPV): 98

+ve/-ve likelihood ratios: 11.27/0.07

True positives (TP): Not reported

False positives (FP): Not reported

False negatives (FN): Not reported

True negatives (TN): Not reported

Other measures reported and conclusions: Also reported multilevel LRs and concluded that threshold of <12kPa and >18kPa were adequate to rule-out or rule-in cirrhosis respectively (LRs above 10 and below 0.1 and considered strong evidence to rule in and rule out respectively). Values between 12 and 18kPa could not reliably predict the presence or absence of cirrhosis at multilevel LRs analysis.

<12kPa: LR 0 (0-0.139); ≥12 and <15: LR 1.34 (0.472-3.831); ≥15 and <18: LR 2.318 (0.986-5.449); ≥18 LR 87.621 (16.760-458.074).

Any complications associated with tests reported: No major complications were associated with percutaneous liver biopsy. Fifteen patients (10%) experienced a self-limiting abdominal and/or right shoulder pain, and 6 patients (4%) required a single dose of intravenous analgesic drug (tramadol). There were no complications associated with TE.

Study	Arena 2008[47]
General limitations according to QUADAS II: Unclear if reference standard interpreted without knowledge of the index test result.	

Study	Aykut 2014[57]
Study type	Prospective cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=88 NAFLD patients). Recruitment period not reported
Countries and Settings	Department of Gastroenterology, University School of Medicine, Turkey
Funding	Academic or Government funding (Marmara University Scientific Research Fund).
Age, gender, ethnicity	Age, mean (SD): 46 (9); Male/female: 50/38; Ethnicity: not reported; ALT (U/l): 84 (56); BMI: 30.3 (4.6)
Patient characteristics	Population: NAFLD Inclusion: persistent (>6 months) elevation of transaminases and steatosis on ultrasound. Or subjects with normal transaminases in presence of hepatomegaly and/or splenomegaly and subjects with normal transaminases but persistently increased gamma-glutamyl transferase. Absent to low alcohol consumption (<30g/day men and <20g/day women) Exclusion: viral hepatitis B or C, Wilson's disease, alpha1-antitrypsin deficiency, autoimmune hepatitis, genetic haemochromatosis and use of steatogenic drugs. Other conditions known to cause liver dysfunction.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan, Echosens, France), optimal cut-off threshold not reported. A single operator performed all examinations according to the manufacturers protocol. With the patient lying in the dorsal secubitus position, the tip of the transducer was placed on the skin between the ribs over the right lobe of the liver. Assessment performed using the M or XL probe as appropriate. Measurement depth between 25 and 65 mm for the M probe and 35 and 75mm for the XL probe. Subjects with failures or unreliable measurements were excluded. Failure defined as zero valid shots and unreliable examinations were defined as fewer than 10 valid shots, a success rate <60% or an IQR >30%.
Reference standard	Liver biopsy (NAFLD activity score F4 (reference McPherson 2010 paper which used Kleiner score): all liver biopsies were at least 20mm long and/or contained more than 11 complete portal tracts.
Time between index test and reference standard	Not reported
Target condition	Cirrhosis

Study	Aykut 2014[57]
Prevalence of cirrhosis according to reference standard	9/88 (10.2%)
Results: Fibroscan AUC (95% CI): 0.907 (SE 0.034) Optimal cut-off threshold (if calculated): Not reported Threshold: sensitivity and specificity values only given from ROC curve and threshold not reported Sensitivity: 100 (threshold not reported) Specificity: 76.3 (threshold not reported) PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: the accuracy of the Fibrometer NAFLD score and the NAFLD fibrosis score developed by Angulo. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II: Consecutive or random recruitment not reported Unclear if results of reference standard were interpreted without knowledge of the index test results or clinical data. Subjects with unreliable transient elastography measurements not included in the analysis. Liver biopsies could be <25mm	

Study	BORRONI 2006[98]

Study	BORRONI 2006[98]
Study type	Retrospective analysis of chart and liver biopsy
Number of studies (number of participants). Recruitment period.	1 study (N=232 consecutive patients, 4 excluded due to liver biopsy <6 portal fields, final analysis n=228). Recruitment between 1999 and 2002
Countries and Settings	Italy. General Hospital
Funding	No external funding
Age, gender, ethnicity	Age, mean (SEM): 42.4(0.9); Male/female: 166/62; Ethnicity: not reported; ALT (U/l): 117(7); duration of infection, mean (SEM): 5.6(0.4); genotype 1: 53.4%
Patient characteristics	Population: chronic hepatitis C infection but no clinical evidence of cirrhosis Inclusion: The diagnosis of chronic HCV infection was based on persistently high serum aminotransferase levels for at least 6 months and a positive polymerase chain reaction assay of HCV-RNA. Active IVDU were included in the study only after a period of at least 6 months of abstinence. Exclusion: (i) a previous biopsy-based diagnosis of cirrhosis; (ii) the presence of clinical (ascites, gastroesophageal varices, hepatic encephalopathy, prominent abdominal venous collaterals, spider angiomata) or ultrasonographic signs of cirrhosis (splenomegaly, liver surface nodularity); (iii) concomitant causes of liver disease diagnosed by means of standard clinical, serological and biochemical criteria; (iv) HIV-Ab positivity; (v) alcohol intake of >20 g/day during the previous 6 months; (vi) previous anti-viral treatment; (vii) any other conditions that may affect AST or platelet count.
Index test (including threshold and whether threshold pre-specified)	APRI: AST to Platelet Ratio Index (APRI) = AST (UNL) / Platelet count(109=L) x 100 (optimal cut-off ≥2, not pre-specified, so sensitivity and specificity maximal) AST/ALT ratio: AST (U/L) / ALT(U/L) (optimal cut-off ≥1, not pre-specified, so sensitivity and specificity maximal)
Reference standard	Liver biopsy (Knodall F4): The biopsies were performed under ultrasound guidance using 16-gauge needles and the lateral transcostal approach. Only samples with a length >20mm analysed (average not reported) and 4 patients excluded as biopsy <6 portal fields. The histological sections were assessed by a single experienced pathologist (M. R.) blinded to the patients' clinical and laboratory characteristics; several sections of each specimen were evaluated in order to minimize variability.
Time between index test and reference standard	Undergone serum markers during the 3 months preceding liver biopsy.
Prevalence of cirrhosis according to reference standard	30/228 (13.2%)
Target condition	Cirrhosis
Results: APRI	

Study	BORRONI 2006[98]
AUC (95% CI): 0.86 (0.79–0.93) Optimal cut-off threshold (if calculated): ≥2 Threshold: ≥2 (optimal) Sensitivity: 43.0 Specificity: 94.0 PPV: 54.0 NPV: 92.0 +ve/-ve likelihood ratios: 7.2 / 0.6 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: AST/ALT ratio AUC (95% CI): 0.76 (0.68–0.84) Optimal cut-off threshold (if calculated): ≥1 Threshold: ≥1 (optimal) Sensitivity: 30.0 Specificity: 97.0 PPV: 57.0 NPV: 90.0 +ve/-ve likelihood ratios: 10 / 0.7 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Any complications associated with tests reported: not reported	
General limitations according to QUADAS II	

Study	BORRONI 2006[98]
Up to 3 months between index test and reference standard Retrospective chart analysis Liver biopsy sample <25mm and 10 portal tracts.	

Study	BOTA 2011A[104]
Study type	Retrospective cohort
Number of studies (number of participants). Recruitment period.	1 study (N=212 patients). Recruitment between January 2008 to March 2010
Countries and Settings	Romania. University Hospital
Funding	None declared
Age, gender, ethnicity	Age, mean (SD): not reported; Male/female: not reported; Ethnicity: not reported; ALT (U/l): not reported
Patient characteristics	Population: Chronic hepatitis C infection Inclusion: Anti-HCV positive for at least 6 months and had detectable levels of HCV-RNA by RT-PCR Exclusion: Not reported
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan, Echosens, France), (cut-off 13.3kPa, not-prespecified, from previous studies): 10 valid TE measurements, included only LS measurements with a success rate (the ratio of the number of successful acquisitions over the total number of acquisitions) of at least 60% and an interquartile range (IQR) lower than 30%. APRI: APRI score = [(AST/upper limit NV AST) ×100]/number of platelets (10^9/l). (cut-off ≥1, not-prespecified, from previous studies) FIB4: FIB-4 score = [age (years)] × AST (U/L)]/[number of platelets (10^9/L)] × ALT (U/L)½].
Reference standard	Liver biopsy (METAVIR F4): Echo-assisted LB was performed in all patients by using modified Menghini needles (1.4 and 1.6 mm in diameter). Only LB fragments including at least 8 portal tracts were included (average 3.35(0.9)cm). The LBs were

Study	BOTA 2011A[104]
	assessed by a senior pathologist blinded to the results of the LS measurements
Time between index test and reference standard	Single hospital visit
Prevalence of cirrhosis according to reference standard	30/212 (14.2%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.977 (CI not reported) Optimal cut-off threshold (if calculated): Not reported Threshold: 13.3kPa (not pre-specified, from previous studies) Sensitivity: 93.3 Specificity: 97.2 PPV: 84.8 NPV: 98.8 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.879 (CI not reported) Optimal cut-off threshold (if calculated): Not reported Threshold: ≥1 (not pre-specified, from previous studies) Sensitivity: 80.0 Specificity: 74.1 PPV: 33.8 NPV: 95.7 +ve/-ve likelihood ratios: Not reported	

Study	BOTA 2011A[104]
TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: FIB4 Not reported Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random selection not reported. Exclusions not reported. Liver biopsy sample < 10 portal tracts.	

Study	BOTA 2015[105]
Study type	Retrospective cohort
Number of studies (number of participants). Recruitment period.	1 study (N=132 patients, 117 included in final analysis due to unreliable ARFI measurements). Recruitment between October 2009 to April 2013
Countries and Settings	University Hospital, Romania
Funding	University Young Researchers Grant
Age, gender, ethnicity	Age, mean (range): 53 (21-65); Male/female: 45/87; Ethnicity: not reported; ALT (U/l): 1.5 (0.5-8)
Patient characteristics	Population: Chronic hepatitis C infection Inclusion: diagnosis of chronic infection with hepatitis C virus with positive serum anti-HCV antibodies for at least 6 months and detectable hepatitis C virus RNA in serum, by real-time polymerase chain reaction (PCR ARN-HCV). Exclusion: co-infection with hepatitis B or HIV; liver focal liver lesions or ascites on abdominal ultrasound examination

Study	BOTA 2015[105]
Index test (including threshold and whether threshold pre-specified)	ARFI (pre-published cut-off 1.87m/s): performed in all patients, in fasting condition, with a Siemens Acuson S2000TM ultrasound system using Virtual Touch Tissue Quantification application (Siemens AG, Erlangen, Germany) with a 4CI transducer. Scanning was performed between the ribs with the patient in supine position, in the right liver lobe (segment V/VIII). 10 valid LS measurements performed in the same place in the right liver lobe and a median value was calculated, the result being measured in m/s. If the measurement was not valid, "x.xx" was displayed on the screen. Reliable LS measurements were defined as median value of 10 valid measurements with an interquartile range interval (IQR) < 30% and a success rate ≥ 60%. Transient elastography (pre-published cut-off 15.3kPa): Transient Elastography was performed using a Fibro-Scan® device (EchoSens, Paris, France) (standard Mprobe) and was available in 123/132 patients (93.1%). In each patient aimed for 10 valid TE measurements using the standard M-probe. The LS measurements were performed under fasting conditions, in supine position, by intercostal approach, with the right arm in maximum abduction; then a median value was calculated and the results were expressed in kiloPascals (kPa). Reliable measurements were defined as: median value of 10 valid LS measurements with IQR <30% and SR ≥ 60%.
Reference standard	Liver biopsy (METAVIR F4): all liver specimens were at least 2 cm long. The biopsy fragment's length was evaluated by the physician who performed the procedure. Assessed by a senior pathologist, blinded to the results of ARFI measurements. Length of LB specimen 3.5 (2-6) cm, number of portal tracts 26.9 ± 10.1.
Time between index test and reference standard	Same session
Prevalence of cirrhosis according to reference standard	14/117 (12.0%)
Target condition	Cirrhosis
Results: ARFI AUC (95% CI): not reported Optimal cut-off threshold (if calculated): n/a Threshold: 1.87m/s (pre-published) Sensitivity: not reported Specificity: not reported PPV: not reported	

Study	BOTA 2015[105]
NPV: 97.8% +ve/-ve likelihood ratios: Not reported TP: 12# FP: 17 FN: 2 TN: 86 Transient elastography results only reported for the FPs by ARFI. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random selection not reported. Some liver biopsies <25mm Reliable LS measurements by means of ARFI elastography were obtained in 117/132 patients (87.9%), patients included in the final analysis.	

Study	CARDOSO2012 [134]
Study type	Prospective cross sectional study
Number of studies (number of participants). Recruitment period.	1 study (hepatitis C population: N=392 consecutively recruited, n=26 excluded due to unreliable results, n=3 excluded due to unsuccessful tests; final analysis CHC n=363). Recruitment between 2006 and 2008. Also recruited a hepatitis B population (N=221).
Countries and Settings	France. Hospital hepatology service
Funding	Author funding or speaker for Roche, Schering Plough, Gilead, Novartis, Pharmasset, Tibotec, Boehringer, Biolex, Intermune, Abbott.
Age, gender, ethnicity	Age, mean (SD): 49.0(10.2); Male/female: 218/145; Ethnicity: 87% Caucasian, 12% Asian, 1% other; ALT (U/l): 2.5(1.2-3.1)
Patient characteristics	Population: treatment naïve chronic hepatitis B or chronic hepatitis C (only CHC population data extracted)

Study	CARDOSO2012 [134]
	Inclusion: presence of anti-HCV antibodies and detectable serum HCV-RNA by PCR (>50IU/ml) Exclusion: excessive alcohol consumption (>30g/day for men, >20g/day for women); co-infection with HIV and/or hepatitis delta virus; decompensated liver disease; HCC; previous liver surgery or transplant.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan; cut-off 12.5kPa, according to previous studies): performed by a single experienced operator. Only patients with at least 10 valid measurements were included (IQR less than 30% median stiffness and at least 60% success rate).
Reference standard	Liver biopsy (METAVIR F4): percutaneous liver biopsy performed under ultrasound guidance using the Menghini technique with disposable 16-gauge diameter needle. A single experienced pathologist who was unaware of the clinical data evaluated all slides. Only patients with a liver biopsy length of ≥15mm and/or at least 6 portal tracts were included.
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	31/363 (8.5%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.947 (SEM 0.027) Optimal cut-off threshold (if calculated): Not reported Threshold: 12.5 (pre-specified from literature) Sensitivity: 83.9 Specificity: 94.3 PPV: 57.8 NPV: 98.4 +ve/-ve likelihood ratios: 14.65 / 0.17 TP: 26 FP: 19 FN: 5 TN: 313 Other measures reported and conclusions: TE is an accurate tool for the non-invasive diagnosis of liver fibrosis in patients with chronic viral hepatitis, either related to	

Study	CARDOSO2012 [134]
HBV or HCV Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Excluded patients with unreliable TE measurements from analysis. Liver biopsy sample <15mm or 10 portal tracts.	

Study	CASTERA 2010A[143]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=314 CHC patients, 12 patients that had a biopsy length of less than 10 mm and/or less than 6 portal tracts were excluded, final analysis N=302, TE could not be performed in 8 patients). Recruitment period from June 2003 to February 2007.
Countries and Settings	France
Funding	Nothing to declare regarding funding from industry or conflicts of interest.
Age, gender, ethnicity, ALT (U/l):	Age: mean (SD): 52 (12) years; male/female: 176/126; ethnicity: not reported; ALT (IU/L): 106 (76)
Patient characteristics	Population: chronic hepatitis C (CHC) Inclusion: CHC was defined by detectable serum anti-HCV antibodies and HCV RNA with chronically elevated serum alanine aminotransferase (ALT) levels. Elevated ALT were defined as values above the upper limit of normal (ULN) range (50 IU/L) on at least 2 consecutive measurements over a period of 6 months. Exclusion: co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), other causes of liver disease, decompensated liver disease, and liver transplantation.
Index test (including threshold and whether threshold pre-specified)	Algorithms: SAFE: Based on sequential use of APRI, FibroTest and liver biopsy. APRI as the initial screening test with a low and high cut-off and FibroTest as a second step. If APRI lower than low cut-off (1.0) then cirrhosis absent, if higher than 1.0 then FibroTest performed. FibroTest ≤0.48 (cirrhosis absent), FibroTest 0.49-0.74 (liver biopsy needed) and ≥0.75 (cirrhosis present) Castera: combination of TE and FibroTest. When TE and FibroTest agree no biopsy is performed whereas when they disagree,

Study	CASTERA 2010A[143]
	liver biopsy is needed. TE ≥12.5 and FT <0.75 (disagree), TE <12.5 and FT ≥0.75 (disagree), TE failure (disagree), TE <12.5 and FT <0.75 (agree cirrhosis absent), TE ≥12.5 and FT ≥0.75 (agree cirrhosis present) Transient elastography (Fibroscan): 10 successful measurements were performed on each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The median value of successful measurements was considered representative of the liver stiffness in a given patient, according to the manufacturer's recommendations IQR < 30% of the median value and success rate >60%. FibroTest: score was purchased from Biopredicitve website (www.biopredictive.com). APRI (cut-off from original publication): Formula taken from the original publication Parameters (aspartate aminotransferase, alanine aminotransferase, c-glutamyl-transpeptidase, total bilirubin, a2-macroglobulin, apolipoprotein A1, haptoglobin and platelet count) allowing to calculate FT and APRI were determined in the same laboratory on blood sampled the day of liver biopsy.
Reference standard	Liver biopsy (METAVIR F4): performed by senior operators using the Menghini technique with a 1.6-mm-diameter needle (Hepafix, Braun, Melsungen, Germany). All biopsy specimens were analysed by the same trained pathologist blinded to the results of non-invasive markers. Specimens with a length of less than 10 mm and/or less than 6 portal tracts were excluded (note: all biopsies would be ≥6 portal tracts even if shorter than 15mm). The mean liver biopsy length was 20 ± 8 mm and the mean number of portal tracts was 15 ± 8. Biopsy length was greater than 15 mm in 70% of patients and greater than 25 mm in 25%.
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	25%
Target condition	Cirrhosis
Results: SAFE algorithm AUC (95% CI): 0.87 (0.84-0.90) Optimal cut-off threshold (if calculated): Not reported Threshold: as above	

Study	CASTERA 2010A[143]
Sensitivity: 86.4 Specificity: 89.7 PPV: 77.6 NPV: 94.1 +ve/-ve likelihood ratios: 8.4 / 0.15 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: Castera algorithm AUC (95% CI): 0.93 (0.90-0.96) Optimal cut-off threshold (if calculated): Not reported Threshold: as above Sensitivity: 89.4 Specificity: 98.2 PPV: 95.0 NPV: 95.9 +ve/-ve likelihood ratios: 49.6 / 0.1 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: liver biopsy saved in 226/302 patients using SAFE algorithm and 238/302 patients using Castera algorithm. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II	

Study	CASTERA 2010A[143]
Liver biopsy could be <25mm or <10 portal tracts	

Study	CATANZARO 2013[147]
Study type	Prospective cohort study
Number of studies (number of participants). Recruitment period.	1 study (N=162 with chronic hepatitis C, consecutively recruited). Recruitment between January 2011 and March 2013. Also recruited 67 healthy controls to assess the diagnostic accuracy of ELF and APRI to distinguish F0 from F≥1 (note: presumed healthy control group not included in the analysis for diagnostic accuracy for F4)
Countries and Settings	Italy. Admitted to Complex Unit for liver biopsy
Funding	None
Age, gender, ethnicity	Age, mean (SD): 55.19(9.53); Male/female: 57/105 Ethnicity: not reported; ALT (U/l): not reported
Patient characteristics	Population: chronic hepatitis C Inclusion: diagnosis of chronic hepatitis C was determined according to the positivity of anti-HCV and HCV-RNA for at least 6 months. The levels of HCV-RNA were determined by RNA extracted from serum, with reverse transcription and amplification of cDNA in real time PCR with TaqMan probes, with a sensitivity of 10 IU/ mL. Exclusion: previous history of antiviral therapy, the presence of ascites, chronic kidney failure or chronic coinfection HBV/HCV or HIV/HCV, chronic liver disease of other aetiology (HBV, non-alcoholic steatohepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis and α-1 anti-trypsin deficiency), liver failure, patients with alcohol abuse (taking more than 30 g/d of ethanol), heart failure or pregnancy, and patients with BMI >30 kg/m2.
Index test (including threshold and whether threshold pre-specified)	ELF test: (best cut-off values were determined by optimization of the Younden index). Laboratory analysis of 0.3 mL of blood taken at MedLab of Catania. Abstinence from alcohol prior to sampling was respected. Serum sample was processed through the ELF test ADVIA Centaur® (Siemens Healthcare Diagnostics Inc.), it generates a single score (ELF score) combined with doses of HA, PIIINP and TIMP-1. ELF score per ADVIA Centaur XP=2.278+0.851 ln[CHA]+0.751 ln[CPIIINP]+0.394 ln[CTIMP-1] APRI: details not reported
Reference standard	Liver biopsy (METAVIR F4): Percutaneous liver biopsies were performed under ultrasound guidance by a specialist, using an 18-G disposable needle. All of the liver biopsies were evaluated by expert pathologists, who were blinded to the patients'

Study	CATANZARO 2013[147]
	clinical histories. Only biopsies longer than 15 mm with at least 6 portal tracts were accepted.
Time between index test and reference standard	ELF test 2 weeks after liver biopsy
Prevalence of cirrhosis according to reference standard	43/162 (26.5%)
Target condition	Cirrhosis
Results: ELF AUC (95% CI): 0.94 (0.88-0.96). Adjusted AUC (DANA method): 0.90 Optimal cut-off threshold (if calculated): 9.3 Threshold: ≥9.3 (optimal) Sensitivity: 79.1 Specificity: 90.8 PPV: 75.6 NPV: 92.3 +ve/-ve likelihood ratios: LH+ 9.55 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.89 (0.83-0.93).Adjusted AUC (DANA method): 0.85 Optimal cut-off threshold (if calculated): 1.19 Threshold: ≥1.19 (optimal) Sensitivity: 74.4 Specificity: 87.4 PPV: 68.1 NPV: 90.4 +ve/-ve likelihood ratios: LH+ 5.9	

Study	CATANZARO 2013[147]
TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: ELF test more reliable than APRI score in the diagnosis of significant fibrosis and cirrhosis. It was not effective in discriminating healthy volunteers from patients with liver fibrosis. Any complications associated with tests reported: not reported	
General limitations according to QUADAS II Liver biopsy sample <25mm and < 10 portal tracts.	

Study	CAVIGLIA 2013[150]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=57 with chronic hepatitis C, consecutively recruited). Recruitment period not reported.
Countries and Settings	Italy. University hospital
Funding	None to declare
Age, gender, ethnicity	Age, mean (SD): 52.5(11.9); Male/female: 32/25; Ethnicity: not reported; ALT (IU/l): 85(47)
Patient characteristics	Population: chronic hepatitis C Inclusion: CHC patients tested positive for anti-HVC (Ortho HCV SAVe 3.0, Raritan, USA) and HCV RNA (TaqMan, Roche, detection limit 15IU/ml). Exclusion: patients with other aetiologies of chronic hepatitis, such as chronic hepatitis B, NASH, autoimmune hepatitis, primary biliary cirrhosis, alcoholic liver disease and haemochromatosis.
Index test (including threshold and	Transient elastography (Fibroscan, Echosens, Paris): (cut-off 13.8kPa, optimal chosen to maximise sensitivity and specificity)

Study	CAVIGLIA 2013[150]
whether threshold pre-specified)	performed on the right lobe of the liver through the intercostal spaces. Measurement depth between 25 and 65mm below the skin surface. Liver stiffness expressed as the median value of the successful measurements. Only data with at least 10 successful measurements, success rate higher than 60% and IQR inferior to 30% considered reliable.
Reference standard	Liver biopsy (METAVIR F4): underwent liver biopsy the year preceding non-invasive assessment (from 6 to 12 months). All biopsy specimens were analysed by an experiences pathologist blinded to the clinical results of the patients. Liver specimens shorter than 20mm were excluded from the analysis.
Time between index test and reference standard	Liver biopsy in the year preceding non-invasive liver assessment (from 6-12 months)
Prevalence of cirrhosis according to reference standard	18/57 (31.6%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.95 (0.86-0.99) Optimal cut-off threshold (if calculated): 13.8kPa Threshold: 13.8kPa (optimal) Sensitivity: 88.9 Specificity: 97.4 PPV: 94.1 NPV: 95.0 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: also assessed the accuracy of serum markers (hyaluronic acid, C-aminopyrine, cytokeratin). Transient elastography performed significantly better than the other tested methods. Any complications associated with tests reported: Not reported	

Study	CAVIGLIA 2013[150]
General limitations according to QUADAS II Up to 12 months between index test and reference standard Liver biopsy sample < 25mm	

Study	CHEN 2012[171]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=142 consecutive patients, 5 refused or were contraindicated for liver biopsy, 2 patients excluded with HCC, 2 with ALD, 1 with end stage renal disease, 2 with unreliable LSM results, and 3 with inadequate specimen quality, final analysis n=127). Recruitment between November 2010 and October 2011
Countries and Settings	Taiwan, University Hospital
Funding	Academic or Government (Department of Medical Research, China Medical University Hospital grant)
Age, gender, ethnicity	Age, mean (SD): F0-3: 51.6(1.2); F4: 62.7(1.5); Male/female: 59/68; Ethnicity: Taiwanese; ALT (IU/l): F0-3: 97.94(8.24); F4: 64.28(8.07).
Patient characteristics	Population: chronic hepatitis C (referred to liver centre for liver biopsy prior to the initiation of standard care for CHC). Inclusion: positive serum anti-HCV antibody (Abbott Laboratories, Abbott Park, Illinois, USA) for more than 6 months with the presence of serum HCV RNA (Cobas Amplicor HCV Monitor 2.0; Roche Diagnostics, New Jersey, USA). Exclusion: interferon or nucleos(t)ide analogue treatment, exposure to hepatotoxic drugs or chemicals, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, autoimmune hepatitis, alcoholic liver disease (ALD), hepatitis B virus (HBV) coinfection, human immunodeficiency virus (HIV) coinfection, liver abscess, acute hepatitis, extrahepatic cholestasis, severe hemolysis, Gilbert's syndrome with high unconjugated hyperbilirubinemia, autoimmune disorders, myeloproliferative disorders, thalassemias, schistosomiasis, major abdominal surgery, cardiac congestion, blood product transfusion within the previous 30 days, pregnancy, liver cancer, serum creatinine higher than 221 umol/L (2.5 mg/dL), hepatic encephalopathy, refractory ascites, and variceal bleeding.
Index test (including threshold and whether threshold pre-specified)	FibroTest (optimal cut-off value from the ROC): Serum markers including α2-macroglobulin, alanine aminotransferase (ALT), apolipoprotein A1, total bilirubin, γ-glutamyl transpeptidase (GGT) and haptoglobin were tested in the same laboratory, and results were then sent to www.biopredictive.com to determine a measure of liver fibrosis (FibroTest F score) using patented artificial

Study	CHEN 2012[171]
	intelligence algorithms ARFI (optimal cut-off value from the ROC): ARFI technology was integrated into a conventional ultrasound system (Acuson S2000 with a Siemens 4C1 curved array, 4.00 MHz for B-mode, 2.67 MHz for push pulses and 3.08 MHz for detection pulses; Siemens Medical Solutions, Mountain View, California, USA). All ARFI stiffness measurements were performed by the same hepatologist, who was experienced in digestive system ultrasonography and blinded to the patient data. The right lobe of the liver was approached intercostally, with the patient lying in a dorsal decubitus position with both arms above the head and holding their breath during VTQ measurements. Each patient received 10 successful LSMs (failed measurements were defined as SWV= "x.xx m/s"). Reliable cases were defined as those with an IQR of less than 30% of the median of 10 successful LSMs, and a successful rate of LSMs greater than 60%. Other cases were deemed unreliable and excluded.
Reference standard	Liver biopsy (METAVIR F4): Senior hepatologists performed the percutaneous right lobe liver biopsy. All biopsy specimens were interpreted by an expert pathologist blinded to the results of LSMs and patient data. Biopsy specimens at least 15 mm in length containing at least 5 portal tracts were defined adequate (mean 21.7 (3.3) mm, range 15-32 mm).
Time between index test and reference standard	Liver biopsy within 1 hour of receiving blood tests (including those for FibroTest) and stiffness measurements
Prevalence of cirrhosis according to reference standard	18/127 (14.2%)
Target condition	Cirrhosis
Results: FibroTest AUC (95% CI): 0.757 (0.648-0.865) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported	

Study	CHEN 2012[171]
TN: Not reported Results: ARFI AUC (95% CI): 0.831 (0.723-0.939) Optimal cut-off threshold (if calculated): 1.98m/s Threshold: 1.98m/s (optimal) Sensitivity: 88.9 Specificity: 79.8 PPV: 42.1 NPV: 97.8 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: 32 FN: Not reported TN: Not reported Other measures reported and conclusions: A comparison of the AUCs using ARFI and FibroTest results showed insignificant differences P = .341. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Liver biopsy sample < 25mm and <10 portal tracts	

Study	CHRYSANTHOS 2006[182]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (hepatitis C population: N=284 consecutively recruited). Recruitment between January 1998 and May 2004. Also recruited a hepatitis B population (N=205).

Study	CHRYSANTHOS 2006[182]
Countries and Settings	Greece, University Hospital
Funding	None reported
Age, gender, ethnicity	Age, mean (SD): 49 (15); Male/female: 145/139; Ethnicity: not reported; ALT (IU/l): 81 (10-647). Alcohol abuse reported in n=16 patients but had no evidence of alcohol induced liver disease.
Patient characteristics	Population: chronic hepatitis C Inclusion: detectable antibodies against HCV (anti-HCV), detectable HCV RNA in serum and increased ALT activity (ALT >upper limit of normal) on at least 2 separate monthly determinations within the last 6 months. Exclusion: patients with chronic hepatitis B virus or chronic hepatitis C virus co-infection, detectable antibodies against hepatitis delta virus (anti-HDV) or against HIV (anti-HIV), other causes of liver injury (alcohol abuse, use of known hepatotoxic drugs, autoimmune hepatitis, metabolic or cholestatic liver diseases), malignancy, or any type of antiviral or immunosuppressive therapy within the past 6 months. No patient had decompensated liver disease (history or evidence of ascites, variceal bleeding, hepatic encephalopathy or jaundice). Excluded patients with an inadequate liver biopsy length.
Index test (including threshold and whether threshold pre-specified)	APRI (2.0 and 1.0 cut-off value pre-specified from the literature): liver function tests evaluated by commercially available assays in all patients on the liver biopsy day. APRI = [(AST/ULN) / PLT (109/l)] x 100
Reference standard	Liver biopsy (Ishak F5/F6): adequate biopsy specimen with length of at least 1.5cm. All liver biopsies were evaluated blindly.
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	58/284 (20.4%)
Target condition	Cirrhosis
Results: APRI AUC (95% CI): Not reported for CHC population separately Optimal cut-off threshold (if calculated): Not reported Threshold: 1.0 (pre-specified from literature) Sensitivity: 72 Specificity: 60 PPV: 35 NPV: 88	

Study	CHRYSANTHOS 2006[182]
	+ve/-ve likelihood ratios: Not reported TP: 35 FP: 64 FN: 23 TN: 162 Threshold: 2.0 (pre-specified from literature) Sensitivity: 38 Specificity: 91 PPV: 52 NPV: 85 +ve/-ve likelihood ratios: Not reported TP: 22 FP: 20 FN: 36 TN: 206 Other measures reported and conclusions: data provided for hepatitis B populations and overall viral hepatitis. Any complications associated with tests reported: Not reported
	General limitations according to QUADAS II Unclear if all the liver biopsy specimens were evaluated by the same pathologist Liver biopsy sample < 25mm

Study	DE 2006[218]
Study type	Multicentre cross-sectional study

Study	DE 2006[218]
Number of studies (number of participants). Recruitment period.	1 study (HIV HCV co-infection: N=77 consecutively recruited, 5 excluded due to unsuccessful liver biopsy <7mm, final analysis N=72). Recruitment between January 2003 and January 2005
Countries and Settings	France
Funding	Equipment made available by Echosens (Paris, France)
Age, gender, ethnicity, ALT (U/l):	Age: mean 42.4 (SD 5.9), gender M/F: 52/20, ethnicity: not reported, ALT: 74.4 (SD 54.7)IU/L
Patient characteristics	Population: HIV infected patients with chronic HCV Inclusion: presence of HCV RNA and HIV antibodies in serum Exclusion: Not reported
Index test (including threshold and whether threshold pre-specified)	TE (Fibroscan, Echosens, Paris, France; optimal calculated for highest sensitivity with specificity forced no less than 90%, cut-off 11.8kPa, and for the highest sensitivity with specificity forced no less than 95%, cut=of 14.5kPa): tip of probe transducer placed on the skin between the ribs at the level of the right lobe of the liver. Measurement depth 25-65mm below the skin surface. At least 5 successful measurements were performed on each patient, with the ratio of the number of successful measurements over the total number of acquisitions not lower than 30%. Platelet count (cut-off <140G/L, published cut-off) APRI index (published cut-off >2): AST X ULN x 100/platelet count (109/L) AST/ALT ratio (published cut-off >1): AST X ULN x 100/platelet count (109/L) FIB-4 (published cut-off >3.25): age x AST /(platelet count x square root ALT)
Reference standard	Liver Biopsy (METAVIR F4): Liver biopsies less than 10 portal tracts (except for cirrhosis) were excluded from histological analysis. Median length 22mm (range 7-48mm) All biopsy specimens were analysed by 2 experienced pathologists blinded to the clinical data and results of TE.
Time between index test and reference standard	Not reported
Prevalence of cirrhosis according to reference standard	17/72 (23.6%)
Target condition	Cirrhosis

Study	DE 2006[218]
Results: Fibroscan AUC (95% CI): 0.97 (0.94-1) Optimal cut-off threshold: 11.8kPa (highest sensitivity with specificity no less than 90%), 14.5kPa (highest sensitivity with specificity no less than 95%), Threshold: 11.8kPa (optimal) Sensitivity: 100 (80.5-100) Specificity: 92.7 (82.4-98) PPV: 81 (58.1-94.6) NPV: 100 (93-100) +ve/-ve likelihood ratios: 13.8 (5.35-35.3) / 0 TP: 17 FP: 4 FN: 0 TN: 51 Threshold: 14.5kPa (optimal) Sensitivity: 88.2 (63.6-98.5) Specificity: 96.4 (87.5-99.6) PPV: 88.2 (63.6-98.5) NPV: 96.4 (87.5-99.6) +ve/-ve likelihood ratios: 24.3 (6.2-95.6) / (0.12 (0.03-0.45) TP: 15 FP: 2 FN: 2 TN: 53 Results: Platelet count (n=64) AUC (95% CI): 0.80 (0.64-0.95) Results: AST/ALT ratio (n=46)	

Study	DE 2006[218]
AUC (95% CI): 0.45 (0.20-0.70) Results: APRI (n=47) AUC (95% CI): 0.76 (0.59-0.92) Results: FIB-4 (n=46) AUC (95% CI): 0.73 (0.57-0.89) Other measures reported and conclusions: AUROC of TE significantly higher than those for platelet count, AST/ALT ratio, APRI and FIB-4 Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Unclear time between index test and reference standard	

Study	Esmat 2013[258]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N = 164 patients). Recruitment period not reported. (Study also included 67 patients with concurrent schistosomiasis but results from these patients were not extracted)
Countries and Settings	Egypt
Funding	None reported
Age, gender, ethnicity	Age, mean (SD not reported): 40 (10.5); Male/female: 111/53; Ethnicity: Egyptian; ALT (U/l): not reported (but multivariate logistic regression found ALT not to be associated with agreement between biopsy and TE)
Patient characteristics	Population: Hepatitis C Inclusion: 18 to 60 years; naivety to antiviral therapy; all patients were referred for assessment prior to interferon therapy as part of the national programme for combating viral hepatitis. HCV diagnosed by seropositivity for HCV antibodies and HCV RNA by polymerase chain reaction.

Study	Esmat 2013[258]
	Exclusion: other liver disease, decompensated liver cirrhosis, HCC, liver biopsy contraindication, those not fit for combined IFN and ribavirin treatment due to persistent haematological abnormalities and those with BMI >30
Index test (including threshold and whether threshold pre-specified)	TE (cut-off 12.5 kPa; from published literature: Castera et al): using the ultrasound TE fibroscan device (Echosens, Paris, France) with a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. Measurements were made in liver segment from 25 and 65 mm below the skin surface in a cylindrical shape 1 cm wide and 4 cm long.
Reference standard	Liver biopsy (METAVIR F4): performed on the same day as TE; performed using a semi-automatic true-cut needle (16G); specimens were analysed by an experienced pathologist blinded to the TE result. Only samples at least 15 mm and with 6 portal tracts were considered for assessment (mean of actual size of samples included was not reported).
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	18/164 (11%)
Target condition	Liver fibrosis and cirrhosis
Results: Fibroscan AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 12.5 kPa (published) Sensitivity: 72.2 Specificity: 92.5 PPV: 54.2 NPV: 96.4 +ve/-ve likelihood ratios: Not reported TP: 13 FP: 11 FN: 5 TN: 135	

Study	Esmat 2013[258]
Other measures reported and conclusions: Multivariate logistic regression, using fibrosis level as the independent variables found OR 7.12 (95%CI 2.38, 21.39, p value 0.00) for the agreement between TE and biopsy in those with liver biopsy F4. Any complications associated with tests reported: none (ARFI was feasible in all patients)	
General limitations according to QUADAS II Consecutive or random selection not reported. Liver biopsy sample < 25mm and <10 portal tracts	

Study	Fahmy 2011[261]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (hepatitis C population: N=110). Recruitment between March 2010 to February 2011
Countries and Settings	Italian Hospital and a fibroscan centre in Cairo
Funding	Not reported
Age, gender, ethnicity, ALT (U/l):	Age, mean (SD): 41 (9); Male/female: 84/26; Ethnicity: not reported; ALT (IU/l): 73.61 (4.24).
Patient characteristics	Population: newly diagnosed CHC patients Inclusion: positive for HCVAb and HCV-RNA by polymerase chain reaction and who did not start interferon treatment Exclusion: patients with other causes of chronic liver disease, bleeding tendency, cardiac disease, and decompensated liver disease
Index test (including threshold and whether threshold pre-specified)	TE (Fibroscan, Echosens, Paris, France; cut-off 16.5 kPa; unclear if published or optimal): The measurements were made on patients lying in dorsal decubitus with the right arm in maximal abduction. The operator, assisted by ultrasound time-motion and A-mode images, located a portion of the liver free of large vascular structures that was at least 6 cm thick. Ten validated measurements were made on each patient. Only procedures with 10 validated measurements and a success rate of at least 60% were considered reliable.
Reference standard	Liver biopsy (METAVIR F4): specimens composed of core >15 mm were assessed
Time between index test and	Within 1 week

Study	Fahmy 2011[261]
reference standard	
Prevalence of cirrhosis according to reference standard	22/110 (20%)
Target condition	cirrhosis
Results: Fibroscan AUC (95% CI): 0.95 (CI not reported) Optimal cut-off threshold (if calculated): Not reported Threshold: 16.5 kPa; unclear if published or optimal Sensitivity: 87 Specificity: 91 PPV: 71 NPV: 96 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: also reported the diagnostic accuracy of Doppler indices (splenic artery pulsatile index, SAPI, and hepatic vein dampening index, DI). TE had a significantly higher (AUROC) in predicting significant fibrosis and cirrhosis than the Doppler indices (p< 0.001), with no significant difference found between DI and SAPI (p> 0.05). Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random selection not reported. Unclear whether reference standard tests results were interpreted with knowledge of other results Liver biopsy sample < 25mm	

Study	Fernandes 2015[271]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=120, transient elastography failed in 2 patients) consecutive patients January 2011 to July 2012
Countries and Settings	2 liver units in Brasil
Funding	Not reported
Age, gender, ethnicity, ALT (U/l):	Age, mean (SD): 53 (11.3); Male/female: 41/79; Ethnicity: not reported; ALT (IU/l): 84.0 (75.4)
Patient characteristics	Population: patients with chronic hepatitis C submitted for liver biopsy to assess the indication for treatment. Inclusion: no other inclusion criteria reported Exclusion: HIV and HBV coinfection; alcohol daily intake >20g for women and 40g for men; cholestasis; chronic kidney failure; right-sided heart failure; fibrogenic drug use; biopsies with < 6 portal tracts.
Index test (including threshold and whether threshold pre-specified)	ELF (cut-off 10.44 optimal): 15ml blood sample taken and serum frozen at minus 70°C within 3 hours). PIIINP, HA and TIMP-1 measured in a random access automated clinical immunochemistry analyser that performs magnetic separation enzyme immunoassay tests (ADIVA Centaur, Siemens). ELF=2.278+0.851 ln[CHA]+0.751 ln[CPIIINP]+0.394 ln[CTIMP-1] Transient elastography (cut-off 12.5kPa, published): performed using Fibroscan (EchoSens) using the M probe and an experienced operator blinded to the biopsy and ELF results. The median value of 10 acquisitions was considered for analysis. Only examinations with a success rate of at least 60% and an IQR/M ratio of 30% were considered for a valid measurement. If no valid measurements were achieved the examination was considered a failure.
Reference standard	Liver biopsy (METAVIR F4): ultrasound guided percutaneous liver biopsies performed under local anaesthesia. Biopsies classified by the same experienced pathologist, blinded to patient data. People with biopsies <6 portal tracts were excluded. Mean (SD) length 22mm (1.02) and the mean number of portal tracts was 11 (4).
Time between index test and reference standard	Maximum time 3 months
Prevalence of cirrhosis according to reference standard	7%
Target condition	cirrhosis
Results: ELF	

Study	Fernandes 2015[271]
AUC (95% CI): 0.78 (0.70-0.85) Optimal cut-off threshold (if calculated): 10.44 Threshold: 10.44 (optimal) Sensitivity: 87.5 (47.2-99.7) Specificity: 77.6 (68.8-85) PPV: 21.9 (9.1-40.3) NPV: 98.9 (93.88-100) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: Transient elastography (AUC, sensitivity/specificity or 2x2 table values not reported) Other measures reported and conclusions: Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Liver biopsy sample < 25mm or <10 portal tracts	

Study	FERRAIOLI 2014[279]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N = 134 total population with viral hepatitis, N = 102 with hepatitis C analysed separately and reported here). Consecutive patients with chronic viral hepatitis.
Countries and Settings	Infectious Diseases Department of Policlinico San Matteo, Italy
Funding	The FibroScan device was made available for this study by Echosens (Paris, France), and the iU22 ultrasound equipment was

Study	FERRAIOLI 2014[279]
	provided by Philips Medical Systems (Bothell, WA, United States)
Age, gender, ethnicity	Age, mean (SD): 45.2 (11); Male/female: 82/20; Ethnicity: not reported; ALT (U/l): 70 (IQR 43-127)
Patient characteristics	Population: chronic viral hepatitis Inclusion: chronic viral hepatitis Exclusion: none reported
Index test (including threshold and whether threshold pre-specified)	Transient elastography (pre-published cut-off 9.3kPa): measurements were performed using the M probe of the FibroScan® device by two physicians with experience performing at least 50 TE procedures. During the acquisition, the patients lay in the dorsal decubitus position with the right arm in maximum abduction. The results were expressed in kilopascals (kPa). Only examinations with 10 valid measurements and an interquartile range/mean (IQR/M) < 30% for values greater than 7.1 kPa were considered reliable Point shear wave elastography (pSWE; optimal cut-off): The examinations were performed using the iU22 ultrasound system (Philips Healthcare, Bothell, WA, United States) with a convex broadband probe and the ElastPQ® technique. If the amount of non-shear wave motion exceeds a threshold, the system does not display a calculation. The two raters performing the PSWE measurements had seven years and two years, respectively, of experience in real-time elastography studies. They received training in PSWE measurements for two days before the study began. The examinations were performed in the right lobe of the liver through intercostal spaces, with the subject lying supine with the right arm in maximal abduction. Each rater performed 10 valid measurements, which were expressed in kPa. Measurements < 1 kPa were rejected by the raters.
Reference standard	Liver biopsy (METAVIR F4): performed by three experienced physicians using a 17-gauge modified Menghini needle (Hepafix; Braun, Melsungen, Germany). The same intercostal space used for the TE and PSWE measurements was chosen for LB. The specimens were assessed on site by a single expert liver pathologist who was blind to both the TE and PSWE results. Out of the total 134 patients, specimen length described as adequate for histology in all but 1 patient and the mean was 2.5 (0.78) cm.
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	10/102 (9.9%) (for transient elastography n=98, for pSWE n=101)
Target condition	Cirrhosis
Results: Transient elastography AUC (95% CI): 0.92 (0.85-0.97)	

Study	FERRAIOLI 2014[279]
Optimal cut-off threshold (if calculated): n/a Threshold: 9.3kPa (pre-published) Sensitivity: 90.0 (55.5-99.7) Specificity: 87.8 (79.2-93.7) PPV: 45.0 (23.1-78.5) NPV: 98.7 (93.2-100) +ve/-ve likelihood ratios: 7.4 (4.1-13.3) / 0.1 (0.02-0.7) TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: point shear wave elastography AUC (95% CI): 0.95 (0.89-0.99) Optimal cut-off threshold (if calculated): 7.2kPa Threshold: 7.2kPa (optimal) Sensitivity: 90.0 (55.5-99.7) Specificity: 88.6 (80.1-94.4) PPV: 47.4 (24.4-71.1) NPV: 98.7 (93.1-100) +ve/-ve likelihood ratios: 7.9 (4.3-14.7) / 0.1 (0.02-0.7) TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Any complications associated with tests reported: Not reported	

Study	FERRAIOLI 2014[279]
General limitations according to QUADAS II Liver biopsy sample < 10 portal tracts and < 25 mm.	

Study	FIERBINTEANU BRATICEVICI 2013[286]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N = 64 patients; of 93 patients with histologically proven NAFLD, 15 excluded because biopsy sample lengths were < 20 mm, 14 because they were considered to have borderline NASH). Recruitment between 2007 and 2010. Note: also includes a healthy control group – presumed not to be included in calculations of diagnostic accuracy for F4).
Countries and Settings	Romania, University Hospital Bucharest
Funding	None reported
Age, gender, ethnicity	Age, mean (SD not reported): 51 (NASH) and 47 (steatosis); Male/female: 28/36; Ethnicity: not reported; ALT (U/l): 92 (NASH) and 67 (steatosis) (SD not reported)
Patient characteristics	Population: NAFLD Inclusion: histologically proven NAFLD Exclusion: history of significant alcohol abuse (> 20g daily), evidence of hepatitis B and C, drug-induced liver disease or other specific liver diseases, haemochromatosis, alpha 1-antitrypsin deficiency, Wilson's disease, autoimmune diseases, congestive heart failure, biopsy < 20 mm including those with biopsies less than 6 (none included had hepatic decompensation such as with ascites, variceal bleeding, or encephalopathy)
Index test (including threshold and whether threshold pre-specified)	ARFI (cut-off 1.636 m/s; determined using ROC curves with sensitivity of 91% and specificity of 92%): using the Virtual Touch Tissue Quantification mode on the Siemens Acuson S2000 ultrasound system (Siemens AG, Erlangen, Germany) with a 4-MHz transducer. Measurements were made in liver segment VIII at 1 cm depth below the liver capsule through intercostal spaces with the patient lying in decubitus dorsal position with the right hand under the head (patients were evaluated at least 8 hours after their last meal). Patients were asked to momentarily stop normal breathing while minimal scanning pressure was applied by the operator. 10 successful acquisitions were performed in each patient with results expressed at mean value of the total measurements in m/s (with values between 0.72 to 2.53 m/s). If measurements were not reliable, "X-X-X" was displayed on the screen. Liver stiffness assessed by the same physician who was blinded to the clinical and biological data.
Reference standard	Liver biopsy (Kleiner, stage 4): performed up to 6 months before ARFI; percutaneous liver biopsy was performed by senior physicians using the Menghini technique with a 1.4 mm diameter needle. All biopsy specimens were analysed by an expert

Study	FIERBINTEANU BRATICEVICI 2013[286]
	pathologist with 25 years of experience who was blinded to the patient's clinical results. Only samples at least 20 mm and with 8 portal tracts were considered for assessment (average 22 mm, range 20 to 24mm).
Time between index test and reference standard	< 6 months
Prevalence of cirrhosis according to reference standard	12/64 (18.75%)
Target condition	Liver fibrosis and cirrhosis
Results: ARFI AUC (95% CI): 0.984 (0.958-1.000) Optimal cut-off threshold (if calculated): 1.636 m/s Threshold: 1.636 m/s Sensitivity: 91.7 Specificity: 92.3 PPV: 73.33 NPV: 97.96 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Spearman's correlation coefficient between ARFI measurements and histologically determined fibrosis Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random selection not reported. Up to 6 months between index test and reference standard Liver biopsy sample < 10 portal tracts and < 25 mm.	

Study	FLOREANI 2011[290]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (Primary biliary cirrhosis: N=120 consecutively recruited, 6 excluded because TE measurement was judged unreliable (due to an unsuccessful acquisition in 4 patients and a success rate below 60% in 2, all obese females with BMI > 34), final analysis N=114). Recruitment between January and December 2009
Countries and Settings	Italy
Funding	Partially supported by a University grant (ex 60% fund), no conflicts declared
Age, gender, ethnicity, ALT (U/l):	Age: mean 58(12), gender M/F: 8/96 (as reported, does not equal n=114), ethnicity: not reported, ALT: 1.1(0.9)xULN
Patient characteristics	Population: Primary biliary cirrhosis (PBC) Inclusion: PBC was defined according to the EASL 2009 guidelines; 112 patients (93.3%) had anti-mitochondrial antibody positivity of at least 1:40, whilst 8 had an antinuclear antibody positivity of at least 1:160, fulfilling the criteria for a diagnosis of AMA-negative PBC. Exclusion: ascites, hepatocellular carcinoma, severe obesity (BMI > 40), hepatitis B or C virus infection, overlap syndrome with autoimmune hepatitis or primary sclerosing cholangitis, a history of alcohol abuse, and any other causes of liver injuries other than PBC.
Index test (including threshold and whether threshold pre-specified)	TE (Fibroscan, Echosens, Paris, France; optimal cut-off obtained analysing the AUROC at the maximum of total sensitivity and specificity): The same dedicated operator took all the measurements, obtained in the right lobe of the liver trough the intercostals spaces and the median depth of measurement was 55 mm. Ten validated measurements were obtained for each patient and the minimum success rate (the ratio of successful acquisition to total acquisitions) was calculated to be 60%. The final LS result was the median of the 10 valid measurements APRI (optimal cut-off obtained analysing the AUROC at the maximum of total sensitivity and specificity): aspartate transaminase (×upper limit of normal)/platelet count (109/L) FIB-4 (optimal cut-off obtained analysing the AUROC at the maximum of total sensitivity and specificity): age (years) × aspartate transaminase (IU/L)/(platelet count (109/L) × alanine transaminase (IU/L)) AST/ALT ratio (optimal cut-off obtained analysing the AUROC at the maximum of total sensitivity and specificity):

Study	FLOREANI 2011[290]
	Combination of TE with each marker
Reference standard	Liver Biopsy (METAVIR F4): All specimens were analysed independently by 2 experienced pathologists blinded to patients' FibroScan results and clinical details. The length of each LB specimen and the number of fragments were recorded and only ones with a minimum length of 14 mm and including at least 10–15 portal space were considered.
Time between index test and reference standard	Within 6 months (80% within the same month)
Prevalence of cirrhosis according to reference standard	17/114 (14.9%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.99 (0.94–1) Optimal cut-off threshold: 11.4 Threshold (11.4 optimal): Sensitivity: 99 Specificity: 94 PPV: 77 NPV: 100 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.84 (0.74–0.97) Results: FIB-4	

Study	FLOREANI 2011[290]
AUC (95% CI): 0.74 (0.58–0.88) Results: AST/ALT ratio AUC (95% CI): 0.58 (0.42–0.74) Results: Fibroscan + APRI AUC (95% CI): 0.99 (0.94–1) Results: Fibroscan + FIB-4 AUC (95% CI): 0.99 (0.94–1) Results: Fibroscan + AST/ALT ratio AUC (95% CI): 0.99 (0.94–1) Other measures reported and conclusions: correlation between liver stiffness and Mayo score prognostic index Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Time between index test and reference standard up to 6 months	

Study	FRIEDRICH-RUST 2010[305]
Study type	Retrospective cohort study
Number of studies (number of participants). Recruitment period.	1 study (N=74 patients with serum available dated around the time of the FibroTest of patients with chronic liver disease, who received a liver biopsy, transient elastography and FibroTest). September 2005 to June 2008. Only N=36 included here (HCV population)
Countries and Settings	University Hospital, Germany

Study	FRIEDRICH-RUST 2010[305]
Funding	None
Age, gender, ethnicity, ALT (U/l):	Not reported for HCV population alone
Patient characteristics	Population: chronic liver disease (HCV, HVB, PBC) Inclusion: serum available dated around the time of the FibroTest of patients with chronic liver disease, who received a liver biopsy, transient elastography and FibroTest Exclusion: Not reported
Index test (including threshold and whether threshold pre-specified)	FibroTest (pre-published cut-off): computed on the Biopredictive website http://www.biopredictive.com. ELF test (pre-published cut-off): Serum samples were analyzed for levels of tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), hyaluronic acid (HA), and amino-terminal propeptide of type III collagen (P3NP) using the proprietary assays developed for ELF test by Siemens Healthcare Diagnostics Inc. (Tarrytown, New York USA). TE (Fibroscan, Echosens, Paris, France; pre-published cut-off): The examination was performed on the right lobe of the liver through the intercostal space. After the area of measurement was located, the examiner pressed the button of the probe to start the acquisition. The measurement depth was between 25 and 65 mm. As suggested by the manufacturer, 10 successful acquisitions were performed on each patient. Only TE-results obtained with 10 valid measurements with a success-rate of at least 60% and an IQR range ≤30% were considered reliable Blood parameters were determined after overnight fasting in the same laboratory on the same day as transient elastography in all patients
Reference standard	Liver biopsy (METAVIR): All biopsy specimens were analysed by an experienced pathologist blinded to the clinical results of the patients. The biopsies were judged as adequate, if the number of portal tracts was at least 6 and the length of liver biopsy at least 1 cm. The mean length of the included liver biopsies was 22.3 ± 9.3 mm (median 20 mm, range 10-54 mm).
Time between index test and reference standard	Up to 12 months
Prevalence of cirrhosis according to reference standard	11/74 (not reported for HCV population alone)
Target condition	Cirrhosis
Results: FibroTest	

Study	FRIEDRICH-RUST 2010[305]
AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 0.73 (pre-published) Sensitivity: 67 Specificity: 81 PPV: 54 NPV: 88 +ve/-ve likelihood ratios: 3.6 / 0.41 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: ELF AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 10.31 (pre-published) Sensitivity: 89 Specificity: 63 PPV: 44 NPV: 94 +ve/-ve likelihood ratios: 2.4 / 0.18 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: Fibroscan AUC (95% CI): Not reported	

Study	FRIEDRICH-RUST 2010[305]
Optimal cut-off threshold (if calculated): Not reported Threshold: 12.5 (pre-published) Sensitivity: 78 Specificity: 84 PPV: 64 NPV: 91 +ve/-ve likelihood ratios: 4.86 / 0.27 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: AUROC for mixed aetiologies and for HBV and PBC separately (for the latter, measured against the Ludwig scoring system) Any complications associated with tests reported:	
General limitations according to QUADAS II Retrospective analysis of samples Time period between index test and reference standard up to 12 months Size of liver biopsy <6 portal tracts	

Study	FRIEDRICH-RUST 2010A[301]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	N=50 consecutive patients with NAFLD or NASH. Recruitment period August 2008 to November 2009

Study	FRIEDRICH-RUST 2010A[301]
Countries and Settings	Germany
Funding	XL probe provided by Echosens. No financial support.
Age, gender, ethnicity	Age, mean (SD): 44 (15), range 21-71 years; Male/female: 27/23 Ethnicity: not reported ; ALT (IU/l): 73 (45); BMI: 29 (5.5), range 20-43kg/m2
Patient characteristics	Population: NAFLD or NASH Inclusion: diagnosis of NAFLD or NASH made histologically by liver biopsy. Exclusion: men with alcohol consumption more than 30g/week and women with alcohol consumption more than 20g/week. Other causes of liver disease (positive hepatitis B surface antigen or anti-hepatitis C virus antibody, positive auto-antibodies) or histological evidence of other chronic liver diseases.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (FibroScan using standard M probe and using the XL probe): distance between the skin and the liver capsule at the site of TE was measured using conventional ultrasound. Performed on the right lobe of the liver through intercostal spaces. Ten successful acquisitions performed on each patient using each probe. Only results with 10 valid measurements, with a success rate of at least 60% and a IQR≤30% of the median were considered reliable. Study aims to compare the M and XL probe in the same patients. Note: the Fibroscan XL probe has been designed specifically for use in obese patients by utilisation of a lower frequency and more sensitive ultrasonic transducer, a deeper focal length, a larger vibration amplitude and a greater depth of measurement below the skin surface.
Reference standard	Liver biopsy (Kleiner F4): All specimens analysed by an experienced pathologist who was blinded to the clinical results. The biopsies were judged to be accurate if the number of portal tracts was at least 6 and the length of the biopsy at least 1cm. Mean length 21.5 (8.0)mm, median 20mm, range 10-40mm.
Time between index test and reference standard	Up to 18 months (median 5.5 months, mean 7.9 (6.2) months, range 0-18)
Prevalence of cirrhosis according to reference standard	3/50 (6%)
Target condition	Cirrhosis
Results: Fibroscan M probe AUC (95% CI): 0.91 (0.75-1.00) Optimal cut-off threshold (if calculated): Not reported	

Study	FRIEDRICH-RUST 2010A[301]
Threshold: Not reported Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Fibroscan XL probe AUC (95% CI): 0.95 (0.85-1.00) Optimal cut-off threshold (if calculated): Not reported Threshold: Not reported Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: number of valid measurements significantly higher for the XL probe than the M probe. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II	

Study	FRIEDRICH-RUST 2010A[301]
Time between reference standard and index test up to 18 months Size of liver biopsy <6 portal tracts	

Study	FUJII 2009[309]
Study type	Unclear
Number of studies (number of participants). Recruitment period.	N=50 patients with NASH (also 100 patients with HCV but liver biopsy fibrosis scoring system does not match reference standard for HCV, Desmet et al (Scheuer classification)). Recruitment period 1998-2007
Countries and Settings	Osaka City University Hospital
Funding	Not reported
Age, gender, ethnicity	Age, mean (SD): 55.8 (15.2); Male/female: 13/37; Ethnicity: presumed Japanese; ALT (IU/l): 106 (24-368)
Patient characteristics	Population: NASH Inclusion: diagnosis of NASH based on histological features of steatohepatitis Exclusion: clinically significant alcohol consumption (20g/day), and other identifiable causes of liver disease including drug-induced hepatotoxicity, infection with hepatitis B or C virus, autoimmune diseases, Wilson's disease, haemochromatosis, and α1-antitrypsin deficiency.
Index test (including threshold and whether threshold pre-specified)	AAR: AST/ALT APRI: [(AST/ULN) / platelet count (x109/l] x 100 AST, ALT, alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, plasma glucose, prothrombin time and platelet count were routinely determined by standard procedures within 4 week of biopsy
Reference standard	Liver biopsy (Brunt F4 for NASH patients): obtained by ultrasound guided biopsy using a 15-guage Tru-cut needle (Hakko, Nagona, Japan). All specimens fulfilled the criteria for size as suggested by Janiec et al. (>1cm with >10 portal tracts). Histological diagnosis was performed.
Time between index test and reference standard	Within 4 weeks
Prevalence of cirrhosis according to	9/50 (18%)

Study	FUJII 2009[309]
reference standard	
Target condition	Cirrhosis
Results: AAR AUC (95% CI): 0.813 (0.674-0.952) Optimal cut-off threshold (if calculated): Not reported Results: APRI AUC (95% CI): 0.786 (0.625-0.947) Optimal cut-off threshold (if calculated): Not reported Other measures reported and conclusions: AP index, CDS, HALT-C score. Sensitivity and specificity values only reported for CDS and HALT-C score. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random recruitment not reported Unclear if reference standard results interpreted without knowledge of the index test results	

Study	GAIA 2011[312]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	290 initially enrolled 21 excluded due to unsuccessful liver stiffness measurements 10 excluded due to inadequate liver biopsy specimens 259 included (77 HCV, 70 HCB, 72 NAFLD, 40 controls) January 2007 – March 2009

Study	GAIA 2011[312]
Countries and Settings	San Giovanni Battista Hospital, Gastroenterology, Italy
Funding	Not reported
Age, gender, ethnicity, ALT (U/l):	HCV: age: 46 (29-69), male/female: 42/35, ethnicity: not reported, ALT: 76 (22-324) UI/L NAFLD: age: 48 (24-65), male/female: 52/20, ethnicity: not reported, ALT: 58 (12-264)
Patient characteristics	Population: All patients with viral or metabolic chronic liver disease who underwent liver biopsy at the Hepatology Unit Inclusion: Chronic hepatitis C was defined by detectable anti-hepatitis C virus antibodies and serum HCV RNA. Diagnosis of NAFLD was confirmed by liver biopsy in patients with abnormal liver function tests or fatty liver at ultrasound and no other known cause of liver disease. Exclusion: Patients with alcoholic liver disease (>40g/day alcohol consumption) and patients with acute viral hepatitis were excluded. TE and biopsy performed before any therapeutic approach, including diet and antiviral therapy.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan; optimal cutoff values to maximize sensitivity, specificity, and diagnostic accuracy): was performed on the right lobe of the liver through intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction. Measurement depth was between 25 mm and 65 mm below the skin surface. TE acquisitions with abnormal vibration shape or propagation were automatically rejected by the software. The success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. Liver stiffness was expressed as the median value of the successful measurements. Only liver stiffness data with at least 10 successful measurements, success rate higher than 60%, and inter quartile ratio inferior to 30%, were considered reliable. TE was performed by officially trained operators who were blinded to liver histology but had access to medical records of the patients. Presumed to have used appropriate probe for patient's BMI according to manufacturer's instructions (not reported).
Reference standard	Liver biopsy (METAVIR F4 for HCV; Brunt F4 for NAFLD): all specimens were analysed by an expert pathologist blinded to the results of TE but not to the clinical and biochemical data. Liver specimens shorter than 20mm were excluded, median length of the available specimens was 25.2 mm (range 20–30.2 mm).
Time between index test and reference standard	Within 6 months
Prevalence of cirrhosis according to reference standard	HCV 13/77 (16.8%) NAFLD 9/72 (12.5%)
Target condition	Cirrhosis
Results: HCV group AUC (95% CI): 0.922 (0.86-0.985) Optimal cut-off threshold (if calculated): 11.5kPa	

Study	GAIA 2011[312]
Threshold: 11.5 kPa (optimal) Sensitivity: 69 Specificity: 93 PPV: (given as positive predictive accuracy, PPA): 64 NPV: (given as negative predictive accuracy, PPA): 94 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: NAFLD group AUC (95% CI): 0.942 (0.881-1.003) Optimal cut-off threshold (if calculated): 10.5kPa Threshold: 10.5kPa (optimal) Sensitivity: 78 Specificity: 96 PPV: (given as positive predictive accuracy, PPA) 70 NPV: (given as negative predictive accuracy, PPA) 97 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Independent predictors of severe fibrosis and cirrhosis, steatosis. TE can be considered a valid support to detect fibrosis in chronic liver disease related to HCV but it should be interpreted with caution in NAFLD patients, where host or	

Study	GAIA 2011[312]
disease-related factors may modify its accuracy. Any complications associated with tests reported:	
General limitations according to QUADAS II Time between index and reference tests up to 6 months. Excluded patients with unsuccessful liver stiffness measurements from the analysis. Length of biopsy <25 mm.	

Study	GUECHOT 2012[362]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	N=590 enrolled, consecutive recruitment reported previously Zarski 2012[964] (512 included in analysis, 42 had insufficient liver biopsy, 5 had previous interferon, 9 had co-infection with HBV, 5 had excessive alcohol consumption, 1 had immunosuppressant therapy, 13 incomplete data, 3 non-confirmed HCV positive status). November 2007 to July 2008.
Countries and Settings	19 academic centres in France, Fibrostar study cohort (previously reported the ELFG score and other fibrosis tests, Zarski 2012)
Funding	The French National Agency for Research on AIDS and Viral Hepatitis (ANRS).
Age, gender, ethnicity, ALT (U/l):	Age: median 50 (18-79), gender: 60% male, ethnicity: not reported, ALT: median 69 (12-594 IU/L)
Patient characteristics	Population: Untreated hepatitis C patients Inclusion: Anti-HCV antibodies positive and RNA-HCV positive Exclusion: Associated co-infection (hepatitis B or HIV), other causes of liver disease (drug hepatitis, Wilsons disease, hemochromatosis, autoimmune hepatitis, alcohol consumption > 30g/day for men and > 20g/day for women, primary biliary cirrhosis, α-1 antitrypsine deficiency), severe systemic diseases. Individuals receiving antiviral drug therapy, immunosuppressive therapy.
Index test (including threshold and whether threshold pre-specified)	ELF score (optimal cut-off calculated by maximising the sum of sensitivity plus specificity): fasting blood samples were collected be venepuncture. The same kinds of tubes from the same lots were used for all patients (BD Vacutainer, type Z, Becton-Dickinson, Plymouth, UK). Each of the biological parameters included in the ELF score were measured in a single laboratory using serum samples immediately separated and fractioned in fractions of 0.5 ml in 1.5 ml screw cap microtubes

Study	GUECHOT 2012[362]
	(Sarstedt, Numbrecht, Germany). All fractions were immediately frozen and stored at -80°C until the assays were undertaken. The transport of samples from the hepatology centres to the laboratory were achieved in carbonic ice by a specialised transporter (Area Time Logisitics, Cergy Pontoise, France). All biological tests were processed blindly without knowledge of the clinical and histological data. Serum HA was assayed using a latex agglutination method that can be applied to general clinical chemistry analysers using an AU640 analyser. Serum PIIINP was assayed using a radio immunoassay and the serum TIMP-1 was assayed using an ELISA kit. ELF score was computed from the results using the simplified algorithm published by Parkes. ELF score = -7.412+[ln HA(ng/ml)x0.681]+[ln PIIINP(ng/ml)x0.775]+[ln TIMP1(ng/ml)x0.494]+10
Reference standard	Liver biopsy (METAVIR F4): performed by 2 senior pathologists, academic experts in liver pathology, without knowledge of any clinical and biological data except that patients had chronic hepatitis C. To be considered as adequate for scoring, the liver biopsies had to measure at least 15 mm and/or contain at least 11 portal tracts except for cirrhosis for which no limitation was required. Mean 25.1 (8.8)mm and longer than 25mm in 40.2%. In case of discrepancies, slides were simultaneously reviewed by 2 pathologists using a multi-pipe microscope in order to reach a consensus.
Time between index test and reference standard	Within 2 months
Prevalence of cirrhosis according to reference standard	76/512 (14.8%)
Target condition	Cirrhosis
Results: ELF score AUC (95% CI): 0.85 (0.81-0.90) Optimal cut-off threshold (if calculated): 9.35 Threshold: 9.35 (optimal) Sensitivity: 0.83 (0.79-0.66) Specificity: 0.75 (0.64-0.84) PPV: 0.44 NPV: 0.95 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported	

Study	GUECHOT 2012[362]
TN: Not reported Youden index 0.59 Other measures reported and conclusions: Obuchowski measures for ELF versus ELFG and FibroTest. This study confirms the ELF score performance as an index to predict liver fibrosis or cirrhosis in chronic HCV. The ELF test, using validated reagents, could be added to the health authorities approved non-invasive tests in assessing fibrosis as surrogate to liver biopsy. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Not all patients included in the analysis and length of time between reference standard and index test up to 2 months. Liver biopsy size <25 mm.	

Study	Halfon 2007[368]
Study type	Retrospective cohort
Number of studies (number of participants). Recruitment period.	N=356. Recruitment from October 1994 to March 2004 in Tours centre and from September 2002 to January 2004 in Provence area
Countries and Settings	University Hospital in Tours, and 5 units (2 University Hospital, 2 public hospitals, 1 private clinic) from Provence-Cote d'Azur area, France
Funding	Not reported
Age, gender, ethnicity, ALT (U/l):	Age: 44.9 ± 12.9; Male: 189 (53%); ethnicity: not reported; ALT (IU/L): 76.5 ± 66.2
Patient characteristics	Population: chronic viral hepatitis C Inclusion: positive HCV-RNA in the serum and a liver biopsy and an alcohol consumption <30 g/day for the past 5 years Exclusion: liver specimen <15 mm or other cause of liver disease or complicated cirrhosis or were given putative anti-fibrotic treatment (e.g. interferon or sartan) in the past 6 months
Index test (including threshold and whether threshold pre-specified)	FibroTest: cut-off of regression score was determined according to the highest Youden index (Se + Spe 1) APRI: cut-off of regression score was determined according to the highest Youden index (Se + Spe 1)

Study	Halfon 2007[368]
	Blood markers were measured either on fresh blood or frozen sample of serum stored at -20C. Sampling was performed for routine diagnostic aim within 1 week of liver biopsy.
Reference standard	Liver biopsy (METAVIR F4): Patients were not included if they had liver specimen <15 mm (average 22.0 ± 7.1). Fibrosis was staged by 2 independent expert pathologists. Observers were blinded for patient characteristics. When the pathologists did not agree, the specimens were re-examined under a double headed microscope to analyse discrepancies and reach a consensus
Time between index test and reference standard	Within 1 week
Prevalence of cirrhosis according to reference standard	13/356 (4%)
Target condition	Cirrhosis
Results: FibroTest AUC (95% CI): 0.86 (0.82; 0.89) Optimal cut-off threshold (if calculated): 0.56 Threshold: 0.56 (optimal) Sensitivity: 85 Specificity: 74 PPV: 11 NPV: 99 +ve/-ve likelihood ratios: 3.19 / 0.21 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.92 (0.88; 0.94) Optimal cut-off threshold (if calculated): 0.83 Threshold: 0.83 (optimal)	

Study	Halfon 2007[368]
Sensitivity: 100 Specificity: 83 PPV: 18 NPV: 100 +ve/-ve likelihood ratios: 5.81 / 0.00 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Fibrometer and hepascore reported. Subgroup analysis by centre and by biopsy size (≥21mm and <21mm) Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random recruitment not reported. Retrospective recruitment Liver biopsy size <25 mm.	

Study	Janssens 2010[433]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=255 patients admitted, 16 excluded due to unsuccessful TE due to obesity or ascites, 167 patients excluded as were F0-2 according to TE value, 72 patients had severe fibrosis according to TE but 21 refused biopsy and biopsy not possible in 2 patients. Final analysis n=49) Recruitment between January 1, 2006 and February 29, 2008.
Countries and Settings	University hospital, Brussels, Belgium
Funding	No conflict of interest or financial support to be declared
Age, gender, ethnicity	Age, median (range): 53 (29-73) years; Male/female: 34/15; Ethnicity: ; ALT (U/l): 62 (36.6). Six patients had diabetes mellitus,

Study	Janssens 2010[433]
	1 patient was hepatitis B surface antigen positive, and 1 patient was hepatitis C antibody and HCV-RNA positive but liver biopsies did not show signs of chronic viral hepatitis and therefore it was decided to keep them in the study.
Patient characteristics	Population: actively drinking alcoholic patients admitted for detoxification and rehabilitation during a 2 week hospitalisation period, separated by 1 outpatient week. Lab tests and TE performed during the first week. Those with a suspicion of severe fibrosis (TE ≥9.5kPa) underwent liver biopsy during the second hospitalisation week. Inclusion: all patients drank actively until the day of their first admission. Self-reported minimum daily alcohol intake was 7 standard drinks (70g of alcohol). Exclusion: patients who desired not to be rehospitalised for a second week. Patients who declined TE or had unsuccessful TE (as it was a prerequisite for liver biopsy). Patients who refused liver biopsy.
Index test (including threshold and whether threshold pre-specified)	APRI (pre-published cut off value of 2.0): calculated from routine lab blood tests collected at admission. APRI calculated as follows: AST/ULN x 100/platelet count (109/L). Transient elastography (Fibroscan, optimal cut-offs for population reported, also used validated cut-off in HCV population but results not reported): performed by an experienced examiner who was unaware of the biological, radiological and clinical data. Final result reported as the median value of at least 10 validated measurements with a minimum success rate of 60% and an IQR <30%.
Reference standard	Liver biopsy METAVIR (F4): performed through the right jugular vein approach using a Ross-modified Colapinto catheter needed with a diameter of 1.5mm (Cook, Denmark). All specimens analysed by an experienced liver pathologist blinded to the biological, radiological and clinical data. Liver biopsy specimen of at least 15mm containing a minimum of 6 portal tracts were considered suitable for fibrosis staging, or when obvious regenerating nodules were present allowing the unequivocal diagnosis of cirrhosis.
Time between index test and reference standard	Within 3 weeks
Prevalence of cirrhosis according to reference standard	20/49 (40.8%) for TE. 11/28 (39.3%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.864 (CI not reported) Optimal cut-off threshold (if calculated): ranged between 19.6 and 23.5kPa Threshold: 19.6kPa	

Study	Janssens 2010[433]
Sensitivity: 80 Specificity: 76 PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 21.1kPa Sensitivity: 75 Specificity: 80 PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 23.5kPa Sensitivity: 65 Specificity: 83 PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	Janssens 2010[433]
Results: APRI (n=48) AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 2.0 Sensitivity: 40 Specificity: 61 PPV: 42 NPV: 59 +ve/-ve likelihood ratios: Not reported TP: 8 FP: 11 FN: 12 TN: 17 Other measures reported and conclusions: Forns score. Evaluation of factors that influence the liver stiffness measurement. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Random or consecutive recruitment not reported. Liver biopsy samples <25mm Indirectness: only patients with severe fibrosis (transient elastography ≥9.5 kPa) underwent liver biopsy	

Study	KAYADIBI 2014[455]
Study type	Retrospective cohort study
Number of studies (number of	1 study (N=214; 202 with sufficient data to complete)

Study	KAYADIBI 2014[455]
participants). Recruitment period.	Recruitment between 2008-2010
Countries and Settings	Department of Gastroenterohepatology of Haydarpasa Numune Training Hospital, Istanbul
Funding	Not reported
Age, gender, ethnicity	Age, mean (range): 52 (42-59) ; Male/female: 61% male Ethnicity: presumed from Istanbul; ALT (U/l): not reported for whole group, only grouped by presence or absence of cirrhosis
Patient characteristics	Population: Hepatitis C patients who underwent liver biopsy Inclusion: anti HCV and HCV RNA positivity Exclusion: co-infection with HIV, hepatitis B, heptatitis D, use of steroids, NSAIDs, antiviral therapy, other liver disorders
Index test (including threshold and whether threshold pre-specified)	FIB-4 = Age (years) x AST (U/L) / [platelet count (109L) x ALT1/2 (U/L)] APRI = ([AST/ULN]/platelet count [109L]) x100 AST/ALT ratio (AAR) AST ALT Platelet count: performed by the blood count analyser All measured by commercial assays using the fasting serum sample results
Reference standard	Liver biopsy METAVIR (F4) obtained with an 18-gauge needle and assessed by a single senior pathologist blinded to the clinical history and lab results. Samples ≥25 mm, ≥8 portal tracts were used.
Time between index test and reference standard	1 week
Prevalence of cirrhosis according to reference standard	47/202 (23%)
Target condition	Cirrhosis
Results: ALT AUC (95% CI): 0.626 (0.534-0.717) Optimal cut-off threshold (if calculated): Not reported Threshold:	

Study	KAYADIBI 2014[455]
Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported AST AUC (95% CI): 0.752 (0.671-0.832) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Platelet Count AUC (95% CI): 0.827 (0.745-0.908) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported	

Study	KAYADIBI 2014[455]
Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported FIB-4 AUC (95% CI): 0.853 (0.784-0.921) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported APRI AUC (95% CI): 0.847 (0.776-0.919) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported	

Study	KAYADIBI 2014[455]
PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported AST/ALT ratio AUC (95% CI): 0.610 (0.510-0.709) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Multivariate regression analysis revealed that fibrosis index was the best predictor of cirrhosis, potentially decreasing the need for biopsy in 83% of patients, and Forns index, platelet count and APRI were statistically significant predictors of cirrhosis. Sensitivity and specificity values at a given cut-off threshold only provided for the created fibrosis index. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II	

Study	KAYADIBI 2014[455]
Random or consecutive recruitment not reported.	

Study	KETTANEH 2007[458]
Study type	Prospective multicentre
Number of studies (number of participants). Recruitment period.	935 consecutive HCV patients enrolled 79 inadequate FibroScan measurements 292 biopsy length <15 mm 54 biopsy length unknown 560 patients included in analysis November 2002 – April 2005
Countries and Settings	Multiple centres in France Hopital Saint-Antoine, Paris; Hopital Beaujon, Paris; Hopital Henri Mondor, Paris; Hopital Jean Verdier, Paris; Hopital Haut-Leveque, Bordeaux
Funding	No funding received from any source
Age, gender, ethnicity, ALT (U/l):	Mean age: 24.5 ± 4.0, gender: 62.3% male, ethnicity: not reported, ALT: 93± 80 IU/l
Patient characteristics	Population: Chronic HCV patients Inclusion: HCV defined by detectable serum anti-HCV antibiodies and HCV RNA in subjects with chronically elevated serum alanine aminotransferase levels. Exclusion: Co-infection with HIV or HBV. Hepatocellular carcinoma.
Index test (including threshold and whether threshold pre-specified)	TE via FibroScan The tip of the probe transducer was placed on the skin, between the rib bones at the level of the right lobe of the liver where liver biopsy would be done. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. The measurement depth was between 25 mm and 65 mm below the skin surface.
Reference standard	Liver biopsy was fixed in formalin and paraffin-embedded. All biopsy specimens were analysed by 1 experienced pathologist

Study	KETTANEH 2007[458]
	blinded to the clinical data and the results of the FibroScan. Fibrosis and necro-inflammatory activity were staged according to METAVIR. Only those with a minimal length of 15mm were eligible as the gold standard for the prediction of cirrhosis by elastography.
Time between index test and reference standard	Not reported
Prevalence of cirrhosis according to reference standard	58/560 (10.4%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 90.7 (87.1-94.3) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Patient and operator characteristics associated with the success rate of liver stiffness measurements. Effect of number of valid Fibroscan shots (at least 3 versus at least 10) on outcome. Fibroscan provides a reasonable performance for the diagnosis of cirrhosis that is not influenced substantially by any other feature. More patients will benefit from this procedure with no significant loss in performance if only 5 valid shots are requested.	

Study	KETTANEH 2007[458]
Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Time between reference standard and index test not reported. Patients with unsuccessful TE excluded from the analysis Liver biopsies <25mm.	

Study	LACKNER 2005[496]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	N=211 consecutive patients with chronic hepatitis C (17 excluded due to inadequate biopsy, final analysis n=194). Between 1994 and 2004.
Countries and Settings	Medical University Graz or at the Landeskrankenhaus Hoergas, Austria
Funding	Not reported. No conflicts of interest
Age, gender, ethnicity, ALT (U/l):	Age: mean 48 (12) years; Male/female: 111/83; ethnicity: not reported; ALT: 2.8 (2.0) ULN.
Patient characteristics	Population: treatment-naiive patients with chronic HCV Inclusion: tested positive for the presence of HCV RNA using a polymerase chain reaction assay and did not suffer from additional causes of chronic liver disease as confirmed by standard clinical, serological, biochemical, and radiological criteria Exclusion: antiviral treatment before liver biopsy, alcohol consumption in excess of 20 g/d, and previous liver transplantation
Index test (including threshold and whether threshold pre-specified)	AST/ALT ratio: pre-published cut-off threshold APRI: pre-published cut-off threshold Platelet count: optimal cut-off from ROC Because of the introduction of the International Federation of Clinical Chemistry reference method for the determination of aminotransferase activities at 37°C, the upper limits of normal (ULN) for AST and ALT changed in the course of the study (ULN before March 2003: AST, 18 U/L; ALT, 22 U/L; after March 2003: AST, 35 U/L male or 30 U/L female, ALT, 45 U/L male or 35 U/L female). Therefore, both AST and ALT were transformed into multiples of the ULN for further analysis except for the calculation of AAR. The reference range for platelet count was 140x109/L.
Reference standard	Liver Biopsy (Ishak F5-6): Biopsy specimens with at least 6 portal fields were considered representative. Histological grading performed independently by 2 Pathologists. Mean biopsy length 19 (8)mm, median number of portal tracts 11 (IQR 9-16).

Study	LACKNER 2005[496]
Time between index test and reference standard	Same day (n=96); within 1 month (n=98)
Prevalence of cirrhosis according to reference standard	32/194 (16.4%) (reported in paper for 2 pathologists opinions separately as 16% and 17%, however, the results in the table show that both pathologists rated 32/194 as F5-6. Results also reported as similar for the 2 pathologists, so results for all tests below taken for pathologist 1)
Target condition	Cirrhosis
Results: AST/ALT ratio AUC (95% CI): 0.73 (0.63–0.83) Optimal cut-off threshold (if calculated): not reported Threshold: 1.0 (pre-published) Sensitivity: 36 Specificity: 90 PPV: 41 NPV: 87 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.90 (0.85–0.95) Optimal cut-off threshold (if calculated): not reported Threshold: 1.0 (pre-published) Sensitivity: 93 Specificity: 70 PPV: 38 NPV: 98 +ve/-ve likelihood ratios: Not reported	

Study	LACKNER 2005[496]
TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 2.0 (pre-published) Sensitivity: 55 Specificity: 93 PPV: 59 NPV: 91 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: platelet count AUC (95% CI): 0.89 (0.83–0.94) Optimal cut-off threshold (if calculated): 150x109L Threshold: 130x109L (published) Sensitivity: 53 Specificity: 93 PPV: 59 NPV: 91 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 150x109L (optimal)	

Study	LACKNER 2005[496]
	Sensitivity: 77 Specificity: 88 PPV: 56 NPV: 95 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: APRI accuracy in good agreement with previous studies but AST/ALT and platelet count accuracies considerably lower than previous reports. Any complications associated with tests reported: Not reported
	General limitations according to QUADAS II Unclear if reference standard result interpreted without knowledge of clinical data or the index test results. Liver biopsy <10 portal tracts

Study	LEROY 2014[518]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	510 patients (CHC n=255, CHB n=255)
Countries and Settings	Clinique Universitaire d'Hepato-Gastroenterologie, CHU de Grenoble, France
Funding	'Direction de la Recherche Clinique' Grenoble University Hospital
Age, gender, ethnicity, ALT (U/l):	Age: 46.5 ± 12.1, gender: 56.9% male, ethnicity: not reported, ALT: 59.5 ± 56.5 IU/L
Patient characteristics	Population: Consecutive naïve patients with chronic HCV addressed to the centre were considered for inclusion if they had

Study	LEROY 2014[518]
	interpretable liver biopsy and a fasting serum sample collected the same day. Inclusion: Presence of HCV RNA for at least 6 months. During the inclusion period a liver biopsy was systematically recommended and performed as part of clinical care for staging and grading liver disease Exclusion: <18 years, HBV or HIV co-infection, hepatitis delta virus, other causes of liver disease alcohol consumption over 30g/day, hepatocellular carcinoma, Gilbert's disease, chronic hemolysis, inflammatory syndrome, previous antiviral treatment, previous liver transplantation.
Index test (including threshold and whether threshold pre-specified)	FibroTest (optimal calculated according to Youden's Index which maximises the sum of sensitivity and specificity): Parameters were measured in fresh blood samples. Alpha-2 macroglobulin, haptoglobin and apolipoprotein A1 were measured by immunonephelometry using a BN ProsPec analyser. GGT and bilirubin were measured using a Roche modular analyser with reagents from the manufacturer and CFAS. Using laboratory values FibroTest was purchased from Biopredictive.
Reference standard	Percutaneous liver biopsy was performed by 2 senior operators using a 16G disposable needle. Tissue samples were fixed in formalin and embedded in paraffin. All specimens were analysed twice by a single senior pathologist. Who was unaware of biochemical markers. Liver fibrosis was evaluated according to the METAVIR system.
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	Nr just for HCV group 56/510 (11% in whole group)
Target condition	
Results: FibroTest AUC (95% CI): 0.87 (0.8-0.94) Optimal cut-off threshold (if calculated): 0.63 (calculated according to Youden method) Threshold 0.63 (optimal): Sensitivity: 74 Specificity: 82 PPV: 53 NPV: 96 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported	

Study	LEROY 2014[518]
	FN: Not reported TN: Not reported Threshold 0.74 (published): Sensitivity: 59 Specificity: 91 PPV: 45 NPV: 95 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Steatosis, Fibrometer, Hepascore. Applicability of HCV cut-offs to HBV. Overall the diagnostic performance of blood tests is similar in hepatitis B and C. The risk of underestimating significant fibrosis and cirrhosis is greater in hepatitis B and cannot be entirely corrected by use of more stringent cut offs. Any complications associated with tests reported: Not reported
General limitations according to QUADAS II	Liver biopsy length <25mm

Study	LUPSORPLANTON 2013[545]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	N=1202 consecutive CHC patients. May 2007 and December 2012

Study	LUPSORPLANTON 2013[545]
Countries and Settings	Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania
Funding	Part of a research project from the "Iuliu-Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.
Age, gender, ethnicity, ALT (U/l):	Age: mean 50.61 (10.84) years, range 21-85; Male/female: 465/737; ethnicity: not reported; ALT: 86.16 (66.88) U/l
Patient characteristics	Population: chronic hepatitis C (CHC) patients Inclusion: positive serum HCV-RNA and underwent percutaneous LB for disease grading and staging Exclusion: evidence of ascites on physical or ultrasound examination (ascites is a physical limitation of the technique because elastic waves do not propagate through fluids), co-infection with HBV and/or HIV, active infectious diseases other than HCV, severe cholestasis, right heart failure, history of alcohol consumption (>30 g/day in men and >20 g/day in women) and pregnancy
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan; optimal cut-off values were chosen to maximize the sum of sensitivity and specificity): after an overnight fast, each patient was examined in a dorsal decubitus position, with the right arm in maximum abduction. The Fibroscan transducer was placed perpendicularly to the intercostal space, in an area free of any large vascular structure. The median value of 10 successful acquisitions was recorded. We considered as representative 10 successful acquisitions, regardless of the success rate (SR) as long as 10 valid LSMs were obtained and with an IQR lower than 30% of the median value.
Reference standard	Liver biopsy (METAVIR F4): performed using the TruCut technique with a 1.8 mm (14G) diameter automatic needle device – Biopsy Gun (Bard GMBH, Karlsruhe, Germany). Only LB specimens with more than 6 intact portal tracts were eligible for evaluation. Median size of the LB sample was 11 (8-27) mm, with a median of 11 (7-30) portal spaces
Time between index test and reference standard	TE 1 day prior to biopsy
Prevalence of cirrhosis according to reference standard	374/1202 (31.1%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.970 (0.969-0.979) (also reports adjusted DANA AUC: 0.9774, no significant difference with AUC) Optimal cut-off threshold (if calculated): 13.2kPa Threshold: 13.2kPa (optimal) Sensitivity: 93.75 (90.8-96.0) Specificity: 93.31 (91.4-94.9)	

Study	LUPSORPLANTON 2013[545]
PPV: 86.5 NPV: 97.0 +ve/-ve likelihood ratios: 14.01 / 0.067 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Any complications associated with tests reported: In 27 patients (2.2%) no valid measurement was obtained. In 11.2% of cases, the SR was <60%, although 10 valid LSM were recorded.	
General limitations according to QUADAS II Unclear who performed fibrosis staging of biopsy and whether it was performed without knowledge of the index test result or clinical data Liver biopsy less than 10 portal tracts	

Study	MACIAS 2006[551]
Study type	Retrospective cross sectional
Number of studies (number of participants). Recruitment period.	1 study (N=357; only n=263 with adequate liver biopsy included in the analysis reported here). Liver biopsy between January 1991 and January 2005
Countries and Settings	Southern Spain, 5 hospitals
Funding	Fondo de Investigaciones Sanitarias, Fundacio Barcelona SIDA, Fundacion para la Investigacion y la Prevencion del SIDA en Espana
Age, gender, ethnicity	Age, mean (range): 37 (34-41) ; Male/female: 84% male Ethnicity: not reported ; ALT (U/l): 80 (UI/L) (54-133)
Patient characteristics	Population: Hepatitis C and HIV co-infected Inclusion: Admitted for liver biopsy to establish prognosis and indicate therapy for chronic hepatitis C.

Study	MACIAS 2006[551]
	Exclusion: Hep B, other causes of liver disease (autoimmune, tumoral, biliary, vascular-associated), prior anti-HCV therapy.
Index test (including threshold and whether threshold pre-specified)	AST:ALT ratio (cut-off value 1, pre-specified from published threshold) Platelet count (cut-off value 150x109/l, pre-specified from published threshold) APRI (cut-off value 1 and 2, pre-specified from published thresholds): calculated by assigning arbitrary scores to 3 laboratory parameters and summing them with a possible value of 0 to 11.
Reference standard	Liver biopsy; Knodall F4. A minimum liver biopsy length of 10 mm was required but only biopsies above 15 mm were included in analysis. Specimens were immediately placed in buffer formalin. After 24 hours of fixation they were embedded in paraffin using routine methods. Histological evaluation was made on sections stained with haematoxylin-eosin and Masson's trichrome by a single pathologist who was blinded to clinical data.
Time between index test and reference standard	Within 1 month
Prevalence of cirrhosis according to reference standard	40/263 (15%)
Target condition	Cirrhosis
Results: APRI AUC (95% CI): 0.79 (0.71-0.87) Optimal cut-off threshold (if calculated): Not reported Threshold: 1 (published cut-off) Sensitivity: 78 Specificity: 57 PPV: 24 NPV: 93 +ve/-ve likelihood ratios: Not reported TP: 31 FP: 97 FN: 9 TN: 126 Threshold: 2 (published cut-off)	

Study	MACIAS 2006[551]
Sensitivity: 53 Specificity: 89 PPV: 46 NPV: 91 +ve/-ve likelihood ratios: Not reported TP: 21 FP: 25 FN: 19 TN: 198 Results: AST/ALT AUC (95% CI): 0.6 (0.5-0.69) Optimal cut-off threshold (if calculated): Not reported Threshold: 1 (published cut-off) Sensitivity: 38 Specificity: 77 PPV: 23 NPV: 87 +ve/-ve likelihood ratios: Not reported TP: 15 FP: 51 FN:25 TN:172 Results: Platelet count AUC (95% CI): 0.79 (0.72-0.86) Optimal cut-off threshold (if calculated): Not reported Threshold: 150x109/l (published cut-off) Sensitivity: 63	

Study	MACIAS 2006[551]
	Specificity: 77 (incorrectly reported in paper, calculated from 2x2 table) PPV: 33 NPV: 92 +ve/-ve likelihood ratios: Not reported TP: 25 FP: 51 FN: 15 TN: 172 Other measures reported and conclusions: Forns and Bonacini models, Saadeh model. The diagnostic accuracy of these models was lower in HIV/HCV coinfected patients than in the validation studies performed in HCV monoinfected patients, however simple fibrosis tests may render liver biopsy unnecessary in deciding anti-HCV treatment in over one-third of patients with HIV infection and chronic hepatitis C. Any complications associated with tests reported: Not reported
	General limitations according to QUADAS II Not all patients included in the analysis Liver biopsy sample <25mm

Study	MARTINEZ 2011A[571]
Study type	Cohort study
Number of studies (number of participants). Recruitment period.	N=340. August 2001 – November 2007
Countries and Settings	Liver Unit, Hospital Clinic, IDIBAPS and Ciberehd, Barcelona, Spain
Funding	Not reported
Age, gender, ethnicity	Mean age = 47.7 years, male/female: 217/123. Ethnicity: not reported; ALT (presented as ALT/upper limit of normal): 2.94 ±

Study	MARTINEZ 2011A[571]
	2.5
Patient characteristics	Population: Chronic hepatitis C patients (established by the presence of HCV RNA using polymerase chain reaction assays) tested prior to antiviral therapy Inclusion: Consecutive patients who underwent antiviral treatment and underwent a pretreatment liver biopsy within 6 months prior to the initiation of therapy Exclusion: Patients with HIV, hepatitis B or other causes of chronic liver disease were not included
Index test (including threshold and whether threshold pre-specified)	APRI, FIB-4, ELF (cut-off values as pre-published): measured in blood samples collected on the day of antiviral treatment initiation, all according to standard cut-offs (also taken following antiviral treatment). Patient values were entered into the ELF algorithm, where the original score was simplified by removing age (J. Parkes, unpublished observation)
Reference standard	Liver biopsy (METAVIR F4): Percutaneous liver biopsies were performed under local anaesthesia and ultrasound guidance with a Tru-Cut 14 gauge needle (Angiomed, Bard, Karlsruhe, Germany) by expert radiologists. A minimum length of 10 mm and the presence of 6 portal tracts were required for diagnosis. Histological grade and stage were determined by the same pathologist, who was blinded to patient data. Liver fibrosis was considered significant (stages 2, 3 or 4) when it spread out of the portal tract. Mean biopsy length was 15 mm (range 10-30 mm) with 55% of specimens >15 mm, 16% >20 mm and 1% >25 mm. Mean number of portal tracts was 9.
Time between index test and reference standard	Within 6 months
Prevalence of cirrhosis according to reference standard	124/340 (36.4%
Target condition	Cirrhosis
Results: APRI AUC (95% CI):0.86 (0.82-0.90) standard threshold Optimal cut-off threshold (if calculated): Threshold: 1 Sensitivity: 82 Specificity: 74 PPV: 64	

Study	MARTINEZ 2011A[571]
NPV: 88 +ve/-ve likelihood ratios: 3.2/0.2 Diagnostic odds ratio: 16 TP: 102 FP: 57 FN: 22 TN: 159 Threshold: 2 Sensitivity: 49 Specificity: 91 PPV: 75 NPV: 76 +ve/-ve likelihood ratios: 5.4/0.6 Diagnostic odds ratio: 9 TP: 61 FP: 20 FN: 63 TN: 196 Results: ELF AUC (95% CI) 0.82 (0.78-0.87) standard threshold Optimal cut-off threshold (if calculated): Threshold: 0.06 Sensitivity: 90 Specificity: 53 PPV: 52 NPV: 90 +ve/-ve likelihood ratios: 1.9/0.2 Diagnostic odds ratio: 9.5	

Study	MARTINEZ 2011A[571]
TP: 111 FP: 102 FN: 13 TN: 114 Threshold: 1.73 Sensitivity: 52 Specificity: 90 PPV: 76 NPV: 77 +ve/-ve likelihood ratios: 5.2/0.5 Diagnostic odds ratio: 10.4 TP: 65 FP: 21 FN: 59 TN: 195 Results: FIB4 AUC (95% CI) 0.89 (0.85-0.92) standard threshold Optimal cut-off threshold (if calculated): Not reported Threshold: Not reported Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	MARTINEZ 2011A[571]
Other measures reported and conclusions: Extracellular matrix tests and virological response to treatment. Simple panel markers and ELF score are accurate at identifying significant fibrosis and cirrhosis in chronic hepatitis C. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Time between reference and index tests up to 6 months. Liver biopsy <10 portal tracts	

Study	MUELLER 2010[613]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	N= 106 patients with histologically staged ALD, 5 excluded because of invalid TE, final analysis 101 (second validation part of study – includes diagnostic accuracy of overall population, in addition to internal validation of accuracy for proposed algorithm depending on glutamic oxaloacetic transaminase (GOT) level)
Countries and Settings	Germany
Funding	The Dietmar Hopp Foundation and the Manfred Lautenschlager Foundation
Age, gender, ethnicity	Age, mean (SD): 53.6 (10.6) years; Male/female: 73/28; Ethnicity: not reported; ALT (IU/l):
Patient characteristics	Population: alcohol-related liver disease (ALD) Inclusion: patients with histologically staged ALD, a full set of blood tests and FS examination at the time of liver biopsy Exclusion: ultrasound examination was routinely performed in addition to FS measurements to exclude extrahepatic cholestasis, liver congestion or liver tumors.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (FibroScan, using the M probe; cut-off of 12.5kPa based on previous studies and cut-off 11.5 to give optimal sensitivity): the tip of the probe transducer was placed on the skin between the rib bones and the level of the right lobe of the liver. The measurement depth was between 25 and 65 mm below the skin surface. Ten measurements were

Study	MUELLER 2010[613]
	performed with success rates of at least 60%. FS measurements with an IQR higher than 40% were excluded.
Reference standard	Liver biopsy (Kleiner F4): All biopsy specimens were analysed independently by 2 experienced pathologists blinded to the results of FS and other clinical data. Only biopsies > 15 mm were included.
Time between index test and reference standard	Same time
Prevalence of cirrhosis according to reference standard	26/101 (25.7%)
Target condition	Cirrhosis
Results: AUC (95% CI): 0.921 (0.87-0.97) Optimal cut-off threshold (if calculated): 11.5kPa (to give 100% sensitivity) Threshold: 11.5kPa (optimal sensitivity) Sensitivity: 100 Specificity: 77 PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 12.5kPa (pre-published) Sensitivity: 96 Specificity: 80 PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported	

Study	MUELLER 2010[613]
TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: development and internal validation of an algorithm for TE in people with ALD based on subgrouping into degree of alcoholic steatohepatitis and GOT level (exclusion of patients with GOT >100U/L, but not with GOT >50U/L, increased the accuracy of TE). Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random recruitment not reported Liver biopsy sample <25mm	

Study	MYERS 2012B[616]
Study type	Multicentre cross-sectional study
Number of studies (number of participants). Recruitment period.	N=276 total. 'Viral' group comprised hepatitis C and B therefore did not extract. NAFLD group = 127 Recruitment period July 2009-July 2010
Countries and Settings	Four academic hospitals in Canada
Funding	Echosens, Paris
Age, gender, ethnicity	Whole group data (n=276): Age, mean (range): 50 (43-57) ; Male/female: 63% male Ethnicity: not reported ; ALT (IU/l): 55 (36-87)
Patient characteristics	Population: NAFLD, BMI≥28 Inclusion: Patients who had undergone percutaneous liver biopsy within 6 months or were scheduled to undergo one in the next month were eligible. Exclusion: Pregnancy, ascities, implantable cardiac devices, previous liver transplant, terminal disease

Study	MYERS 2012B[616]
Index test (including threshold and whether threshold pre-specified)	Transient elastography (FibroScan M probe and Fibroscan XL probe): (optimal liver stiffness cut-offs that maximized the sum of sensitivity and specificity: M probe 22.3kPa, XL probe 16kPa) performed by 9 experienced operators as per manufacturer's instructions. Both M (standard) and XL (specifically designed for obese patients) were used on all subjects. No successful measurements after 10 attempts was deemed a failure. Exams with fewer than 10 valid measurements, an IQR>30% or <60% were considered unreliable. Study aims to compare the M and XL probe in the same patients. Note: the Fibroscan XL probe has been designed specifically for use in obese patients by utilisation of a lower frequency and more sensitive ultrasonic transducer, a deeper focal length, a larger vibration amplitude and a greater depth of measurement below the skin surface.
Reference standard	Liver biopsy (METAVIR F4): specimens analysed by 2 experienced hepatopathologists without knowledge of other clinical data. Biopsies less than 15 mm in length and/or with fewer than 6 portal triads were deemed uninterpretable (length range 15-53mm, portal tracts range 7-39), obtained under ultrasound guidance. Tissue was fixed, paraffin-embedded and stained with at least hematoxylin, eosin and Masson's trichrome
Time between index test and reference standard	Within 6 months
Prevalence of cirrhosis according to reference standard	32/276, 12%, not reported for NAFLD population separately.
Target condition	Cirrhosis
Results: Fibroscan M probe AUC (95% CI): 0.88 (0.75-1.00) Optimal cut-off threshold (if calculated): 22.3kPa Threshold: 22.3kPa Sensitivity: 80 (28-99) Specificity: 91 (82-97) PPV: 40 (12-74) NPV: 98 (92-100) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	MYERS 2012B[616]
Fibroscan XL probe AUC (95% CI): 0.95 (0.89-1.00) Optimal cut-off threshold (if calculated): 16.0kPa Threshold: 16.0kPa Sensitivity: 100 (54-100) Specificity: 91 (84-96) PPV: 40 (16-68) NPV: 100 (96-100) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Invalid liver stiffness measurements in whole population: XL probe 1.1%, M probe 16%. Failure of the M probe increased as BMI increased. Also reported data for a mixed hep B and C population (did not use) Comparable with the M probe, the FibroScan XL probe reduces TE failure and facilitates reliable LSM in obese patients. Although the probes have comparable accuracy, lower liver stiffness cutoffs will be necessary when the XL probe is used to non-invasively assess liver fibrosis. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Random or consecutive recruitment not reported Up to 6 months between index test and reference standard Liver biopsy sample <25mm and 10 portal tracts.	

Study	RIZZO 2011[735]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=146 consecutive patients evaluated, 5 excluded for suboptimal liver biopsy, 2 excluded with alcohol abuse, enrolled n=139). Recruitment between November 2008 and October 2009
Countries and Settings	Italy, 3 Hospitals (Infectious Diseases Units of the Garibaldi Nesima and Ferrarotto Hospitals in Catania and to the Hepatology Unit of the University Hospital, Palermo)
Funding	None
Age, gender, ethnicity	Age, mean (SD): 55 (12); Male/female: 83/56; Ethnicity: not reported; ALT (U/l): 77.2 (33.0)
Patient characteristics	Population: chronic hepatitis C (viral and histologic diagnosis) Inclusion: presence of active HCV replication, and on a liver histology consistent with chronic hepatitis Exclusion: HBV/ HIV coinfection, alcohol abuse (> 20 g/ day in the last year or more, evaluated by questionnaire), with Child B or C cirrhosis, and those under antiviral treatment
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan, Echosens, France)(cut-off 11kPa, determined as optimal cut-off by Kolmogorov – Smirnov index): done by 2 expert physicians, 1 in Palermo and 1 in Catania, according to the manufacturer ' s instructions. Both examiners were blinded to clinical and pathological data. ARFI (cut-off 2m/s, determined as optimal cut-off by Kolmogorov – Smirnov index): B-mode standard ultrasonography scanning and ARFI elastography were performed using a Siemens Acuson S2000 (Siemens AG, Erlangen, Germany) with a 4Cl transducer. Liver stiffness was measured with ARFI elastography by 2 independent investigators: 1 in Catania and 1 in Palermo. Both investigators were blinded to all patients ' clinical, serological, and histological data. ARFI elastography was performed on fasting patients, choosing as the target the right lobe of the liver, which was accessed through the intercostal spaces. The velocity of the shear wave (in m/s) in the liver tissue was collected and recorded from 20 different sites, 5 sites for each segments (V, VI, VII, and VIII) within the right lobe. A median of the 20 results has been calculated.
Reference standard	Liver biopsy (METAVIR F4): Liver biopsy specimens were obtained using Menghini 16G disposable needles. All biopsy specimens contained at least 10 portal tracts and were minimum 1.5 cm in length. All biopsy specimens were coded and evaluated by a single experienced pathologist, who was blinded to the patients ' clinical and imaging results.
Time between index test and reference standard	Within 6 months, median 3 months (range 1-6 months)
Prevalence of cirrhosis according to reference standard	30/139 (21.6%)

Study	RIZZO 2011[735]
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.80 (0.72 – 0.86) Optimal cut-off threshold (if calculated): 11kPa Threshold: 11kPa (optimal) Sensitivity: 70 Specificity: 82 PPV: 53 NPV: 90 +ve/-ve likelihood ratios: 3.9 / 0.4 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: ARFI AUC (95% CI): 0.89 (0.83 – 0.94) Optimal cut-off threshold (if calculated): 2m/s Threshold: 2m/s (optimal) Sensitivity: 83 Specificity: 86 PPV: 63 NPV: 95 +ve/-ve likelihood ratios: 6.1 / 0.2 TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	RIZZO 2011[735]
Other measures reported and conclusions: TE was unreliable in 9 patients (6.5 %). In an extra analysis to check interobserver agreement, there was no significant difference between the ARFI values of the 21 patients obtained from the 2 different sonographers. ARFI performance was not statistically significantly higher than TE performances for the diagnosis of cirrhosis (P = 0.09). Also analysed partial AUC Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Up to 6 months between index test and reference standard Liver biopsy sample < 25mm	

Study	SANCHEZ-CONDE 2010[762]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study. N=105 (3 excluded due to inadequate biopsies, 2 excluded due to uninterpretable TE). N=100 included in analysis. January 2007-January 2008
Countries and Settings	HIV outpatient clinic of 2 teaching hospitals in Spain, Madrid
Funding	Spanish AIDS investigation group and Spanish Health Research Fund
Age, gender, ethnicity	Age, mean (range): 42 (39-46); Male/female: 29% female Ethnicity: not reported; ALT (U/l): 67.6 ± 41.8 IU/ml
Patient characteristics	Population: Hepatitis C and HIV co-infected, mostly potential candidates for HCV therapy Inclusion: Detectable HCV-RNA by polymerase chain reaction Exclusion: Hepatic decompensation, hepatitis B, anti HCV therapy.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan): optimal cut-off values based on the highest NPV with an acceptable PPV higher than 50%. Performed according to standard procedure. Performed by the same trained personnel at each centre. IQR < 30% and procedures with at least 10 validated measurements and a success rate of 60% accepted. APRI, FIB-4: diagnostic accuracy for significant fibrosis only
Reference standard	Liver biopsy (METAVIR F4): ultrasound routinely performed to determine percutaneous biopsy site. Biopsies evaluated by an experienced pathologist who had no knowledge of clinical and laboratory data. Biopsies were '25mm in length in most cases'. Formalin-fixed, paraffin-embedded liver tissue was stained by haematoxylin-eosin, Mason's trichrome and Perl's iron.

Study	SANCHEZ-CONDE 2010[762]
Time between index test and reference standard	No more than 6 months
Prevalence of cirrhosis according to reference standard	8/100, 8%
Target condition	Cirrhosis
Results: Transient elastography AUC (95% CI): 0.99 (0.97-1.00) Optimal cut-off threshold (if calculated): (chosen threshold) 14 kPa Threshold: 14kPa (optimal) Sensitivity: 100 (93.7-100.0) Specificity: 93.5 (87.9-99.1) PPV: 57.1 (27.6-86.6) NPV: 100 (99.4-100) +ve/-ve likelihood ratios: 15.33 (7.07-33.24) / not reported TP: 8 FP: 6 FN: 0 TN: 86 Other measures reported and conclusions: TE accurately predicted liver fibrosis and outperformed other simple non-invasive indexes in HIV/HCV-coinfected patients. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Random or consecutive recruitment not reported Up to 6 months between index test and reference standard Some liver biopsies <25mm (unclear how many)	

Study	Shehab 2014[798]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study. N=994 (split into training and validation cohorts for the development of a new fibrosis marker, PLASA. But, all patients used for diagnostic accuracy of index tests measures reported here, minus those without available data on all variables, final analysis N=842). Consecutive treatment naïve patients with chronic hepatitis C. January 2010-October 2013
Countries and Settings	Two hospitals in Egypt
Funding	Not reported
Age, gender, ethnicity	Age, mean (SD): 42.4 (9.7); Male/female 875/119; Ethnicity: not reported; ALT (U/l): 56.6 (14-350)
Patient characteristics	Population: treatment-naïve patients with chronic HV Inclusion: positive HCV RNA, compensated liver disease and availability of serum biomarker results done within 1 month prior to liver biopsy. Exclusion: coinfection with HBV or HIV; other causes of liver disease; alcohol consumption higher than 20g/day, HCC, prior liver transplant; Gilbert disease; chronic haemolysis; previous antiviral treatment and use of medications that could alter the measured laboratory parameters.
Index test (including threshold and whether threshold pre-specified)	APRI; FIB4: from routine lab parameters and basic clinical data, retrieved from medical records. Only lab tests performed within 1 month before the biopsy were included. APRI (pre-published cut-off values of 0.5 and 2.0): [(AST/ULN) x100] / platelet count 109/l FIB4 (pre-published cut-off of 3.25): [age (years) x AST (IU/l)] / platelet count 109/l x ALT (IU/l)1/2
Reference standard	Liver biopsy (METAVIR F4): patients with biopsy samples shorter than 1.5 cm or containing less than 7 portal tracts were excluded. A single experienced pathologist examined the biopsy specimens in each centre. This person was blind to the laboratory data of the patient.
Time between index test and reference standard	Within 1 month
Prevalence of cirrhosis according to reference standard	260/994 (26.2%). Not reported for the 842 included in the final analysis.

Study	Shehab 2014[798]
Target condition	Cirrhosis
Results: APRI AUC (95% CI): not reported Optimal cut-off threshold (if calculated): not reported Threshold: 0.5 (published) Sensitivity: 100 Specificity: 12.8 PPV: 5.3 NPV: 100 +ve/-ve likelihood ratios: not reported TP: not reported FP: not reported FN: not reported TN: not reported Threshold: 2.0 (published) Sensitivity: 15.4 Specificity: 96 PPV: 15.8 NPV: 95.9 +ve/-ve likelihood ratios: not reported TP: not reported FP: not reported FN: not reported TN: not reported Results: FIB4 AUC (95% CI): not reported Optimal cut-off threshold (if calculated): not reported	

Study	Shehab 2014[798]
Threshold: 3.25 (published) Sensitivity: 28.2 Specificity: 93.5 PPV: 17.5 NPV: 96.4 +ve/-ve likelihood ratios: not reported TP: not reported FP: not reported FN: not reported TN: not reported Other measures reported and conclusions: Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Liver biopsies <25mm and <10 portal tracts Data were not available for all variables for a large proportion of patients and only 842 included in the final analysis.	

Study	SILVIA JUNIOR 2014[806]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=51 consecutive patients). Recruitment from January 2012-March 2013

Study	SILVIA JUNIOR 2014[806]
Countries and Settings	Santa Casa de Sao Paulo Hospital, Brazil
Funding	Not stated
Age, gender, ethnicity	Age, mean (SD): 53.8±1.53 ; Male/female: 18 male, 33 female Ethnicity: not reported ; ALT (IU/l): 60.55 ± 6.3
Patient characteristics	Population: Chronic untreated hepatitis C Inclusion: CHC diagnosis was established by the presence of hepatitis C virus RNA using qualitative polymerase chain reaction. Exclusion: HIV, Hepatitis B, alcohol abuse, cholestatic chronic hepatitis, non-alcoholic steatohepatitis, autoimmune chronic hepatitis, hemochromatosis, Wilson's disease, hepatocellular carcinoma, prior liver transplantation, prior interferon therapy, immunosuppressive therapy.
Index test (including threshold and whether threshold pre-specified)	ARFI elastography (optimal cut-off value 1.95m/s determined by a common optimisation step that maximised the sum of the sensitivities in predicting the single stages): performed with Siemens Acuson S2000 ultrasound system (Siemens Medical Solutions, Brazil) using a standard ultrasonographic probe on the right lobe of the liver. All procedures performed in a single centre by a single physician, experienced in digestive system ultrasonography and blinded to the clinical, serological and histological data. A median was calculated based on 10 measurements. APRI (optimal cut-off value 1.71 determined by a common optimisation step that maximised the sum of the sensitivities in predicting the single stages): [(AST/ULN) x100] / platelet count 10^9/l FIB4: [age (years) x AST (IU/l)] / platelet count 10^9/l x ALT (IU/l)$^{1/2}$ Blood tests performed within the same week as liver biopsy (ARFI and FIB-4).
Reference standard	Liver biopsy METAVIR F4. Biopsy length median 20.6mm (range 15-28mm), median portal tracts 10.1 (range 8-14). Percutaneous liver biopsy was performed by senior operators using the TruCut technique with manual or semi automatic instruments. Tissue was fixed in formalin paraffin-embedded and stained with hematoxylin-eosin and Masson's trichrome. Specialised were analysed by an expert pathologist blinded to biological and clinical data.
Time between index test and reference standard	Up to 6 months (median 2.8 months)
Prevalence of cirrhosis according to	9/51 (17.6%)

Study	SILVIA JUNIOR 2014[806]
reference standard	
Target condition	Cirrhosis
Results: ARFI AUC (95% CI): 0.98 (CI not reported) Optimal cut-off threshold (if calculated): 1.95m/s Threshold: 1.95 m/s (optimal) Sensitivity: 100 Specificity: 95.2 PPV: 81.8 NPV: 100 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.89 (CI not reported, value taken from table, incorrectly reported in text) Optimal cut-off threshold (if calculated): 1.71 Threshold 1.71 (optimal): Sensitivity: 66.7 Specificity: 92.9 PPV: 60 NPV: 90.5 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported	

Study	SILVIA JUNIOR 2014[806]
FN: Not reported TN: Not reported Results: FIB4 AUC (95% CI): 0.94 (CI not reported) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Forns score, King score. ARFI elastography had very good accuracy for the assessment of fibrosis and was more effective for the prediction of cirrhosis than the blood tests. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Up to 6 months between index test and reference standard Liver biopsies <25mm	

Study	SIRLI 2010[817]
Study type	Retrospective cohort study
Number of studies (number of participants). Recruitment period.	1 study (N=150; TE measurements only obtained for 144 patients) Recruited from January – December 2008
Countries and Settings	Department of Gastroenterology and Hepatology, Timisoara, Romania
Funding	Not stated
Age, gender, ethnicity	Age, mean (SD): 50.1± 10.3 ; Male/female: 48/102; Ethnicity: not stated ; ALT (U/l): not stated
Patient characteristics	Population: Chronic hepatitis C Inclusion: Normal iron load and ceruloplasmin Exclusion: Ascites, Hepatitis B, alcohol abuse, cholestasis, steatosis, autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan): (optimal cut-off value of 13.3kPa chosen to maximise the sum of the sensitivity and specificity): performed by 3 experienced physicians by standard method. 10 valid measurements. Only those with a success rate of at least 60% with IQR <30%. APRI (optimal cut-off value of 1.38 chosen to maximise the sum of the sensitivity and specificity): [(AST/ULN) x100] / platelet count 10^9/l FIB-4 (optimal cut-off value of 2.3122 chosen to maximise the sum of the sensitivity and specificity): [age (years) x AST (IU/l)] / platelet count 10^9/l x ALT (IU/l)$^{1/2}$ Platelet count (optimal cut-off value of 155000/mm^3 chosen to maximise the sum of the sensitivity and specificity) Blood collected in the same session as TE and liver biopsy.
Reference standard	Liver biopsy (METAVIR F4). Echoassisted using Menghini-type modified needles, 1.4 and 1.6 mm in diameter. Only biopsies of at least 20mm and 8 portal tracts considered adequate and included in the study. Assessed by a senior pathologist.
Time between index test and reference standard	Same day

Study	SIRLI 2010[817]
Prevalence of cirrhosis according to reference standard	15/150 (10%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.979 (0.85-0.951) Optimal cut-off threshold (if calculated): 13.3kPa Threshold 13.3kPa (optimal): Sensitivity: 93.3 Specificity: 96.1 PPV: 73.7 NPV: 99.2 +ve/-ve likelihood ratios: 24.08/0.07 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.909 (0.85-0.951) Optimal cut-off threshold (if calculated): 1.38 Threshold 1.38 (optimal): Sensitivity: 93.3 Specificity: 83 PPV: 37.8 NPV: 99 +ve/-ve likelihood ratios: 5.48/0.08 TP: Not reported FP: Not reported	

Study	SIRLI 2010[817]
FN: Not reported TN: Not reported Results: FIB-4 AUC (95% CI): 0.842 (0.772-0.898) Optimal cut-off threshold (if calculated): 2.3122 Threshold 2.3122 (optimal): Sensitivity: 80 Specificity: 77.8 PPV: 28.6 NPV: 97.2 +ve/-ve likelihood ratios: 3.6/0.26 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: Platelet count AUC (95% CI): 0.899 (0.838-0.943) Optimal cut-off threshold (if calculated): 155000mm^3 Threshold 155000mm^3 (optimal): Sensitivity: 86.7 Specificity: 83.7 PPV: 37.1 NPV: 98.3 +ve/-ve likelihood ratios: 5.32 / 0.16 TP: Not reported FP: Not reported FN: Not reported	

Study	SIRLI 2010[817]
TN: Not reported Other measures reported and conclusions: Forns test, Lok test LSM better than blood fibrosis tests for predicting cirrhosis but all had excellent predictive value Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random selection not reported. Unknown if the reference standard results were interpreted without knowledge of the index test results Liver biopsies <25mm and <10 portal tracts	

Study	SPOREA2011A[836]
Study type	Prospective cross sectional
Number of studies (number of participants). Recruitment period.	1 study (N=197 patients). Recruitment period not reported
Countries and Settings	Romania. Two university hospitals
Funding	None reported
Age, gender, ethnicity	Age, mean (SD): 50(9.8); Male/female: 78/119; Ethnicity: not reported; ALT (U/l): not reported
Patient characteristics	Population: chronic HCV hepatitis Inclusion: anti HCV antibodies positive, with or without cytolysis for at least 6 months, PCR HCV RNA positive). Exclusion: Patients with other causes of chronic hepatitis (HBV infection, chronic alcohol abuse, cholestatic chronic hepatitis, nonalcoholic steatohepatitis, autoimmune chronic hepatitis, haemochromatosis, Wilson's disease)

Study	SPOREA2011A[836]
Index test (including threshold and whether threshold pre-specified)	Transient elastography (optimal cut-off value 12.2kPa was chosen to maximize the sum of sensitivity and specificity): Fibroscan device (Echosens, Paris, France) by experienced physicians (more than 500 TE), blinded to the results of LB and ARFI measurements. In each patient, 10 valid measurements were performed, after which a median value of LS was obtained. Only patients in which LS measurements by means of TE had a success rate of at least 60%, with an IQR < 30%, were included. ARFI (optimal cut-off value 1.8m/s was chosen to maximize the sum of sensitivity and specificity): ultrasound device ACUSON S2000 (Siemens). Scanning was performed between the ribs in the right liver lobe in order to avoid cardiac motion (approximately in the place where we usually perform LB), 1 cm under the capsule. 10 measurements in every patient, and a median value was calculated, the result being measured in m/s. Only patients in which LS measurements by means of ARFI had a success rate of at least 60%, with an IQR < 30%, were included. Operators were blinded to the results of LB and TE measurements. Combination of TE **and** ARFI (values both for TE and ARFI above the mentioned cut-offs) Combination of TE **or** ARFI (values both for TE and ARFI above the mentioned cut-offs)
Reference standard	Liver biopsy (METAVIR F4): echoguided TruCut technique, with a 1.8 mm (14 G) diameter automatic needle device-Biopty Gun (Bard GMBh), or echoassisted, using Menghini type modified needles, 1.4 and 1.6 mm in diameter. Only LB fragments including at least 6 portal tracts were included. The LBs were assessed, by a senior pathologist (1 in each center) blinded to the results of TE and ARFI measurements.
Time between index test and reference standard	Same session
Prevalence of cirrhosis according to reference standard	53/197 (26.9%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.97 Optimal cut-off threshold (if calculated): 12.2kPa Threshold: 12.2kPa (optimal)	

Study	SPOREA2011A[836]
Sensitivity: 96.2 Specificity: 89.6 PPV: 78.1 NPV: 98.3 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported <u>Results: ARFI</u> AUC (95% CI): 0.91 Optimal cut-off threshold (if calculated): 1.8m/s <u>Threshold: 1.8m/s (optimal)</u> Sensitivity: 90.4 Specificity: 85.6 PPV: 50.3 NPV: 95.8 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported <u>Results: Combination of Fibroscan and ARFI</u> AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported <u>Threshold: values both for TE and ARFI above the cut-offs12.2 kPa and 1.8m/s (optimal)</u> Sensitivity: 84.9	

Study	SPOREA2011A[836]
Specificity: 94.4 PPV: 84.9 NPV: 94.4 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: Combination of Fibroscan or ARFI AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: values for TE or ARFI above the cut-offs12.2 kPa or 1.8m/s (optimal) Sensitivity: 96.2 Specificity: 83.3 PPV: 68.0 NPV: 98.3 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: obtained valid TE measurements in 187/197 patients (94.9%) and valid ARFI measurements in 191/197 patients (96.9%). Any complications associated with tests reported: Not reported	

Study	SPOREA2011A[836]
General limitations according to QUADAS II Consecutive or random selection not reported. Liver biopsy sample < 10 portal tracts.	

Study	SPOREA 2012A [835] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[247,287,548,692,834] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[306,854] (presumed authors were contacted for further information).
Study type	Retrospective multi-centre
Number of studies (number of participants). Recruitment period.	914 (10 centres, 5 countries) ARFI obtained in 911 TE measured in 400
Countries and Settings	Romania, Japan, Germany, Italy, Austria
Funding	Not reported (however 4 authors are associated with Siemens and 1 is associated with Echosens)
Age, gender, ethnicity, ALT (U/l):	Mean age: 55.7 ± 13.1, gender: 53.7% women , ethnicity: 49.6% European, 50.4% Asian, ALT: 1.6 ± 1.7 x ULN
Patient characteristics	Population: Chronic HCV Inclusion: Positive anti-HCV antibodies and positive PCR HCV RNA for more than 6 months. Homogenous liver structure (without liver masses). Exclusion: HIV or hepatitis B co-infection, ascities
Index test (including threshold and whether threshold pre-specified)	ARFI (Optimal cut-off values were chosen so that the sum of sensitivity (Se) and specificity (Sp) would be the highest) – performed in all patients with a Siemens Acuson S2000TM ultrasound system with 4Cl transducers. Scanning was performed with a right inter-costal approach, in the right liver lobe, segment V-VIII, 1-2cm (Hyogo, Timisoara) or 2-3 cm (other centres) under the liver capsule, with minimal scanning pressure applied by the operator, while the patients were asked to stop normal breathing for a moment in order to minimize breathing motion. The operator selects the depth at which the liver elasticity is evaluated by placing a “measuring box” (10 mm long, 5mm wide) in the desired

Study	SPOREA 2012A [835] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[247,287,548,692,834] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[306,854] (presumed authors were contacted for further information).
	area. The maximum depth at which ARFI measurements can be performed is 8 cm. A total of 5 (Saga), 6 (Bologna, Verona) or 10 (all other centres) valid measurements were performed in every patient and the median value was calculated. Operators who performed ARFI measurements were blinded to all patients' clinical, serological and histological data. TE (Optimal cut-off values were chosen so that the sum of sensitivity (Se) and specificity (Sp) would be the highest) – measured using FibroScan. 10 measurements were performed in each patient and the median calculated. Only measurements with a success rate ≥ 60% and an interquartile range < 30% were considered reliable. ARFI and TE were performed in the same session.
Reference standard	Liver Biopsy (METAVIR F4): Percutaneous liver biopsy using Menghini needle in 5 centres (Timisoara – needle diameter 1.4 or 1.6) Bucharest 1.4 mm, Bologna and Verona – 1.4 or 1.6 mm and Frankfurt – 1.2 mm). Percutaneous biopsy using TruCut technique with automatic needle device in 2 centres (Cluj-Napoca – 14G needle and Hyogo – 16G needle) percutaneous biopsy using semi-automatic instruments in 2 centres (Saga – 16G needle and Tokyo – 18 G needle) and transjugular biopsy in 1 centre (Vienna). Only fragments of at least 1.5 cm in length were included. Biopsies were performed in the right lobe and assessed by a senior pathologist, blinded to the results of liver stiffness measures.
Time between index test and reference standard	Up to 6 months
Prevalence of cirrhosis according to reference standard	223/911 (24.4% in whole group) 95/400 (23.8% in TE subgroup)
Target condition	Cirrhosis
Results: ARFI AUC (95% CI): 0.842 Optimal cut-off threshold (if calculated): 1.55 m/s (or 1.69m/s reported for n=400 subgroup who also had TE) Threshold: 1.55m/s (optimal) Sensitivity: 84.3 Specificity: 76.3 PPV: 53.1 NPV: 93.7	

Study	SPOREA 2012A [835] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[247,287,548,692,834] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[306,854] (presumed authors were contacted for further information).
+ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Accuracy: 77.9% <u>Results: TE (n=400)</u> AUC (95% CI): 0.932 Optimal cut-off threshold (if calculated): 11.9 kPa *Note: Sporea 2012a did not report the sensitivities and specificities for TE at a cut-off threshold. This information was extracted separately for 5 of the studies used in the Sporea 2012 pooled data and is reported below (this did not include additional patients included in Sporea 2012a who weren't reported in previous papers, nor did it include Takahashi 2012 or Friedrust 2009A as these papers did not report data separately for HCV and/or for people with biopsy as the reference standard). ARFI data were not extracted from these papers separately, as this will be included in the above analysis.* <u>Lupsor 2009[548] (n=112); cirrhosis F4: 42/112 (37.5%):</u> <u>Threshold: >13.1 (optimal)</u> Sensitivity: 95.12 Specificity: 89.17 PPV: 84.8 NPV: 96.8 +ve/-ve likelihood ratios: 9.24 / 0.05 TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	SPOREA 2012A [835] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[247,287,548,692,834] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[306,854] (presumed authors were contacted for further information).
Fierbinteanu-braticeuici 2009[287] (n=74) TE not assessed by study, APRI assessed by study but accuracy values not reported Ebinuma 2011[247]; cirrhosis F4: Diagnostic accuracy not reported separately for TE for HCV aetiology separately (only splits into viral and non-viral aetiologies) Piscaglia 2011[692]; cirrhosis F4: Diagnostic accuracy of TE for cirrhosis not reported Sporea 2011D[834]; cirrhosis F4: Diagnostic accuracy of TE for cirrhosis not reported (only for diagnosis of significant fibrosis) Other measures reported and conclusions: Predictive ARFI values separated by ethnicity. Performance of ARFI according to ALT level Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Consecutive or random recruitment not reported Up to 6 months between reference standard and index test Liver biopsies < 25mm.	

Study	STIBBE 2011[843]
Study type	Cross-sectional study

Study	STIBBE 2011[843]
Number of studies (number of participants). Recruitment period.	N=89 (48 HBV patients, 41 HCV patients (only 40 included in FibroTest, 36 included in TE), 31 controls) February 2007 – November 2007
Countries and Settings	Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands
Funding	Not reported
Age, gender, ethnicity, ALT (U/l):	Mean age: 47 years, 66% men, ethnicity: not reported, ALT: not reported for HCV patients separately
Patient characteristics	Population: Chronic viral hepatitis C Inclusion: Monoinfected HCV patients referred for liver biopsy to the outpatient clinic. Exclusion: Alcohol intake >20g/day, co-infection with HIV or hepatitis D, presence of hepatocellular carcinoma
Index test (including threshold and whether threshold pre-specified)	FibroTest (pre-published cut-off from Poynard et al.): blood samples were obtained from all patients on the day of biopsy. FibroTest was based on sex, age, α2M, haptoglobin, total bilirubin, γGT and ApoA1. Transient elastography (Fibroscan; pre-published cut-off Verveer, personal communication): preceded the biopsy in the same session. TE measured low-frequency elastic waves (50 Hz) through a medium and the speed of these waves was positively correlated with stiffness of the liver. A success rate of >60% was considered reliable in 10 validated measurements with interquartile range (IQR) < 30% of the median.
Reference standard	Liver Biopsy (METAVIR F4): 2 well-experienced hepatologists performed all biopsies. To reduce complications, during this procedure abdominal ultrasound was used to identify liver parenchymal and vascular structures. Biopsies were taken with a 14G true-cut needle and required a length ≥ 20mm. Two expert hepatopathologists scored all specimens (double read) for different fibrosis categories using Metavir scoring. No biopsies obtained from controls.
Time between index test and reference standard	Same day
Prevalence of cirrhosis according to reference standard	11/41
Target condition	Cirrhosis

Study	STIBBE 2011[843]
Results: FibroTest (n=40) AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 0.75 (published) Sensitivity: 100 Specificity: 24 PPV: 64 NPV: 100 +ve/-ve likelihood ratios: 1.31/0 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: TE (n=36) AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 14kPa (pre-published) Sensitivity: 88 Specificity: 73 PPV: 88 NPV: 73 +ve/-ve likelihood ratios: 3.23/0.16 TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	STIBBE 2011[843]
Other measures reported and conclusions: Breath tests, APRI, FIB-4. For APRI and FIB-4, and for a combination of TE and fibrosis tests, results were only given for all patients combined and not HCV sesparately. Hyaluronic acid, APRI, FibroTest, Fib-4 and TE reliably distinguish non-cirrhotic and cirrhotic patients. Any complications associated with tests reported:	
General limitations according to QUADAS II Consecutive or random recruitment not reported. Blinding unclear during interpretation of reference standard test results. Liver biopsy size <25mm.	

Study	Wong 2010B[939]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=309 consecutive patients, 35 excluded due to biopsy length, 28 excluded due to failure to obtain 10 valid LSM acquisitions, final analysis n=246). Recruitment between May 2003 and April 2009
Countries and Settings	France and Hong Kong. 2 University Hospitals.
Funding	Academic. Supported in part by the research fund of the Department of Medicine and Therapeutics, The Chinese University of Hong Kong
Age, gender, ethnicity	Age, mean (SD): 51(11); Male/female 135/111: Ethnicity: Caucasian (n=128) and Chinese (n=118); ALT (IU/L): 75(54); BMI: 28.0(4.5); Diabetes: 36.2%.
Patient characteristics	Population: NAFLD Inclusion: Aged 18 years or older, with NAFLD undergoing liver biopsy. Exclusion: Men who consumed more than 30 g alcohol per day and women who consumed more than 20 g alcohol per day; secondary causes of hepatic steatosis (such as chronic use of systemic corticosteroids), positive hepatitis B surface antigen, anti-hepatitis C virus antibody, or histological evidence of other concomitant chronic liver diseases; patients with clinical and radiological evidence of cirrhosis were excluded (for example, bilirubin 30 ≥mol/L, albumin <35 g/L,

Study	Wong 2010B[939]
	INR>1.3, platelet count <150x10^9/L, ascites, varices, splenomegaly).
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan), optimal cut-off threshold calculated (10.3kPa) according to highest Youden's index. Accuracy also given at cut-off of 11.5kPa (not pre-specified) Performed according to the instructions and training provided by the manufacturer. Ten successful acquisitions were performed on each patient. The median value represented the liver elastic modulus. Only cases with 10 successful acquisitions were evaluated. The operators were blinded to all clinical data and the diagnoses of the patients. ***Presumed to have used appropriate probe for patient's BMI according to manufacturer's instructions (not reported).*** APRI, AST/ALT and FIB4
Reference standard	Liver biopsy (NAFLD specific scoring system, Kleiner et al 2005, F4): percutaneous liver biopsy was performed using the 16G Temno or Menghini needle. Liver histology was assessed by experienced histopathologists (B.L.B., P.C.C.) who were blinded to the clinical data. Liver specimens shorter than 15 mm were excluded (mean (SD) length 21(7)mm)
Time between index test and reference standard	Index test 1 week before
Prevalence of cirrhosis according to reference standard	25/246 (10.2%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.95 (0.91-0.99) Optimal cut-off threshold (if calculated): 10.3kPa Threshold: 10.3kPa (optimal) Sensitivity: 92.0 Specificity: 87.8 PPV: 46.0 NPV: 99.0 +ve/-ve likelihood ratios: 7.5/0.091 TP: Not reported FP: Not reported	

Study	Wong 2010B[939]
FN: Not reported TN: Not reported Threshold: 11.5kPa (not pre-specified: cut-off giving specificity >90%) Sensitivity: 76.0 Specificity: 91.0 PPV: 48.7 NPV: 97.1 +ve/-ve likelihood ratios: 8.4/0.26 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: APRI AUC (95% CI): 0.75 (0.64-0.85) Results: FIB4 AUC (95% CI): 0.81 (0.73-0.89) Results: AST/ALT AUC (95% CI): 0.66 (0.55-0.77) Other measures reported and conclusions: transient elastography had high accuracy in detecting advanced fibrosis and cirrhosis Any complications associated with tests reported: Not reported	

Study	Wong 2010B[939]
General limitations according to QUADAS: Patients with unreliable TE excluded from the analysis Liver biopsy sample <25mm and 10 portal tracts.	

Study	WONG 2012[938]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	N=205 consecutive NAFLD patients (12 patients were excluded because of liver biopsy length < 15 mm, final analysis 193). Recruitment period October 2009 to September 2011. Reliable results were obtained in 67 % with M probe and 75 % with XL probe (*note: report intention to diagnose results here and cases with failed liver stiffness measurements were labelled as incorrect classifications, study also reports accuracies not including those without valid TE measurements*)
Countries and Settings	France and Hong Kong. 2 University Hospitals.
Funding	Partially supported by the PROCORE-France / Hong Kong Joint Research Scheme (F-HK17 / 10T) and a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. CUHK477710).
Age, gender, ethnicity	Age, mean (SD): 52 ± 11 years; Male/female: 110/83; Ethnicity: Caucasian 77, Chinese 116; ALT (IU/L): 73 (76); BMI: 28.9 ± 4.8. Sixty-eight (35 %) patients had BMI ≥ 30
Patient characteristics	Population: NAFLD Inclusion: indications of liver biopsy included persistently abnormal liver biochemistry and the presence of risk factors of advanced disease such as type 2 diabetes. We enrolled patients aged ≥ 18 years Exclusion: men who consumed more than 30 g alcohol per day and women who consumed more than 20 g alcohol per day; patients with secondary causes of hepatic steatosis (such as use of systemic corticosteroids and methotrexate), positive hepatitis B surface antigen, anti-hepatitis C virus antibody, or histological evidence of other concomitant liver diseases
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan) optimal cut-offs chosen at points with the highest Youden 's index based on cases with 10 valid measurements, cutoffs with sensitivity and specificity over 90% were also determined: Measurements

Study	WONG 2012[938]
	were performed on the right lobe of the liver through intercostal spaces with the patient lying in dorsal decubitus with the right arm in maximal abduction. Ten successful acquisitions were performed on each patient. The success rate was calculated as the number of successful measurements divided by the total number of measurements. In each patient, measurements were performed by M probe followed by XL probe. The maximum number of measurements by each probe was limited at 20. The operators were blinded to all clinical data and the diagnoses of the patients, and had performed LSM on at least 50 patients before this study. An LSM was considered reliable only if 10 valid acquisitions were obtained, the success rate was over 60 %, and the IQR-to-median ratio (IQR / M) of the measurements was below 0.3. ***Study aims to compare the M and XL probe in the same patients.***
Reference standard	Liver biopsy (NAFLD specific scoring system, Kleiner et al 2005, F4): Percutaneous liver biopsy was performed using the 16G Temno or Menghini needle. Liver histology was assessed by 2 experienced histopathologists who were blinded to the clinical data. Liver specimens shorter than 15 mm were excluded (mean 24 ± 6).
Time between index test and reference standard	TE 24 hours before liver biopsy
Prevalence of cirrhosis according to reference standard	25/193 (13%)
Target condition	Cirrhosis
Results: Fibroscan M probe AUC (95% CI): 0.53 (0.36 – 0.70) Optimal cut-off threshold (if calculated): 10.3kPa (Youden's) Threshold: 10.3 (Youden's and highest sensitivity) Sensitivity: 52 (32-72) Specificity: 69 (62-76) PPV: 20 (10-30) NPV: 91 (86-96) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported	

Study	WONG 2012[938]
Threshold: 11.5 (highest specificity?) Sensitivity: 44 (25-64) Specificity: 71 (64-78) PPV: 18 (9-28) NPV: 90 (84-95) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: Fibroscan XL probe AUC (95% CI): 0.86 (0.79 – 0.94) Optimal cut-off threshold (if calculated): 7.9kPa (Youden's) Threshold: 7.9kPa (Youden's) Sensitivity: 84 (70-98) Specificity: 72 (65-79) PPV: 31 (20-42) NPV: 97 (94-100) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 7.2kPa (best sensitivity) Sensitivity: 88 (75-100) Specificity: 67 (60-74) PPV: 28 (18-38) NPV: 97 (95-100)	

Study	WONG 2012[938]
+ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 11.0kPa (best specificity) Sensitivity: 68 (50-86) Specificity: 86 (81-92) PPV: 43 (27-58) NPV: 95 (91-98) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: By intention-to-diagnose analysis, the performance of M probe was unsatisfactory due to the large number of patients with failed LSM Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Liver biopsy sample <25mm	

Study	Yamanda 2006[945]
Study type	Pilot study

Study	Yamanda 2006[945]
Number of studies (number of participants). Recruitment period.	N=74 HCV and HBV in total (including 44 with hepatitis C)
Countries and Settings	Chiba University Hospital, Japan
Funding	Not reported
Age, gender, ethnicity	In the whole group mean age = 51±11 years (range 19-70 years), 55.4% males, ethnicity not stated (presumed Japanese).
Patient characteristics	Hepatitis C infected
Index test (including threshold and whether threshold pre-specified)	Ultrasound (SSA 770A, Toshiba Medical Systems, Tokyo, Japan) Fibrosis extraction ratios (FER) (fiber volume/total volume): . Transforming and receiving frequencies were 2.0 and 4.0 MHz respectively. The transducer was applied lengthways to the epigastric lesion of the patient's body surface, moving it in a linear fashion along the patient's skin manually about 3 cm for 100 consecutive ultrasound images. Patients held their breath during scanning (approx. 15 seconds).
Reference standard	Percutaneous liver biopsy by 18-gauge needle with 20-mm specimen notch. Only samples presenting at least 10 portal tracts were considered suitable for evaluation. Specimens were evaluated with regard to inflammatory activity and fibrosis in a blind fashion by 2 independent liver pathology specialists based on the New European Classification (same as METAVIR).
Time between index test and reference standard	A few days
Prevalence of cirrhosis according to reference standard	Nr for HCV population
Target condition	Cirrhosis
Results: Ultrasound AUC (95% CI): 0.79 (CI not reported) Optimal cut-off threshold (if calculated): Not reported Other measures reported and conclusions:	

Study	Yamanda 2006[945]
The fibrosis extraction method has great potential for diagnosing liver fibrosis using ultrasound. Any complications associated with tests reported:	
General limitations according to QUADAS II Random or consecutive recruitment not reported. Indirectness: Patient exclusion criteria unclear and 5 patients had partial liver resection because of malignancy.	

Study	Yoneda 2008[954]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	102 (5 excluded due to unreliable TE measurement (all BMI>30) leaving 97 included)
Countries and Settings	Yokohama City University Hospital and Dokkyo Medical University, Japan
Funding	Grant-in-Aid from Ministry of Health, Labour and Welfare of Japan Ministry of Education, Culture, Sports, Science and Technology of Japan National institute of Biomedical Innovation
Age, gender, ethnicity	Age, mean (SD): 51.8 ± 13.7; Male/female: 40, 57 Ethnicity: Presumed Japanese; ALT (U/l): 80.0 ± 62.3
Patient characteristics	Population: NASH. No evidence of hepatic decompensation Inclusion: Presence of macrovesicular fatty change in hepatocytes with displacement of the nucleus to the edge of the cell Exclusion: Hepatitis C, hepatitis B, autoimmune hepatitis, primary biliary hepatitis, sclerosing cholangitis, hemochromatosis, α1-antitrypsin deficiency, Wilson's disease, hepatic injury caused by substance abuse, current or past history of more than 20g alcohol daily

Study	Yoneda 2008[954]
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan): performed on right lobe of the liver through intercostal spaces with patients lying in dorsal decubitus position. Success rate of at least 60% or IQR <30% considered reliable. ***Presumed to have used appropriate probe for patient's BMI according to manufacturer's instructions (not reported).***
Reference standard	Liver biopsy (Brunt scoring system, 4 = cirrhosis) obtained with an 18-gauge needle. Specimens were stained with haematoxylin-eosin, reticulin and Masson trichrome stains. Minimum length 20 mm. Minimum 7 portal tracts. Analysed independently by 2 experience pathologists blinded to the results of the clinical data.
Time between index test and reference standard	Within 3 months
Prevalence of cirrhosis according to reference standard	9/97 (9.3%)
Target condition Cirrhosis	
Results: [TE] AUC (95% CI): 0.991 (CI not reported) Optimal cut-off threshold (if calculated): 17.5 unclear if published or calculated Threshold: 17.5kPa (unclear if published or calculated) Sensitivity: 100 Specificity: 96.6 PPV: 75 NPV: 100 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Other measures reported and conclusions: Very highly significant correlations between liver stiffness measure and serum hyaluronic acid and type IV collagen 7s domain	

Study	Yoneda 2008[954]
Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Random or consecutive recruitment not reported. Length of time between index test and reference standard not reported. Liver biopsy samples <10 portal tracts	

Study	Yoneda 2010[955]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	1 study (N=54 consecutive patients with NAFLD, also a healthy control group n=10 – not included in calculations of diagnostic accuracy). Recruitment between January 2008 and December 2008
Countries and Settings	Yokohama City University Hospital
Funding	Supported in part by a Collaborative Development of Innovative Seeds program grant from the Japan Science and Technology Agency. A.N. supported in part by a grant from the National Institute of Biomedical Innovation. M.Y. supported by a grant from the Yokohama Foundation for Advancement of Medical Science
Age, gender, ethnicity	Age, mean (SD): 50.6 (13.7); Male/female: 25/29; Ethnicity: Presumed Japanese; ALT (U/ml): men: 66.4 (29.1), women: 54.9 (33.1)
Patient characteristics	Population: liver biopsy confirmed diagnosis of NAFLD Inclusion: undergone liver biopsy for the diagnosis and staging of NASH, histologic criterion for the diagnosis of NAFLD is the presence of macrovesicular fatty changes in hepatocytes, with displacement of the nucleus to the edge of the cell

Study	Yoneda 2010[955]
	Exclusion: history of hepatic disease, such as chronic hepatitis C or concurrent active hepatitis B (seropositive for hepatitis B surface antigen) infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, hemochromatosis, α1-antitrypsin deficiency, Wilson disease, or hepatic injury caused by substance abuse and current or past history of the consumption of more than 20 g of alcohol daily. No patients had any clinical evidence of hepatic decompensation, such as hepatic encephalopathy, ascites, variceal bleeding, or elevation of the serum bilirubin level to more than twofold the upper limit of normal.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan; optimal cut-off calculated): Measurements of the right lobe of the liver were performed through the intercostal spaces with the patient lying in the dorsal decubitus position with the right arm in maximal abduction—the same site used for the ARFI sonoelastography measurements. Ten successful acquisitions were performed in each patient, and the median value was determined. ***Presumed to have used appropriate probe for patient's BMI according to manufacturer's instructions (not reported).*** ARFI (optimal cut-off calculated): performed by using a Siemens Acuson S2000 US System (Mochida Siemens Medical System, Tokyo, Japan). ARFI sonoelastography was performed with a curved array US probe at 4 MHz for B-mode imaging. The right lobe of the liver was examined through the intercostal space with the patient lying in a dorsal decubitus position with the right arm in maximal abduction. An area where the liver tissue was at least 6 cm thick and free of large blood vessels was chosen. A measurement depth of 2 cm below the liver capsule was chosen. Ten successful acquisitions were performed in each patient, and the median value was determined.
Reference standard	Liver biopsy (Brunt scoring system, 4 = cirrhosis): specimens were obtained by using an 18-gauge needle biopsy apparatus (Pro-Mag; Medical Device Technologies, Gainesville, Fla) with a minimum of 7 portal tracts and a minimum length of 20 mm. Analysed independently by a pathologist with 27 years of experience in pathology who was unaware of the clinical data.
Time between index test and reference standard	TE and ARFI within 12 months of liver biopsy (mean 5.8 months (3.6)).
Prevalence of cirrhosis according to reference standard	6/54
Target condition Cirrhosis	

Study	Yoneda 2010[955]
Results: ARFI AUC (95% CI): 0.976 Optimal cut-off threshold (if calculated): 1.90 m/sec Threshold: 1.90 m/sec (optimal) Sensitivity: 100 Specificity: 96 PPV: 75 NPV: 100 +ve/-ve likelihood ratios: Not reported TP: 6 FP: Not reported FN: Not reported TN: 46 Results: Fibroscan AUC (95% CI): 0.998 Optimal cut-off threshold (if calculated): 16kPa Threshold: 16kPa (optimal) Sensitivity: 100 Specificity: 98 PPV: 86 NPV: 100 +ve/-ve likelihood ratios: Not reported TP: 6 FP: Not reported FN: Not reported TN: 47	

Study	Yoneda 2010[955]
Other measures reported and conclusions: Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II Time period between index test and reference standard up to 12 months Biopsy length <25mm	

Study	Zarski 2012[964]
Study type	Multicentre prospective study
Number of studies (number of participants). Recruitment period.	Multicentre. Enrolled N=590 (excluded n=78: 42 biopsies did not conform to criteria; 11 patients without blood sample; 9 patients with HBV co-infection; 5 patients with an excessive consumption of alcohol; 5 patients who received a treatment at the same time as the biopsy or less than 1 month before; 3 patients with unknown HCV status; 1 patient taking immunosuppressive treatment; 2 patients for whom a lot of data were missing). Fibrosis tests – N=436; Fibroscan – N=382 (not interpretable in 113 patients who were excluded from the analysis, some statistically significant differences were observed between patients with or with failed Fibroscan). Recruitment Nov 2006 – July 2008.
Countries and Settings	19 French academic hospitals, Fibrostar study cohort
Funding	French agency for research on AIDS and viral hepatitis (ANRS)
Age, gender, ethnicity	**Fibroscan (n=382)** **Fibrosis tests (n=436)** Age, mean (SD): : 50.9±10.6,: 51.2±10.9; Male/female: 60.7%/39.3%, 61.5%/38.5% Ethnicity: ns; ns; ALT (U/l): 87.9 ± 65.4 88.0 ±64.9

Study	Zarski 2012[964]
Patient characteristics	Population: Untreated chronic hepatitis C Inclusion: Time between liver biopsy and other diagnostic tests < 3 months. No hep C treatment in past 6 months. All patients had been referred for tests in order to make a decision on treatment strategy. CHC was confirmed by HCV-RNA polymerase chain reaction. Cirrhotic patients were compensated and asymptomatic at time of inclusion. Exclusion: Co-existing liver disease attributed to alcohol, hep B, auto-immune hepatitis, primary biliary cirrhosis, hemochromatosis, alpha-1-antitrypsine deficiency, Wilson's disease, HIV infected, post-transplant.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan) – measurements made on right lobe of liver, through intercostal spaces. At least 10 valid shots obtained/ IQR <30% deemed successful. FibroTest APRI FIB-4
Reference standard	Liver biopsy (METAVIR F4). Performed using Menghini's technique with a 1.6 mm needle, formalin-fixed in the centres and paraffin embedded. Sections were stained with hematoxylin-eosin-saffron and picrosirius red. Evaluated independently by 2 senior liver pathologists blind to clinical and biological data: Minimum length 15mm and/or at least 11 portal tracts (only 2.5% had < 15mm).
Time between index test and reference standard	< 3 months (median 5 days, range 0-65 days)
Prevalence of cirrhosis according to reference standard	56/382, 14.7%
Target condition	Cirrhosis
Results: **FibroTest n=382 (AUC also provided in paper for n=436 sample but without sensitivity and specificity values)** AUC (95% CI): 0.87 (0.82, 0.91) Optimal cut-off threshold (if calculated): Not reported Threshold: 0.74 (published) Sensitivity: 71.4% Specificity: 81.0% PPV: 39.2% NPV: 94.3%	

Study	Zarski 2012[964]
+ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported **APRI n=382 (AUC also provided in paper for n=436 sample but without sensitivity and specificity values)** AUC (95% CI): 0.87 (0.82, 0.91) Optimal cut-off threshold (if calculated): Not reported Threshold: 2.0 (published) Sensitivity: 7.1 Specificity: 99.7 PPV: 80.0 NPV: 86.2 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported **FIB4 n=382 (AUC also provided in paper for n=436 sample but without sensitivity and specificity values)** AUC (95% CI): 0.84 (0.77, 0.90) Optimal cut-off threshold (if calculated): Not reported Threshold: Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported	

Study	Zarski 2012[964]
TP: Not reported FP: Not reported FN: Not reported TN: Not reported **Fibroscan (n=382)** AUC (95% CI): 0.93 (0.89, 0.96) Optimal cut-off threshold (if calculated): Not reported <u>Threshold: 12.9kPa (published)</u> Sensitivity: 76.8 Specificity: 89.6 PPV: 55.8 NPV: 95.7 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported <u>Other measures reported and conclusions:</u> Contrarily to blood tests, performance of Fibroscan was reduced due to uninterpretable results. Percentage of well classified patients and theoretically avoided liver biopsies according to 1 or a combination of 2 tests. For the diagnosis of cirrhosis, no combination was superior to the best blood tests or Fibroscan alone in the 'per-protocol' analysis (382 patients). However, when we considered the population of 436 patients (''intention to diagnose population'') the combination of Fibroscan plus a blood test markedly improved the percentage of well classified patients for the diagnosis of cirrhosis. <u>Any complications associated with tests reported:</u> Not reported	

Study	Zarski 2012[964]
General limitations according to QUADAS II Up to 3 months between index test and reference standard. Large number of missing data for Fibroscan (and sensitivity and specificity data for fibrosis tests only provided for n=382 sample) Liver biopsy samples <25mm	

H.3 Severity risk tools

Study	Aravinthan 2013[46]
Study type	Cohort study
Number of studies (number of participants	77 patients with biopsy-confirmed alcoholic liver disease cirrhosis
Countries and Settings	University Hospital, Southampton
Funding	Hepatology Endowment Fund and Addenbrooke's Charitable Fund
Duration of study	Median follow-up 57 months (1–120) after liver biopsy
Age, gender, ethnicity	Age: median 50 (26–80), gender: 56% men
Patient characteristics	All patients gave a history of sustained excessive alcohol consumption (men >30 g/d; women >20 g/d). All but one were consuming alcohol in excess at the time of liver biopsy (median 164 g/day (57–600). During follow-up, 61% of those who were consuming alcohol at the time of liver biopsy continued to consume alcohol. Other recognised causes of liver disease were excluded after appropriate investigations. All patients had routine haematology and biochemistry blood tests performed at the time of liver biopsy and were reviewed at least every 6 months until death, an adverse liver-related outcome or the censor point. Only those patients with complete follow-up data were included.
Severity risk tool (for example transient elastography, Child-Pugh, MELD)	MELD score
Outcome and timepoint	Adverse liver-related outcome (liver-related death, decompensation, variceal bleed, ALD and sepsis, liver transplantation,

Study	Aravinthan 2013[46]
	hepatocellular carcinoma)
During follow-up, 47% died of liver-related causes and two were considered for and underwent liver transplantation. A further 5 patients died of causes related to liver diseases. 26% experienced decompensation, 17% experienced variceal bleeding, 4% experienced sepsis, 0% developed hepatocellular carcinoma. Results : MELD score to predict adverse liver-related outcome AUC (95% CI): 0.59 (0.47–0.72) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): General limitations according to PROBAST Some components of the composite outcome do not match the protocol (sepsis, liver transplantation) therefore evidence is slightly indirect.	

Study	Ferlitsch 2012[270]
Study type	Prospective
Number of studies (number of participants	Patients referred to the hepatic haemodynamic lab and scheduled for baseline HPVG measurements were included. 286 patients with liver cirrhosis were included. Transient elastography measurements were performed on 145/189 patients who were compensated at baseline.
Countries and Settings	Department of Internal Medicine III, Division of Gastroenterology, Medical University of Vienna (Austria)
Funding	Skoda grant 2011 of the Austrian Society of Internal Medicine
Duration of study	September 2006–December 2009
Age, gender, ethnicity	(For whole group, n=286) age: median: 55, IQR, 48–62); gender: 201 males, 65 females; ethnicity: not reported.
Patient characteristics	Liver cirrhosis was diagnosed histologically, clinically or by typical radiological findings. Aetiology of liver disease, age, HPVG, medical history including the presence of oesophageal varices, ascites, Child Pugh Score, haematological status, clinical chemistry and liver stiffness measured by transient elastography were recorded for each patient at the day of HPVG measurement. Exclusion: presence of pre- and post-hepatic causes of portal hypertension. Severe cardiopulmonary or renal impairment, active infections, diabetes, anticoagulant therapy, antiplatelet drugs, current treatment with beta-blockers, statins or

Study	Ferlitsch 2012[270]
	interferon. Patients with alcoholic liver disease needed to be abstinent from alcohol for at least 3 months.
Severity risk tool (eg. transient elastography, Child-Pugh, MELD)	Measurement of liver stiffness was performed by transient elastography (transient elastography, Echosens) after an overnight fast. Results of liver stiffness were considered as adequate if the IQR was within the 30% interval of the median value and if the success rate was ≥70%. Results were recorded in kPa.
Outcome and timepoint	Patients were followed prospectively at least every 6 months at the outpatient clinic. All events, particularly decompensation by ascites, jaundice, grade 3/4 hepatic encephalopathy, variceal bleeding, death and liver transplantation were recorded. The national register of death was also screened.
Cumulative deaths at 12 months (total n=189): 16; 24 months: 32; 36 months: 41; 48 months: 45 Cumulative deaths or decompensation at 12 months (total n=189): 26; 24 months: 39; 36 months: 55; 48 months: 58 Results : Performance of transient elastography for predicting decompensation (in patients compensated at baseline only) AUC (95% CI): Optimal cut-off threshold for determining people who will/will not have the event (if calculated): Threshold: Sensitivity: 20.3 Specificity: 88.2 PPV: 56.8 NPV: 28.3 +ve/-ve likelihood ratios: 98.4/2.0 General limitations according to PROBAST Transient elastography was unsuccessful in 41 of 128 compensated patients (mainly because of obesity) therefore ROC curves were calculated with the ITD approach.	

Study	Finkenstedt 2012[289]
Study type	Prospective longitudinal study
Number of studies (number of participants	429 All adult patients with cirrhosis referred to the department August 2007–September 2009 plus analysis was carried out on

Study	Finkenstedt 2012[289]
	frozen samples from a cohort of consecutive patients who were treated November 2005–January 2007.
Countries and Settings	Department of Gastroenterology and Hepatology at the University Hospital of Innsbruck, Austria
Funding	No commercial relationships
Duration of study	Median 1.3 years (IQR 0.6–3.5)
Age, gender, ethnicity	Age: mean 57.2 (SD: 12.0), gender: 136 female, 293 male, ethnicity: not reported.
Patient characteristics	Inclusion criteria: 18 years and above, diagnosed with cirrhosis (based on imaging studies, CT scan and/or ultrasound showing morphological signs compatible with end stage liver disease, oesophageal/cardiac varices or portal hypertensive gastropathy in the upper GI endoscopy and/or biochemical signs of cirrhosis). Exclusion criteria: missing laboratory parameters for calculation of MELD score, prior liver or kidney transplantation, renal replacement therapy prior to entry into the study, malignancies (including HCC) and loss to follow-up within 90 days. Patients lost to follow up after 90 days were censored with the last day they were known to be alive and patients who underwent liver transplantation were censored at that date.
Severity risk tool (for example transient elastography, Child-Pugh, MELD)	MELD was calculated according to the formula 0.957 * ln(creatinine) + 0.378 * ln(bilirubin) + 1.120 * ln(INR) + 0.643. The resulting score was multiplied by 10.
Outcome and timepoint	90-day mortality
Results : During follow-up 50 patients (12%) underwent liver transplantation and 83 patients (19%) died. Main causes of death were multi-organ failure with or without sepsis (59%), variceal or non-variceal bleeding (19%) and hepatic decompensation (17%). Mean transplant-free survival was 1470 days with 3-month, 1-year and 3-year transplant-free survival rate of 92, 84 and 77% respectively. MELD AUC (95% CI): 0.9 (0.84-0.96) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): Threshold: ≥16 Sensitivity: 85	

Study	Finkenstedt 2012[289]
Specificity: 83 Calibration: Calibration of MELD for 3-month mortality was poor for scores within the lower three quintiles but seemed to be fairly good in the fourth and fifth quintile of each score. The calibration of the scores for 1 year mortality was better but still remained imprecise within the lower quintiles. General limitations according to PROBAST 90-day mortality slightly indirect outcome due to timing. At risk of bias due to optimal threshold calculated.	

Study	Kim 2012H[466]
Study type	Prospective, longitudinal study
Number of studies (number of participants	n=217 consecutive patients with HBV diagnosed with cirrhosis by liver biopsy and undergoing liver stiffness measurement on the same day. Recruitment from January 2005 to December 2007.
Countries and Settings	University Hospital, Seoul, Korea
Funding	Grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea
Duration of study	Median 42.1 months (range 6.1–58.4 months). Followed up every 3 months.
Age, gender, ethnicity	Age, mean: 50.1 years; male/female: 141/76; mean liver stiffness measurement 16.2 (11.5) kPa; ethnicity: not reported. Fourty-two patients had already been under antiviral therapy before enrolment, 29 patients started at the time of enrolment and 36 after inclusion during the follow-up.
Patient characteristics	Inclusion: diagnosed with cirrhosis by liver biopsy (F4 by METAVIR) and undergoing liver stiffness measurement on the same day. Indications for liver biopsy included assessment of severity of liver fibrosis and inflammation. All patients had well-preserved liver function (Child-Pugh A) and none of them had experienced prior decompensation. Exclusion: any aetiologies for liver disease other than HBV, including liver cancer, coinfection with HCV, HDV, or HIV, other comorbidities (NASH, PSC, PBC), BMI >35, alcohol ingestion in excess of 40 g/day for <5 years, previous liver resection or transplantation, unreliable liver stiffness measurement with an IQR/M ratio >30% or a success rate <60%, or validated measurements <10, cardiac failure, liver biopsy unsuitable for staging (<15 mm).

Study	Kim 2012H[466]
Severity risk tool (eg. transient elastography, Child-Pugh, MELD)	Transient elastography: performed by a single experienced technician. Only examinations with an IQR/M ratio <30%, at least 10 valid measurements and a success rate of at least 60% were considered reliable. Operator blinded to patient's clinical and laboratory data.
Outcome and timepoint	Hepatic decompensation events (defined as the occurrence of any one of the following: ascites development, hepatic encephalopathy, variceal haemorrhage, deterioration of liver function to Child-Pugh class B or C).

26/217 (12%) had at least one hepatic decompensation event

Results : transient elastography
AUC (95% CI): 0.773 (0.686–0.860)
Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 18 kPa (Youden method)
Threshold:
Sensitivity: not reported
Specificity: not reported
PPV: not reported
NPV: not reported
+ve/-ve likelihood ratios: not reported
TP: not reported
FP: not reported
FN: not reported
TN: not reported

Other measures:
Calibration: not reported

Score on Risk Tool:	Risk of event:
<13 kPa	0.93, 0.9, 2.31 and 4.02% at 1, 2, 3 and 4 years
13–18 kPa	5.88, 10.54, 132.74 and 23.10% at 1, 2, 3 and 4 years
≥18 kPa	13.38, 23.21, 30.5 and 55.32% at 1, 2, 3 and 4 years

Study	Kim 2012H[466]
General limitations according to PROBAST One component of the composite outcome does not match the protocol (deterioration of liver function to Child-Pugh class B or C) therefore evidence is slightly indirect.	

Study	Kim 2014D[469]
Study type	Prospective longitudinal study
Number of studies (number of participants	207 patients with chronic hepatitis B (CHB) who underwent transient elastography examinations and then started entecavir (0.5 mg/d) as the first-line antiviral agent within 2 weeks after transient elastography examination between June 2007 and May 2010 and completed two years of treatment at the hospital. A subgroup of 69 patients had cirrhosis.
Countries and Settings	Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
Funding	Grant of the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea. The funders had no role in the study design, data and analysis, decision to publish or preparation of the manuscript.
Duration of study	2 years
Age, gender, ethnicity	For whole study population: age: 51 (20–72), gender: (61.1% male), ethnicity: not reported. Data not reported separately for cirrhotic subgroup.
Patient characteristics	Inclusions: CHB was defined as persistent presence of serum hepatitis B surface antigen for >6 months and HBV DNA positivity by PCR. Exclusions: Liver stiffness measurement failure (no valid shots, n=2), invalid liver stiffness measurement (n=5), HCC at enrolment or a history of HCC (n=8), Child-Pugh class B or C (n=6), evidence of hepatic decompensation (n=4), coinfection with hepatitis C, hepatitis D or HIV (n=2), right-sided heart failure (n=1), ascites or pregnancy (n=2), follow-up loss (n=15). Therefore 45 patients were excluded in total. A subgroup of 69 patients with cirrhosis were analysed separately. Cirrhosis was defined as: a platelet count <100,000/µL and ultrasonographic findings suggestive of cirrhosis including a blunted, nodular liver edge accompanied by splenomegaly >12 cm or oesophageal or gastric varices.

Study	Kim 2014D[469]
Severity risk tool (eg. transient elastography, Child-Pugh, MELD)	Liver stiffness measurement was performed on the right lobe of the liver through the intercostal spaces in patients lying in the dorsal decubitus position with the right arm in maximal abduction. The operator located a liver portion that was at least 6 cm thick and free of large vascular structures and pressed the probe button to commence the measurement. One experienced technician (> 20,000 examinations) who was blinded to patients' clinical data performed all liver stiffness measurements. The success rate was calculated by dividing the number of valid measurements by the total number of measurements. The IQR was defined as an index of intrinsic variability of liver stiffness measurement corresponding to the interval of liver stiffness measurement results containing 50% of the valid measurements between the 25th and 75th percentiles. When the liver stiffness measurement showed an IQR/M of >0.3, success rate of <60% or <10 valid measurements, it was regarded as invalid and excluded from the analysis.
Outcome and timepoint	All patients were screened ultrasonographically for HCC at their initial screening visit. Patients were followed up with α-fetoprotein and ultrasonography every 3 or 6 months. In addition to baseline liver stiffness measurements, follow-up values were measured during the course of ETV treatment (at 1 and 2 years). Furthermore, patients were monitored to detect clinical evidence of hepatic decompensation including variceal bleeding, ascites, hepatic encephalopathy, SBP and hepatorenal syndrome.
12 (17.4%) of the cirrhotic subgroup experienced development of liver-related events Results : Liver stiffness to predict development of liver-related events within 2 years AUC (95% CI): 0.793 (0.62–0.852) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 19.0 kPa Threshold: 19.0 kPa (optimal) Sensitivity: 93.3 Specificity: 42.2 General limitations according to PROBAST At risk of bias due to optimal threshold calculated.	

Study	Klibansky 2012[481]
Study type	Prospective, longitudinal study

Study	Klibansky 2012[481]
Number of studies (number of participants	Final analysis n=667 consecutive recruitment (prior to this, 114 excluded due to no follow-up after transient elastography and 60 excluded because transient elastography was not performed successfully). Cirrhosis subgroup n=160. Recruitment between November 2004 and July 2007
Countries and Settings	Medical Centre, Israel
Funding	One author reports receiving consultant and grant research support from Echosens (producers of FibroScan), Quest and Prometheus.
Duration of study	Median 854 days after transient elastography. Followed up every 12 months and electronic medical records from these visits formed the database.
Age, gender, ethnicity	Whole population. Age: 51.0 (45–56); male/female: 415/262; ethnicitiy: White 514, Black 62, Asian 46, Hispanic 42, Native American 3; liver stiffness measurement 8.7 (5.9–17.9) kPa.
Patient characteristics	Inclusion: patients with chronic liver disease of varying aetiology and liver fibrosis staging (study reports a subgroup of people with cirrhosis at baseline, proven by biopsy (15 mm in length with >5 portal tracts and performed within 3 years retrospectively or 6 months prospectively of transient elastography, or 10 mm in length if non-fragmented and deemed adequate) or clinical evidence (from imaging or evidence of portal hypertension or the presence of varices). Exclusion: patients who had previously experienced a clinical endpoint or had a Child-Pugh score >7 prior to or at the time of transient elastography were excluded.
Severity risk tool (eg. transient elastography, Child-Pugh, MELD)	Transient elastography: at entry into the study. Transient elastography was considered successful only if a minimum of 8 acquisitions were obtained with >60% success rate.
Outcome and timepoint	Composite of individual predetermined clinical endpoints including death from any cause, first variceal bleed, new-onset ascites, new-onset encephalopathy, increase in Child-Pugh score by 2 or more, HCC or listing for liver transplant.
40/160 (25%) had an event in the cirrhosis subgroup during follow-up Results: transient elastography AUC (95% CI): 0.59 (0.50–0.69) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): Threshold: 10.5 kPa Sensitivity: 0.975 Specificity: 0.1	

Study	Klibansky 2012[481]
PPV: 0.265 NPV: 0.923 +ve/-ve likelihood ratios: 1.08/0.25 Threshold: 8.0 kPa Sensitivity: 1.0 Specificity: 0.06 PPV: 0.26 NPV: 1.0 +ve/-ve likelihood ratios: 1.06/0 Threshold: 12.5 kPa Sensitivity: 0.93 Specificity: 0.16 PPV: 0.27 NPV: 0.86 +ve/-ve likelihood ratios: 1.1/0.47 Threshold: 15 kPa Sensitivity: 0.85 Specificity: 0.27 PPV: 0.28 NPV: 0.84 +ve/-ve likelihood ratios: 1.16/0.56 Threshold: 20 kPa Sensitivity: 0.8 Specificity: 0.39 PPV: 0.31	

Study	Klibansky 2012[481]
NPV: 0.86 +ve/-ve likelihood ratios: 1.32/0.51 Threshold: 30 kPa Sensitivity: 0.31 Specificity: 0.53 PPV: 0.66 NPV: 0.2 +ve/-ve likelihood ratios: 0.65/1.32 Threshold: 50 kPa Sensitivity: 0.05 Specificity: 0.93 PPV: 0.18 NPV: 0.75 +ve/-ve likelihood ratios: 0.67/1.03 Threshold: 70 kPa Sensitivity: 0.03 Specificity: 0.98 PPV: 0.75 NPV: 0.25 +ve/-ve likelihood ratios: 1.0/1.0 Other measures: Calibration: not reported General limitations according to PROBAST Two components of the composite outcome do not match the protocol (increase in Child-Pugh score by 2 or more, listing for liver transplantation) therefore evidence is	

Study	Klibansky 2012[481]
slightly indirect.	

Study	Perez-Latorre 2014[686]
Study type	Retrospective review
Number of studies (number of participants	All consecutive patients with HCV-related liver cirrhosis who underwent a liver workup comprising simultaneous assessment with transient elastography and determination of hepatic venous pressure gradient between January 2005 and December 2011. 60 patients with HCV-related liver cirrhosis, 36 of whom were co-infected with HIV.
Countries and Settings	Hospital Gregorio Maranon, Madrid
Funding	AIDS Research Network
Duration of study	Median follow-up 42 months
Age, gender, ethnicity	HCV/HIV (n=36): age: 46 years (42–49), 75% male, ethnicity: not reported HCV (n=24): age: 51 years (48–58), 67% male, ethnicity: not reported
Patient characteristics	HCV-related liver cirrhosis. The diagnosis of cirrhosis was confirmed by liver biopsy or by a liver stiffness measurement using transient elastography (≥14 kPa). Excluded: patients with decompensated liver disease or a prior diagnosis of hepatocellular carcinoma.
Severity risk tool (eg. transient elastography, Child-Pugh, MELD)	Transient elastography was performed using a transient elastography device (Echosens, Paris, France) after an overnight fast. A median value of 10 successful acquisitions was considered to be the representative measurement of liver stiffness. 10 acquisitions with a success rate ≥60% and an interquartile range to ratio <30% of the median value as representative measurements.
Outcome and timepoint	Liver decompensation (ascites, hepatic encephalopathy, variceal bleeding, jaundice) Hepatocellular carcinoma Liver-related events (decompensation or HCC, whichever occurred first) Note: Hepatic encephalopathy was diagnosed based on clinical findings; HIV-associated encephalopathy was excluded on the basis of clinical and laboratory parameters and neuroimaging. The source of gastrointestinal bleeding was confirmed by

Study	Perez-Latorre 2014[686]
	endoscopy where possible.
Results: Transient elastography, decompensation All patients: AUC (95% CI): 0.85 (0.69–1.0) Optimal cut-off threshold for determining people who will/will not have the event: not reported Results: Transient elastography, liver-related event (decompensation or HCC, whichever occurred first) 12/60 (20%) had a liver-related event All patients: AUC: 0.85 (0.73–0.97) Optimal cut-off threshold for determining people who will/will not have the event: <25 kPa (absence of liver-related events) and ≥40 kPa (presence of liver-related events) Threshold: <25 kPa Sensitivity: 92 (72–100) Specificity: 65 (50–79) PPV: 39 (19–55) NPV: 0.97 (0.89–0.1) +ve/-ve likelihood ratios: 2.59 (1.7–3.93)/0.13 (0.02–0.8) TP: 11 FP: 17 FN: 1 TN: 31 Threshold: ≥40 kPa Sensitivity: 67 (36–98) Specificity: 90 (80–99) PPV: 0.62 (0.31–0.92) NPV: 91 (82–100) +ve/-ve likelihood ratios: 6.4 (2.55–16.08)/0.37 (0.17–0.8) TP: 8 FP: 5	

Study	Perez-Latorre 2014[686]
FN: 4 TN: 43 Results: Transient elastography, hepatocellular carcinoma All patients: AUC: 0.77 (0.59–0.95) Optimal cut-off threshold for determining people who will/will not have the event: not reported Other measures: Calibration: not reported General limitations according to PROBAST At risk of bias due to optimal threshold calculated.	

Study	Robic 2011[736]
Study type	Prospective longitudinal study
Number of studies (number of participants	n=150 patients with chronic liver disease: 8 refused follow-up, 24 followed up in other hospitals, 18 had exclusion reasons such as decompensation at inclusion, final analysis n=100 (subgroup analysis provided for n=65 with cirrhosis at baseline). Transient elastography failure in 4 patients due to obesity. Recruitment between 15 November 2005 and 15 October 2006.
Countries and Settings	France
Funding	Not reported. Nothing to disclose regarding funding or conflict of interests.
Duration of study	Patients were followed up for 2 years or until the first occurrence of a clinical decompensation, liver transplantation, or death. Mean follow up 491 days.
Age, gender, ethnicity	Whole populations: age (mean, SD): 56±13 (range 47–66), male female: 59/41; ethnicity: not reported, liver stiffness measurement: 30.7±26.3 (30.8–75) kPa. Cirrhosis F4 n=65 (mean Child-Pugh 7.6 [5–11] and MELD 12.2 [5–15]). Oesophageal varices were grade 1 in 18 patients

Study	Robic 2011[736]
	(27.7%), grade 2 in 25 patients (39%), and grade 3 in 4 patients (6%).
Patient characteristics	Inclusion: compensated chronic liver disease Exclusion: at the time of inclusion, none of the patients had antiviral therapy or portal pressure modifying treatment.
Severity risk tool (for example transient elastography, Child-Pugh, MELD)	Transient elastography: 10 validated measures were performed for each patient. IQR was lower than 30% of the median value and success rate was at least 60%, according to the manufacturer's recommendations. The operator was not aware of HVPG values when conducting the analyses.
Outcome and timepoint	PHT related complication (variceal bleeding and/or ascites) Clinical decompensation (defined as PHT-related bleeding, ascites, hepatorenal syndrome, hepatic encephalopathy, hepatocellular carcinoma, and/or sepsis) outcome also reported but not for subgroup with cirrhosis at baseline.
18/65 (27.7%) had a PHT-related complication Results: transient elastography for predicting PHT-related complications AUC (95% CI): 0.734 (0.609–0.859) Optimal cut-off threshold for determining people who will/will not have the event: not reported (used pre-published) Threshold: 21.1 kPa (pre-published) Sensitivity: 100 Specificity: 41 PPV: 41 NPV: 100 +ve/-ve likelihood ratios: not reported TP: not reported FP: not reported FN: not reported TN: not reported Other measures: Calibration: not reported	

Study	Robic 2011[736]
Score on Risk Tool: Risk of event: <21.1 kPa 47% ≥21.1 kPa 100% General limitations according to PROBAST One component of the composite outcome does not match the protocol (sepsis) therefore evidence is slightly indirect.	

Study	Said 2004[754]
Study type	Retrospective cohort study
Number of studies (number of participants	1,611 consecutive patients from hepatology clinics and hepatology inpatient service Compensated patients=204
Countries and Settings	University of Wisconsin-Medison medical school university hospital, USA
Funding	Not reported
Duration of study	January 1994–December 2001 Median follow up was 24 months (1–72)
Age, gender, ethnicity	(Whole group) age: 50±12.5 (18–86), gender: 55% male, ethnicity: 88% Caucasian
Patient characteristics	Patient records were identified by discharge diagnosis codes. Patients with transient liver test abnormalities, acute liver diseases, hepatocellular carcinoma, cholangiocarcinoma and HIV and those who died of cardiac disease were excluded.
Severity risk tool (for example transient elastography, Child-Pugh, MELD)	MELD score was calculated at the initial visit using the formula: 3.8 lnBilirubin + 11.2 lnINR + 9.6 creatinine + 6.4
Outcome and timepoint	Survival was calculated from the date of first clinical contact. Mortality data were abstracted from hospital records and the national social security death index. Survival was censored at transplantation. ROC curves were plotted to measure the performance of MELD and Child-Pugh for predicting 1-year mortality.

Study	Said 2004[754]
Results : MELD score for predicting 1-year mortality AUC (95% CI): 0.75 (0.59–0.9) Results : Child-Pugh score for predicting 1-year mortality AUC (95% CI): 0.66 (0.50–0.82) General limitations according to PROBAST None	

Study	Wang 2014B[921]
Study type	Prospective study
Number of studies (number of participants	271 consecutive patients were enrolled from January 2008 to October 2011. 51 were excluded (12 patients had failed liver stiffness measurements, 5 had unreliable liver stiffness measurements, 15 did not fulfil the inclusion criteria, 12 did not have follow-up liver stiffness measurements, 7 had hepatocellular carcinoma (HCC) development within 6 months after enrolment). 220 were included in the analysis.
Countries and Settings	Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Taiwan
Funding	A grant from Chang Gung Memorial Hospital
Duration of study	Median follow-up 36.9 months. All patients received baseline liver function reserve assessment, ultrasound to exclude the presence of ascites and HCC and esophagogastroduodenoscopy (EGD) to detect the presence of varices. Liver stiffness measurement was assessed at an interval of 6–12 months. Medical records were reviewed regularly. Patients were followed up with ultrasound surveillance for HCC at an interval of 3–6 months regularly. EGD was repeatedly performed at an interval of 1–3 years.
Age, gender, ethnicity	Age: 56.7±11.4, gender: 61.34% male, ethnicity: not reported
Patient characteristics	Inclusion: patients with hepatic cirrhosis in liver function reserve Child-Pugh classification A, without histories of decompensation or HCC. Hepatic cirrhosis was diagnosed with histological fibrosis stage 4 according to METAVIR, ultrasonography cirrhosis with splenomegaly and/or thrombocytopenia or ultrasonography cirrhosis based on an objective

Study	Wang 2014B[921]
	scoring system. Exclusion: presence of ascites or HCC.
Severity risk tool (eg. transient elastography, Child-Pugh, MELD)	Liver stiffness measurements were performed with an M-probe using the transient elastography (Echosens, Paris, France) in a fasting state by technicians with at least a 50-patient experience. The operator located a portion of the liver at least 60 mm thick and free of large vascular structures with assistance of ultrasound time-motion and A-mode images, and pressed the acquisition button to obtain a liver stiffness value. Liver stiffness was expressed as a median with an IQR in kPa. Liver stiffness measurement was deemed reliable only when 10 successful shots were performed, with greater than 60% success rate of measurements and the ratio of IQR to median less than 30% was obtained.
Outcome and timepoint	Hepatic decompensation was defined as variceal bleeding, ascites, spontaneous bacterial peritonitis or hepatic encephalopathy. Portal hypertension (PHT) progression included hepatic decompensation, varices development and varices growth. Clinical disease progression included PHT progression, HCC development and liver-related death.
CDP occurred in 49/220 (22.3%) patients, including HCC in 19 patients and PHT progression in 30 patients (of these 30, 9 had decompensation and 21 had varices growth) Results: Baseline liver stiffness measurement (transient elastography) – prediction of CDP (49/220) AUC (95% CI): 0.668 (0.577–0.759) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 14 kPa Threshold: 14 kPa (optimal) Sensitivity: 57% (43–70) Specificity: 68% (61–75) Accuracy: 65% (59–72) PPV: 34 (24–44) NPV: 85 (78–90) +ve/-ve likelihood ratios: 1.78 (1.28–2.46)/0.63 (0.45–0.89) Results : Baseline liver stiffness measurement (transient elastography) – prediction of PHT (30/220) AUC (95% CI): 0.744 (0.65–0.838)	

Study	Wang 2014B[921]
Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 17 kPa Threshold: 17 kPa (optimal) Sensitivity: 57% (39–73) Specificity: 78% (72–83) Accuracy: 75% (69–80) PPV: 29% (118–41) NPV: 92% (87–95) +ve/-ve likelihood ratios: 2.56 (1.7–3.87) /0.56 (0.37–0.84) Results : Baseline liver stiffness measurement (transient elastography) – prediction of decompensation AUC (95% CI): 0.929 (0.875–0.984) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 21.1 kPa Threshold: 21.1 kPa (optimal) Sensitivity: 78 (48–95) Specificity: 84 (79–89) Accuracy: 84 (79–89) PPV: 18 (8–31) NPV: 99 (97–100) +ve/-ve likelihood ratios: 4.97 (3.11–7.95)/0.26 (0.08–0.9) Results: Baseline liver stiffness measurement (transient elastography) – prediction of HCC AUC (95% CI): 0.504 (0.358–0.651) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 11.5 kPa Threshold: 11.5 kPa (optimal) Sensitivity: 53 (32–73) Specificity: 52 (45–59) Accuracy: 52 (46–59) PPV: 9 (5–16) NPV: 92 (86–96)	

Study	Wang 2014B[921]
+ve/-ve likelihood ratios: 1.1 (0.7–1.76) 0.91 (0.55–1.48) Results : Baseline liver stiffness measurement (transient elastography) – prediction of varices progression AUC (95% CI): 0.638 (0.525–0.75) Optimal cut-off threshold for determining people who will/will not have the event (if calculated): 12 kPa Threshold: 12 kPa Sensitivity: 62 (38–82) Specificity: 60 (53–67) Accuracy: 60 (54–67) PPV: 14 (8–23) NPV: 94 (88–97) +ve/-ve likelihood ratios: 1.56 (1.07–2.27) / 0.63 (0.36–1.1) General limitations according to PROBAST Four of the five outcomes contain a component which does not match the protocol (variceal development or growth).	

H.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Study	Giannini 2000[325]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in Italy; setting: Department of Internal Medicine
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: presence of cirrhosis assessed on the basis of clinical signs of portal hypertension, Doppler ultrasonography measurements, and/or endoscopic presence of oesophageal or gastric varices.
Stratum	Overall

Study	Giannini 2000[325]
Subgroup analysis within study	Not applicable
Inclusion criteria	Anti-HCV positive cirrhosis associated HCC
Exclusion criteria	HBV, HIV or autoimmunity. Metabolic causes of liver disease or alcohol abuse.
Recruitment/selection of patients	Consecutive patients meeting inclusion criteria from August 1993 to September 1998
Age, gender and ethnicity	Age - mean (SD): 68 (9) years. Gender (M:F): 42/19. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Hepatitis C. 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (CP A 35 [57.4%], CP B 18 [29.5%], CP C 8 [13.1%]). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not treated for underlying condition/not abstaining from alcohol (11 patients had previously undergone a course of interferon therapy, and none of them had responded to anti-viral therapy).
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Surveillance - ultrasound+AFP 6-monthly. Biannual biochemical (AFP) and ultrasound follow-up. Diagnosis of HCC made by cytological examination of the smear obtained from an ultrasound-guided fine needle biopsy of hepatic nodules revealed by ultrasound or CT scan. Duration: unclear. Concurrent medication/care: therapeutic intervention was chosen following clinical and functional staging, according to recommended criteria (n=27). Intervention 2: No surveillance (HCC detected incidentally). Found during examinations performed at non-scheduled intervals or referred to the centre for evaluation of liver masses found during examinations performed due to extrahepatic diseases. Duration: unclear. Concurrent medication/care: therapeutic intervention was chosen following clinical and functional staging, according to recommended criteria.
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6-MONTHLY versus NO SURVEILLANCE (HCC DETECTED INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: Survival at end of study; HR 2.61 (95% CI 1.15 to 5.93) (B: estimated coefficient of regression [SE] 0.96 [0.0419]); risk of bias: high (not adjusted for lead time bias; not adjusted for all key confounders); indirectness of outcome: no indirectness. Adjusted relative hazard RH (RH=e^B). Variables: gender, Child-Pugh score, number of tumoral nodules (1/>1), AFP value, AFP (normal/increased), type of treatment (treated/not treated) and modality of diagnosis (follow-up/incidental).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3cm, greater than 3cm; number of lesions; liver

Study	Giannini 2000[325]
	cancer staging (according to BCLC system); liver transplant

Study	Miquel 2012[597]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Spain; setting: hepatology unit
Line of therapy	Not applicable
Duration of study	Recruited people diagnosed with HCC between January 2004 and December 2006. Prospectively followed up until February 2011.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: the diagnosis of cirrhosis was established from clinical, laboratory test, ultrasound and/or endoscopic data, or according to histological criteria.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed with HCC. All patients had cirrhosis.
Exclusion criteria	Not reported
Recruitment/selection of patients	All patients diagnosed with HCC between January 2004 and December 2006 in the Hepatology Unit (Corporació Sanitària Parc Taulí, Sabadell, Catalonia, Spain).
Age, gender and ethnicity	Age – mean (SD): 65.8 (11.2) years. Gender (M:F): 77/33. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (HCV: 56.1%, alcohol: 25.1%, HBV: 2%, HCV+alcohol: 11.2%, cryptogenic: 5.2%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (only 3.6% Child-Pugh C). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Surveillance - ultrasound+AFP 6-monthly. Patients mainly derived from the outpatient clinic, diagnosed with cirrhosis and enrolled in a screening program. EASL diagnostic criteria for HCC: compatible biopsy findings, two imaging methods with consistent findings in lesions < 2 cm in size, one imaging method with consistent findings in lesions ≥2 cm in size, and AFP >200 ng/ml. Duration: Follow-up: end of the study (5–7 years from recruitment). Concurrent medication/care: treatment for HCC in each patient was decided by the tumor committee

Study	Miquel 2012[597]
	according to the criteria proposed by the BCLC staging system. Two management groups: potentially curative (resective surgery, liver transplant or percutaneous treatment) and palliative (embolisation or symptomatic treatment). (n=54) Intervention 2: No surveillance. Patients not enrolled in the screening program and who were referred to the unit from primary care for the study of liver lesions detected as a result of imaging explorations, following confirmation of the diagnosis of HCC. EASL diagnostic criteria for HCC: compatible biopsy findings, two imaging methods with consistent findings in lesions <2 cm in size, one imaging method with consistent findings in lesions ≥2 cm in size, and AFP >200 ng/ml. Duration: Follow-up: end of the study (5–7 years from recruitment). Concurrent medication/care: treatment for HCC in each patient was decided by the tumor committee according to the criteria proposed by the BCLC staging system. Two management groups: potentially curative (resective surgery, liver transplant or percutaneous treatment) and palliative (embolisation or symptomatic treatment).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6-MONTHLY versus NO SURVEILLANCE Protocol outcome 1: Survival - Actual outcome: Survival at end of study; OR 1.13 (95% CI 0.64 to 2.01) (p value 0.68); risk of bias: high (not adjusted for lead time bias; not adjusted for all key confounders); indirectness of outcome: no indirectness. Multivariate analysis considered those factors found to be statistically significant in the univariate analysis: degree of liver function, screening, tumor size, and curative versus palliative. In this analysis, screening was not statistically significant (not an independent predictor of survival).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3cm, greater than 3cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Pascual 2008[676]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=290)
Countries and setting	Conducted in Spain; setting: university hospital
Line of therapy	Not applicable

Study	Pascual 2008[676]
Duration of study	Minimum follow-up 6 months from recruitment. Recruited at time of HCC diagnosis (duration of surveillance unclear). Recruitment started January 1996 and data collected until December 2004.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: method of diagnosis of cirrhosis not reported
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with cirrhosis and HCC (unclear if all patients had cirrhosis – reported in paper that the liver unit records data for all patients with HCC and cirrhosis – presume all HCCs in study had cirrhosis)
Exclusion criteria	Not reported
Recruitment/selection of patients	All patients with cirrhosis and HCC attending the University Hospital since January 1996.
Age, gender and ethnicity	Age – mean (SD): surveillance: 68.8 years; no surveillance: 68.2 years. Gender (M:F): 218/72. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (alcohol: 29.3%, HCV: 45.9%, HBV: 4.8%, alcohol+virus: 8.3%, other: 11.7%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (14.5% Child-Pugh C). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear
Indirectness of population	No indirectness
Interventions	(n=117) Intervention 1: Surveillance – ultrasound+AFP 6-monthly. Patients being diagnosed with HCC during the course of surveillance. Diagnosis of HCC based on criteria of EASL Barcelona conference: combining an increased AFP with typical features and one imaging technique (CT or MRI) or two HCC-compatible imaging techniques. In the rest of the cases, HCC diagnosis was confirmed by histology. Duration: minimum 6 months after HCC diagnosis. Concurrent medication/care: treatment according to tumor characteristics and protocol of care: i) liver transplantation for patients younger than 65 years, with a solitary tumor ≤5 cm or 3 nodules in diameter without vascular invasion or extrahepatic dissemination; ii) percutaneous ethanol injection or radiofrequency thermal ablation in patients not suitable for liver transplantation with small tumors (<3.5–4 cm); iii) transarterial chemoembolisation considered for patients with large/multinodular tumors without portal thrombosis and preserved liver function; iv) symptomatic treatment was applied for end-stage patients. (n=173) Intervention 2: No surveillance (HCC detected by symptoms or incidentally). Patients diagnosed with HCC outside surveillance (because of symptoms or at the same time as cirrhosis diagnosis). Diagnosis of HCC based on criteria of EASL Barcelona conference: combining an increased AFP with typical features and one imaging technique (CT or MRI) or two HCC-compatible imaging techniques. In the rest of the cases, HCC diagnosis was confirmed by histology. Duration: minimum 6 months after HCC diagnosis. Concurrent medication/care: treatment according to

Study	Pascual 2008[676]
	tumor characteristics and protocol of care: i) liver transplantation for patients younger than 65 years, with a solitary tumor ≤5 cm or 3 nodules in diameter without vascular invasion or extrahepatic dissemination; ii) percutaneous ethanol injection or radiofrequency thermal ablation in patients not suitable for liver transplantation with small tumors (<3.5–4cm); iii) transarterial chemoembolisation considered for patients with large/multinodular tumors without portal thrombosis and preserved liver function; iv) symptomatic treatment was applied for end-stage patients.
Funding	Academic or government funding (supported in part by a grant from Instituto de Salud Carlos III, Madrid, Spain and from Diputacion Provincial de Alicante)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6-MONTHLY versus NO SURVEILLANCE (HCC DETECTED BY SYMPTOMS OR INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: Survival (following HCC diagnosis) at end of study (median 13 months, 0.5–100 months); Other: beta coefficient from multivariate analysis: 0.4 (95% CI 0.3 to 0.6) (p value 0.0003); risk of bias: high (not adjusted for lead time bias; not adjusted for all key confounders); indirectness of outcome: no indirectness. Multivariate analysis included the following variables: Child-Pugh status, tumor characteristics, treatment applied for HCC.	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3 cm, greater than 3 cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Santi 2010[768]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=649)
Countries and setting	Conducted in Italy; setting: 10 medical institutions
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis was histologically confirmed in 271 patients and by laparotomy or laparoscopy in 11. In the remaining patients, the diagnosis was made unequivocal by clinical evaluation, presence of nodular liver margins at ultrasound examination, endoscopic and/or ultrasound findings suggesting the presence of

Study	Santi 2010[768]
	portal hypertension, and laboratory features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Child-Pugh class A or B; (2) HCC diagnosis made during a regular surveillance based on liver ultrasound, with or without AFP performed every 6 (±1 month) or 12 months (±1 month); (3) description of presenting cancer stage available.
Exclusion criteria	Child-Pugh class C or unspecified; diagnosis of HCC made outside any surveillance; unspecified modality of HCC diagnosis; unspecified interval of surveillance; interval outside the above mentioned ranges.
Recruitment/selection of patients	Analysed patients matching inclusion criteria from the ITA.LI.CA database (HCC patients seen consecutively from January 1987 to December 2006)
Age, gender and ethnicity	Age: median (range): 67 (30–89). Gender (M:F): 457/192. Ethnicity: Italian.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (HCV 63.3 %; HBV 9.1%; alcohol 7.9 %; multiple 15.9%; others 3.9%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B. 3. treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear
Extra comments	HBV 9.1% (unclear how many people with multiple aetiologies had HBV)
Indirectness of population	No indirectness
Interventions	(n=139) Intervention 1: Surveillance - ultrasound+AFP yearly. HCC detected during annual (+/-1 month) ultrasound surveillance (with or without AFP). The diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200 ng/ml) of AFP with typical features of the lesion in one imaging technique CT scan or MRI or contrast-enhanced ultrasound [CEUS]) or, in the absence of diagnostic AFP elevation, in at least two techniques. Cancer was staged by CT scan or MRI. For the purpose of this study, HCC was staged as: solitary nodule ≤2 cm without macrovascular invasion (V0), lymph-node invasion (L0) or distant metastases (M0); solitary nodule of 2.1–3 cm, V0, L0, M0; solitary nodule of 3.1–5 cm, V0, L0, M0; 2–3 nodules, each ≤3 cm (paucifocal), V0, L0, M0; advanced tumor (outside the Milano criteria). Duration: median duration of surveillance: 9 years, range: 1–40. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and

Study	Santi 2010[768]
	surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=510) Intervention 2: Surveillance - ultrasound+AFP 6 monthly. HCC detected during semiannual (+/-1 month) ultrasound surveillance (with or without AFP). The diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200 ng/ml) of AFP with typical features of the lesion in one imaging technique CT scan or MRI or contrast-enhanced ultrasound [CEUS]) or, in the absence of diagnostic AFP elevation, in at least two techniques. Cancer was staged by CT scan or MRI. For the purpose of this study, HCC was staged as: solitary nodule ≤2 cm without macrovascular invasion (V0), lymph-node invasion (L0) or distant metastases (M0); solitary nodule of 2.1–3 cm, V0, L0, M0; solitary nodule of 3.1–5 cm, V0, L0, M0; 2–3 nodules, each ≤3 cm (paucifocal), V0, L0, M0; advanced tumor (outside the Milano criteria). Duration: median duration of surveillance: 10 years, range: 0.5–42. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.
Funding	Academic or government funding (supported by a grant from the Ministero del l'Istruzione, dell'Università e della Ricerca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP YEARLY versus ULTRASOUND+AFP 6-MONTHLY	

Study	Santi 2010[768]
Protocol outcome 1: Survival - Actual outcome: mortality (in group 1 patients, the survival was corrected for the lead time bias) at mean follow up after HCC diagnosis 38.6 ± 32.8 months; HR 1.39 (95% CI 1.05 to 1.82); risk of bias: low; indirectness of outcome: no indirectness. Adjusted HR from multivariate analysis (variables: age, platelet count, AFP, Child-Pugh class and esophageal varices). Protective effect of semiannual surveillance disappeared when cancer stage was added to the model (HR for surveillance not provided as an independent variable). Protocol outcome 2: Liver cancer staging (according to BCLC system) - Actual outcome: detection of a HCC beyond the very early stage (that is, solitary nodule >2 cm or multinodular tumor with/without vascular invasion and/or metastases) at unclear; OR 5.99 (95% CI 2.57 to 13.98); risk of bias: low; indirectness of outcome: no indirectness. Adjusted OR from multivariate analysis (variables included those associated with a tumor beyond the very early stage: surveillance interval, sex, aetiology, ALT, AFP, and Child-Pugh class).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; number of lesions; lesion of HCC less than or equal to 3 cm, greater than 3 cm; liver transplant

Study	Stroffolini 2011[848]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=418)
Countries and setting	Conducted in Italy; setting: hospital
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: liver cirrhosis was diagnosed by liver biopsy or in the presence of unequivocal clinical, biochemical and ultrasound signs. Presence of cirrhosis 94.7%.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	HCC cases
Exclusion criteria	Not reported
Recruitment/selection of patients	All HCC cases consecutively observed over a six-month period (October 2008–March 2009) in 23 hospitals throughout the country. All the areas of our country were adequately represented due to the large geographical distribution of the participating centres.

Study	Stroffolini 2011[848]
Age, gender and ethnicity	Age – mean (SD): 67.5 (10.6). Gender (M:F): 310/108. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (HBsAg−/HCV+ 56.1% [15% HBsAg positive or HBsAg positive and anti-HCV positive]). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (Child-Pugh A 70.8%, B 20.6%, C 8.6%). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear
Indirectness of population	No indirectness
Interventions	(n=247) Intervention 1: Surveillance – ultrasound 6-12 monthly. Reports that people had ultrasound surveillance (unclear if also used AFP). Surveillance had been performed twice a year in 80.3% of cases and annually in 19.7%. The diagnostic criteria for HCC were: (1) histological, based on internationally accepted criteria and (2) clinical, based on an alpha-fetoprotein (AFP) value greater than 200 ng/ml and evidence of focal liver lesions at imaging techniques, according to the guidelines of EASL or, for tumors diagnosed after 2005, of the AASLD. Duration: unclear. Concurrent medication/care: treatment not reported but staging according to the following criteria: best stage for curative treatment ("very early stage": single nodule ≤2 cm) or at a stage when curative options are still applicable, that is, within the Milan criteria ("non-advanced stage": single nodule ≤5 cm or no more than 3 nodules, each ≤3 cm, without vascular invasion and metastases). (n=154) Intervention 2: No surveillance. The diagnostic criteria for HCC were: (1) histological, based on internationally accepted criteria and (2) clinical, based on an alpha-fetoprotein (AFP) value greater than 200 ng/ml and evidence of focal liver lesions at imaging techniques, according to the guidelines of EASL or, for tumors diagnosed after 2005, of the AASLD. Duration: unclear. Concurrent medication/care: treatment not reported but staging according to the following criteria: best stage for curative treatment ("very early stage": single nodule ≤2 cm) or at a stage when curative options are still applicable, that is, within the Milan criteria ("non-advanced stage": single nodule ≤5 cm or no more than 3 nodules, each ≤3 cm, without vascular invasion and metastases).
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND 6–12 MONTLY versus NO SURVEILLANCE

Protocol outcome 1: Liver cancer staging (according to BCLC system)
- Actual outcome: Detection of HCC at a very early stage (single nodule ≤2 cm) at unclear; OR 5.4 (95%CI 2.4 to 12.4); risk of bias: low; indirectness of outcome: no indirectness. OR adjusted for the confounding factors of age, gender, surveillance, aetiologies, AFP levels, cirrhosis.
- Actual outcome: Detection of HCC at a non-advanced stage (single nodule ≤5 cm or 3 nodules each ≤3 cm without vascular and lymphonodal invasion and metastases) at unclear; OR 3.1 (95% CI 1.9 to 5.2); risk of bias: low; indirectness of outcome: no indirectness. OR adjusted for the confounding factors of age, gender, surveillance,

Study	Stroffolini 2011[848]
aetiologies, AFP levels, cirrhosis.	
Protocol outcomes not reported by the study	Survival; quality of life; HCC occurrence; number of lesions; lesion of HCC less than or equal to 3cm, greater than 3cm; liver transplant

Study	Trevisani 2004[877]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=363)
Countries and setting	Conducted in Italy; setting: 7 medical institutions
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: the diagnosis of chronic liver disease was based on histology, laparoscopy, or laparotomy in 130 patients (all but 9 had cirrhosis). In the remaining 233 the diagnosis of cirrhosis was made unequivocal by clinical (endoscopic and/or ultrasound signs of portal hypertension, and/or an irregular margin of the liver at ultrasound examination) and laboratory features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with HCC. Presence of underlying chronic liver disease; indication of the modality of HCC diagnosis; description of the cancer stage; aged 70 years or over.
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive from January 1988 to December 2001
Age, gender and ethnicity	Age – mean (SD): surveillance: 73.9 (3.6), incidental HCC 74.9 (3.7); symptomatic HCC 74.6 (4.5). Gender (M:F): 242/121. Ethnicity: Italian.
Further population details	1. Aetiology of liver injury: Hepatitis C (79.6% HCV or HCV co-infection (not including people with mixed alcohol and viral aetiology, proportion of people with HCV in this group not reported). 2. Severity of the underlying liver disease/ degree of liver decompensation at the time of HRS: Child-Pugh A or B (Child-Pugh A 67.2%, Child-Pugh B 27.6%, Child-Pugh C 5.2%). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear

Study	Trevisani 2004[877]
Extra comments	All but 9 patients had cirrhosis. 12.7% HBV or HBV co-infection (not including people with mixed alcohol and viral aetiology, proportion of people with HBV in this group not reported).
Indirectness of population	No indirectness
Interventions	(n=158) Intervention 1: Surveillance - ultrasound+AFP 6–12 monthly. Diagnosis made during regular surveillance performed every 6 (96 patients) or 12 months (62 patients). Diagnosis of HCC corroborated by histology or cytology. In the remaining cases it was made according to the Italian guidelines for the diagnosis of HCC, by combining an AFP increase (>200 ng/mL) with typical features on one imaging technique, or coincident findings were found on at least 2 techniques. Cancer was staged with both ultrasound and CT scan features and, when appropriate, by angiography and MRI. Macroscopic HCC was classified as: solitary nodular; paucifocal ≤3 nodules, multifocal >3 nodules, diffuse and massive type. The cancer stage was considered advanced or non-advanced according to the Milano criteria. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=138) Intervention 2: No surveillance (HCC detected incidentally). HCC detected incidentally outside surveillance or during diagnostic procedures for other diseases. Diagnosis of HCC corroborated by histology or cytology. In the remaining cases it was made according to the Italian guidelines for the diagnosis of HCC, by combining an AFP increase (>200 ng/ml) with typical features on one imaging technique, or coincident findings were found on at least 2 techniques. Cancer was staged with both ultrasound and CT scan features and, when appropriate, by angiography and MRI. Macroscopic HCC was classified as: solitary nodular; paucifocal ≤3 nodules, multifocal >3 nodules, diffuse and massive type. The cancer stage was considered advanced or non-advanced according to the Milano criteria. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria"

Study	Trevisani 2004[877]
	proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=67) Intervention 3: No surveillance (HCC detected by symptoms). HCC discovered because of symptom appearance. Diagnosis of HCC corroborated by histology or cytology. In the remaining cases it was made according to the Italian guidelines for the diagnosis of HCC, by combining an AFP increase (>200 ng/ml) with typical features on one imaging technique, or coincident findings were found on at least two techniques. Cancer was staged with both ultrasound and CT scan features and, when appropriate, by angiography and MRI. Macroscopic HCC was classified as: solitary nodular; paucifocal ≤3 nodules, multifocal >3 nodules, diffuse and massive type. The cancer stage was considered advanced or non-advanced according to the Milano criteria. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.
Funding	Academic or government funding

Study	Trevisani 2004[877]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6–12 MONTHLY versus NO SURVEILLANCE (HCC DETECTED INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: survival; other: adjusted HR for surveillance not reported as it was not found to be an independent prognostic factor Protocol outcome 2: Liver cancer staging (according to BCLC system) at end of study - Actual outcome: HCC advanced stage according to Milano criteria at unclear; OR 0.29 (95% CI 0.17 to 0.49) (p value <0.001); risk of bias: low; indirectness of outcome: no indirectness. Surveillance shown to be an independent protective factor against advanced HCC. Adjusted OR (multivariate analysis adjusted for centre of enrolment, age, sex, aetiology of cirrhosis, Child-Pugh class, AFP level and type of diagnosis. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6–12 MONTHLY versus NO SURVEILLANCE (HCC DETECTED BY SYMPTOMS) Protocol outcome 1: Survival - Actual outcome: survival; other: adjusted HR for surveillance not reported as it was not found to be an independent prognostic factor Protocol outcome 2: Liver cancer staging (according to BCLC system) at end of study - Actual outcome: HCC advanced stage according to Milano criteria at unclear; OR 0.18 (95% CI 0.09 to 0.37) (p value <0.001); risk of bias: low; indirectness of outcome: no indirectness. Surveillance shown to be an independent protective factor against advanced HCC. Adjusted OR (multivariate analysis adjusted for centre of enrolment, age, sex, aetiology of cirrhosis, Child-Pugh class, AFP level and type of diagnosis.	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3cm, greater than 3cm; number of lesions; liver transplant

Study	Trevisani 2007[880]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=608)
Countries and setting	Conducted in Italy; setting: 10 medical institutions
Line of therapy	Adjunctive to current care
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis was confirmed by histology in 168 patients and by

Study	Trevisani 2007[880]
	laparotomy/laparoscopy in 10. In the remaining cases, the diagnosis was made unequivocally by clinical (endoscopic and/or ultrasound signs of portal hypertension and a nodular margin of the liver at ultrasound examination) and laboratory features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	HCC and cirrhosis
Exclusion criteria	Class A Child-Pugh; surveillance interval not reported
Recruitment/selection of patients	ITA.LI.CA database: data of HCC patients seen consecutively from January 1987 to December 2004
Age, gender and ethnicity	Age - Mean (SD): Child Pugh B: surveillance 63.8 ± 9.2, no surveillance 65.7 ± 10.0; Child-Pugh C: surveillance 61.6 ± 10.6, no surveillance: 60.4 ± 10.8. Gender (M:F): 455/153. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: mixed aetiologies (predominantly HCV). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: not applicable/not stated/unclear (Child-Pugh A excluded. Results stratified by Child-Pugh B and C). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear
Extra comments	10.4% HBV included (unclear how many of the people with multiple aetiologies had HBV)
Indirectness of population	No indirectness
Interventions	(n=252) Intervention 1: Surveillance - ultrasound+AFP 6-12 monthly. HCC was detected during regular surveillance based on liver ultrasound and AFP performed every 6 (172 cases [68.3%]) or 12 (80 [31.7%]) months. These patients were grouped since their prognosis was unaffected by the interval (data not shown, p=0.531). Allocated to group 1 even if the surveillance was brought forward due to the occurrence of symptoms. Diagnosis of HCC was based on histology or cytology in 42 patients. Otherwise, diagnosis was made by combining a diagnostic AFP increase (>200 ng/ml) with a typical feature of the lesion (arterial hypervascularity) in one imaging technique or, in the absence of diagnostic AFP, in at least two techniques. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally,

Study	Trevisani 2007[880]
	transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=356) Intervention 2: No surveillance (HCC detected by symptoms or incidentally). HCC was detected "incidentally," that is, outside any programmed surveillance or during examination for other diseases (181 patients [50.8%]), or because of symptom appearance (175 patients [49.2%]). These patients were grouped because both modalities of diagnosis reproduce an alternative to surveillance in detecting HCC in clinical practice. Most cases were referred to our centres by their GPs or other institutions to confirm diagnosis or start treatment of HCC (concomitant non-randomized controls). No conclusive information on surveillance (interval decided by referring physician). Diagnosis of HCC was based on histology or cytology in 42 patients. Otherwise, diagnosis was made by combining a diagnostic AFP increase (>200 ng/ml) with a typical feature of the lesion (arterial hypervascularity) in one imaging technique or, in the absence of diagnostic AFP, in at least two techniques. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumor nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumor was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumor was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumor not treatable with PEI or a multifocal tumor involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.
Funding	Academic or government funding (supported by a grant [Ricerca Fondamentale Orientata 2001–2003, Fondi ex 60%] from the Ministero della Istruzione, della Universita e della Ricerca [MIUR)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6–12 MONTHLY versus NO SURVEILLANCE (HCC DETECTED BY SYMPTOMS OR INCIDENTALLY) Protocol outcome 1: Survival	

Study	Trevisani 2007[880]
- Actual outcome: survival at median follow up 17 months from the diagnosis of HCC; other: adjusted HR for surveillance not reported as it was not found to be an independent prognostic factor	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3 cm, greater than 3 cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Trinchet 2011[884]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=1,340 randomized patients. Sixty-two were subsequently excluded from analysis after revision of individual data due to either immediate loss to follow-up [n=12] or to the presence of a focal liver lesion at inclusion [n=50]). Final number of subjects included = 1,278
Countries and setting	Conducted in Belgium, France, multiple countries; setting: 43 specialist liver disease centers in France and Belgium
Line of therapy	Not applicable
Duration of study	Intervention + follow up: median 47 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: histologically proven compensated cirrhosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomized
Inclusion criteria	(1) age older than 18 years; (2) histologically proven cirrhosis, whatever the time of biopsy; (3) cirrhosis related to either excessive alcohol consumption (80 g per day in males and 60 g per day in females for at least 10 years), chronic infection with hepatitis C virus (HCV) (serum anti-HCV antibodies-positive) or hepatitis B virus (HBV) (serum hepatitis B surface antigen (HBsAg)-positive), or hereditary haemochromatosis (liver-iron overload and C282Y homozygosity); (4) absence of previous complications of cirrhosis (particularly ascites, gastrointestinal haemorrhage or HCC); (5) patients belonging to Child-Pugh class A or B and without a focal liver lesion at inclusion; and (6) written informed consent
Exclusion criteria	(1) Patients belonging to Child-Pugh class C; (2) severe uncontrolled extrahepatic disease resulting in estimated life expectancy of less than 1 year; and (3) coinfection with human immunodeficiency virus (HIV), even if controlled by an antiviral treatment.
Recruitment/selection of patients	June 2000 to May 2005
Age, gender and ethnicity	Age – M=median (IQR): 3 month: 54 (47-61); 6 month: 55 (48-64). Gender (M:F): 883/395. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: mixed aetiologies (alcohol 39.2%; HCV 44.1%; HBV 13.2%; haemochromatosis 1.6%; other

Study	Trinchet 2011[884]
	2.5%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (Child-Pugh C excluded [1% were Child-Pugh C]). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear
Extra comments	HBV 13.2%
Indirectness of population	No indirectness
Interventions	(n=668) Intervention 1: Surveillance - ultrasound 3-monthly. Patients received either ultrasound every 3 months and a serum AFP assay every 6 months or ultrasound every 3 months and no serum AFP assay. For a given patient it was recommended to perform ultrasound in the same centre by the same experienced operator. Diagnosis of HCC: contrast enhanced imaging, a serum AFP assay, and/or a guided biopsy were performed according to EASL guidelines. HCC diagnosis was established in the following situations: (1) histological proof of HCC; and (2) when a focal lesion was >2 cm in diameter, assessed by early arterial hypervascularization, using two contrast-enhanced methods (CT scan, MRI, arteriography), or when there was an association between serum AFP level of >400 ng/mL plus early arterial hypervascularization, assessed by one contrast enhanced method. In case of an increase in serum AFP level without liver focal lesion at ultrasound, a CT scan was performed according to recommendations. Duration: mean follow-up 47.1 months. Concurrent medication/care: when a HCC diagnosis was established treatment was determined using a multidisciplinary approach at each medical centre, by the physicians in charge of the patient. It was recommended to perform curative treatment (percutaneous ablation, resection, or transplantation) whenever possible. Regular endoscopic surveillance was performed to detect esophageal varices and other portal hypertension-related lesions. In cases of esophageal varices, preventive therapy was recommended either by beta-blockers or endoscopic ligation, according to international recommendations. (n=672) Intervention 2: Surveillance - ultrasound 6-monthly. Patients received either ultrasound and a serum AFP assay every 6 months or ultrasound every 6 months and no serum AFP assay. For a given patient it was recommended to perform ultrasound in the same centre by the same experienced operator. Diagnosis of HCC: contrast enhanced imaging, a serum AFP assay, and/or a guided biopsy were performed according to EASL guidelines. HCC diagnosis was established in the following situations: (1) histological proof of HCC; and (2) when a focal lesion was >2 cm in diameter, assessed by early arterial hypervascularization, using two contrast-enhanced methods (CT scan, MRI, arteriography), or when there was an association between serum AFP level of >400 ng/ml plus early arterial hypervascularization, assessed by one contrast enhanced method. In case of an increase in serum AFP level without liver focal lesion at ultrasound, a CT scan was performed according to recommendations. Duration: mean follow-up 46.8 months. Concurrent medication/care: when a HCC diagnosis was established treatment was determined using a multidisciplinary approach at each medical centre, by the physicians in charge of the patient. It was recommended to perform curative treatment (percutaneous ablation, resection, or transplantation) whenever possible. Regular endoscopic surveillance was performed to detect esophageal varices and other portal hypertension-related lesions. In

Study	Trinchet 2011[884]
	cases of esophageal varices, preventive therapy was recommended either by beta-blockers or endoscopic ligation, according to international recommendations.
Funding	Academic or government funding (funded by the French Ministry of Health [PHRC 1998 and 2003] and the French Ligue de Recherche contre le Cancer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND 3-MONTHLY versus ULTRASOUND 6-MONTHLY

Protocol outcome 1: Mortality at 5 years
- Actual outcome: Survival at median follow-up 47 months; HR 0.87 (95 %CI 0.63 to 1.19) calculated – from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 2: HCC occurrence at end of study
- Actual outcome: Final diagnosis of focal liver lesion=HCC at median follow-up 47 months; Group 1: 53/640, Group 2: 70/638; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: Lesion of HCC less than or equal to 3cm, greater than 3cm at end of study
- Actual outcome: Diameter of the largest HCC nodule (≤30 mm) – results categorised in study by ≤10, 11–20, 21–30, 31–50, ≥50 at median follow-up 47 months; Group 1: 42/640, Group 2: 49/638; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: Diameter of the largest HCC nodule (>30 mm) – results categorised in study by ≤10, 11–20, 21–30, 31–50, ≥50 at median follow-up 47 months; Group 1: 11/640, Group 2: 21/638; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 4: Number of lesions at end of study
- Actual outcome: Uninodular tumor at median follow-up 47 months; Group 1: 31/640, Group 2: 41/638; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome: 2 or 3 nodules at median follow-up 47 months; Group 1: 15/640, Group 2: 12/638; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome: >3 nodules at median follow-up 47 months; Group 1: 4/640, Group 2: 7/638; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome: Infiltrative at median follow-up 47 months; Group 1: 3/640, Group 2: 10/638; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 5: Liver cancer staging (according to BCLC system) at end of study
- Actual outcome: Within Milan criteria (one nodule ≤50 mm or 2 or 3 nodules ≤30 mm) at median follow-up 47 months; Group 1: 42/640, Group 2: 50/638; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: Beyond Milan criteria (Milan criteria=one nodule ≤50 mm or 2 or 3 nodules ≤30 mm) at median follow-up 47 months; Group 1: 11/640, Group 2: 20/638; risk of bias: high; indirectness of outcome: no indirectness

Study	Trinchet 2011[884]
Protocol outcome 6: Liver transplant at end of study - Actual outcome: Transplantation at median follow-up 47 months; Group 1: 17/640, Group 2: 13/638; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life

H.5 Surveillance for the detection of varices

None

H.6 Prophylaxis of variceal haemorrhage

Study	Andreani 1990[42]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in France; setting: multicentre (2 centres)
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis proven by histological examination (or if unavailable, on the basis of clinical or lab test results, regardless of origin)
Stratum	Size of varices (overall): presence of oesophageal varices on endoscopy regardless of size
Subgroup analysis within study	Post-hoc subgroup analysis: Size of varices (grade I: non-confluent oesophageal varices flattened by insufflation; grade II: oesophageal varices separated by zones of normal oesophagus and not flattened by insufflation; grade III: confluent oesophageal varices not flattened by insufflation)
Inclusion criteria	All adult patients with 1) cirrhosis proven by histological examination (or if unavailable, on the basis of clinical or lab test results, regardless of origin); 2) presence of oesophageal varices on endoscopy regardless of size; 3) no history of gastrointestinal bleeding by rupture of oesophageal varices.
Exclusion criteria	1) HCC; 2) contraindication to the use of propranolol (cardiac insufficiency, asthma, disturbance of auriculoventricular conduction); 3) refusal or unfeasibility of treatment; 4) unfeasibility of regular surveillance; 5) serious associated illness reducing life expectancy to <1 year; 6) previous treatment with endoscopic sclerosis of oesophageal varices,

Study	Andreani 1990[42]
	propranolol or surgery for portal hypertension.
Recruitment/selection of patients	All eligible adult patients. November 1985 to February 1988.
Age, gender and ethnicity	Age - other: mean (SEM) propranolol: 55.0 (1.3), placebo: 55.6 (1.7). Gender (M:F): 50/34. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (propranolol: 55.0 [1.3], placebo: 55.6 [1.7]. Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 23.8%; Child-Pugh B: 47.6%; Child-Pugh C: 27.4% [overall 75% Child-Pugh B and C]).
Extra comments	Size of varices (Grade I/II/III): propranolol 15/24/4; placebo 17/16/6. Child-Pugh class (A/B/C): propranolol 10/19/13; placebo 10/21/10. Ascites (absent/moderate/intractable): propranolol 17/20/6; placebo 18/16/7. Study has a third arm (sclerotherapy).
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Oral non-selective beta-blockers - propranolol. Propranolol twice daily. Dose titrated to achieve a 25% reduction in resting heart rate. Patients seen after 1 month and then at 3 month intervals. Duration 2 years. Concurrent medication/care: not reported. (n=41) Intervention 2: Placebo. Vitamin K (10mg) twice daily as placebo. Patients seen after 1 month and then at 3 month intervals. Duration 2 years. Concurrent medication/care: other associated treatment authorised with the exception of beta-blockers.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (overall): mortality at 2 years; Group 1: 13/37, Group 2: 18/39; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (small): variceal bleeding (active bleeding from the varices or the presence of a clot on a varix and no other detectable cause of haemorrhage) at 2 years; Group 1: 0/15, Group 2: 2/17; risk of bias: very high; indirectness of outcome: serious indirectness
- Actual outcome for size of varices (medium/large): variceal bleeding (active bleeding from the varices or the presence of a clot on a varix and no other detectable cause of haemorrhage) at 2 years; Group 1: 2/28, Group 2: 8/22; risk of bias: very high; indirectness of outcome: serious indirectness

Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study

Study	Andreani 1990[42]
- Actual outcome for size of varices (small): gastrointestinal bleeding (variceal or other) at 2 years; Group 1: 0/15, Group 2: 3/17; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for size of varices (medium/large): gastrointestinal bleeding (variceal or other) at 2 years; Group 1: 2/28, Group 2: 10/22; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (overall): variceal or gastrointestinal bleeding death at 2 years; Group 1: 1/37, Group 2: 4/39; risk of bias: very high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Conn 1991[192] (Groszmann 1990[360])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=102)
Countries and setting	Conducted in multiple countries, Spain, USA; setting: multicentre (3 centres)
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 16.3 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: well-established clinical diagnosis of cirrhosis (approximately 50% had histological confirmation)
Stratum	Size of varices (overall): endoscopically documented oesophageal varices.
Subgroup analysis within study	Post-hoc subgroup analysis: size of varices (grade 1: 1-3mm with Valsalva, grade 2: 1-3mm without Valsalva, grade 3: 3-3mm; grade 4: >6mm). Results reported separately for small varices (defined in study as grade 1 and 2) and large varices (defined in study as grade 3 and 4).
Inclusion criteria	Patients with a well-established clinical diagnosis of cirrhosis (approximately 50% had histological confirmation), endoscopically documented oesophageal varices and portal hypertension who had not previously bled from oesophageal varices or from an unknown upper gastrointestinal site.
Exclusion criteria	Known neoplasms or severe hepatic disease (for example hepatorenal syndrome) or non-hepatic disorders (for example cardiovascular, respiratory or renal failure) severe enough to interfere with participation.

Study (subsidiary papers)	Conn 1991[192] (Groszmann 1990[360])
Recruitment/selection of patients	Admitted to 1 of the participating hospitals between October 1982 and August 1986
Age, gender and ethnicity	Age - mean (SD): propranolol: 54 (9), placebo: 54 (11). Gender (M:F): 73/29. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (propranolol: 54 (9), placebo: 54 (11). Mean age in both groups <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score A (Child-Pugh A: 57.8%; Child-Pugh B & C: 42.2%).
Extra comments	Child-Pugh class (A/B/C): propranolol 35/11/5, placebo 24/24/3. Ascites: propranolol 22, placebo 31. Varices (small/large): propranolol 26/25, placebo 29/22.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: oral non-selective beta-blockers - propranolol. Dose for placebo/propranolol for the study determined prior to randomisation by the response of HVPG to increasing doses of propranolol during hepatic vein catheterisation (in order to keep the study blind by not adjusting dose according to resting heart rate). Dose not increased above the level determined during titration. Dose could be reduced because of bradycardia or hypotension. Seen as outpatients monthly for 3 months and then every 3 months thereafter. Duration mean 16.3 months. Concurrent medication/care: not reported. (n=51) Intervention 2: placebo. Dose for placebo/propranolol for the study determined prior to randomisation by the response of HVPG to increasing doses of propranolol during hepatic vein catheterisation (in order to keep the study blind by not adjusting dose according to resting heart rate). Dose not increased above the level determined during titration. Seen as outpatients monthly for 3 months and then every 3 months thereafter. Duration mean 16.3 months. Concurrent medication/care: not reported.
Funding	Study funded by industry (supported by Ayerst Laboratories, New York; Imperial Chemical Industries, Spain and the Veterans Administration Merit Review Program.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (overall): death at mean 16.3 months; Group 1: 8/51, Group 2: 11/51; risk of bias: low; indirectness of outcome: serious indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (small): endoscopic visualisation of an actively bleeding varix, a fresh clot or eschar on the surface of a varix or the absence of any other possible bleeding site in the upper gastrointestinal tract at mean 16.3 months; Group 1: 2/26, Group 2: 2/29; risk of bias: high; indirectness of outcome: serious

Study (subsidiary papers)	Conn 1991[192] (Groszmann 1990[360])
indirectness - Actual outcome for size of varices (medium/large): endoscopic visualisation of an actively bleeding varix, a fresh clot or eschar on the surface of a varix or the absence of any other possible bleeding site in the upper gastrointestinal tract at mean 16.3 months; Group 1: 0/25, Group 2: 9/22; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (overall): gastrointestinal haemorrhage at mean 16.3 months; Group 1: 4/51, Group 2: 14/51; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (overall): death due to variceal haemorrhage at mean 16.3 months; Group 1: 2/51, Group 2: 3/51; risk of bias: low; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Gluud 2012[340] (Drastich 2011,[239] Gheorghe 2002,[324] Jutabha 2000,[444] Schcpka 2003,[778] Song 2000,[825] Chen 1998,[163] De 1999,[222] Sarin 1999,[773] De la Mora 2000,[217] Lui 2002,[542] Abulfutuh 2003,[15] Schepke 2004,[779] Jutabha 2005,[443] Thuluvath 2005,[872] Anon 2005,[3] Lay 2006,[503] Abdelfattah 2006,[9] Lo 2004,[531] Norberto 2007,[639] Perez-Ayuso 2010,[685] Psilopoulos 2005,[712] Sarin 1997,[776] Tripathi 2009[885])
Study type	Systematic review
Number of studies (number of participants)	19 studies (23 references) (n=Total 1504. Mean [range] in individual studies 79 [24-152])
Countries and setting	Conducted in China, Czech Republic, Egypt, Germany, Greece, India, Italy, Mexico, Romania, South Korea, Taiwan, United Kingdom, USA; setting: 13 trials were single-centre trials. The remaining five trials included 2 to 13 clinical sites.
Line of therapy	1st line
Duration of study	Intervention + follow up: range of average follow-up times (10-55 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: included patients with cirrhosis were diagnosed based on clinical, biochemical, or histological signs
Stratum	Size of varices (medium/large): included studies specified only patients with large or high-risk oesophageal varices were considered for inclusion. The criteria used for assessing the risk of bleeding were red colour signs, tortuous varices protruding as far as at least one third of the oesophageal lumen, or pseudotumorous varices (also known as F2

Study (subsidiary papers)	**Gluud 2012[340] (Drastich 2011,[239] Gheorghe 2002,[324] Jutabha 2000,[444] Schcpka 2003,[778] Song 2000,[825] Chen 1998,[163] De 1999,[222] Sarin 1999,[773] De la Mora 2000,[217] Lui 2002,[542] Abulfutuh 2003,[15] Schepke 2004,[779] Jutabha 2005,[443] Thuluvath 2005,[872] Anon 2005,[3] Lay 2006,[503] Abdelfattah 2006,[9] Lo 2004,[531] Norberto 2007,[639] Perez-Ayuso 2010,[685] Psilopoulos 2005,[712] Sarin 1997,[776] Tripathi 2009[885])**
	or F3 varices). Other trials classified as high risk if they had a diameter of at least 5mm or at least 3mm plus at least 1 red colour sign.
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with endoscopically verified oesophageal varices that have never bled were included regardless of the underlying liver disease (cirrhosis or other cause).
Exclusion criteria	The reported exclusion criteria were contraindications to beta-blockers or severe concurrent illness, such as renal or malignant disease.
Recruitment/selection of patients	Systematic review - not reported
Age, gender and ethnicity	Age - mean (range): banding Ligation: 53 (42-62), beta-blockers: 52 (39-59). Gender (M:F): 66% / 34%. Ethnicity: systematic review - not reported
Further population details	1. Age of patient: 65 years and under. 2. Severity of underlying liver disease at the time of intervention (measured by MELD): systematic review: mixed.
Extra comments	In 2 trials, all patients were eligible for liver transplantation (Gheorghe 2002, Norberto 2007). Mean number of patients with alcohol related liver disease 22%. Seven trials published in abstract form.
Indirectness of population	Sarin 1999: cirrhosis not an inclusion criteria for study (7 patients had another underlying cause of portal hypertension); Chen 1998: risk or size of varices not stated.
Interventions	(n=731) Intervention 1: band ligation - multiband. Banding ligation performed with conventional or multiband ligators and was repeated at 3 to 4 week intervals until the varices were eradicated. On average, 2 to 3 sessions were necessary to achieve eradication. Patients were followed up at 3 to 6 month intervals and banding ligation repeated in the case of variceal recurrence. Duration range of average follow-up times (10-55 months). Concurrent medication/care: not stated. (n=773) Intervention 2: oral non-selective beta-blockers - propranolol. One trial assessed nadolol (Lo 2004). The initial daily dose was 40 mg adjusted based on the heart rate (mean 60 mg). One trial assessed carvedilol (Tripathi 2009). The initial daily dose of carvedilol was 6.25 mg. The dose was increased to 12.5 mg if tolerated (the mean dose was not reported). The remaining trials assessed propranolol. The initial daily dose of propranolol ranged from 20 to 120 mg (mean 60 mg). The dose was adjusted to achieve a 20% to 25% reduction in heart rate, a resting heart rate of 55 beats per minute or less, or to a maximum dose of 160 or 320 mg. The mean dose administered in the trials was 70 mg/day (range 30 mg to 93 mg). Duration range of average follow-up times (10-55 months). Concurrent

Study (subsidiary papers)	**Gluud 2012[340] (Drastich 2011,[239] Gheorghe 2002,[324] Jutabha 2000,[444] Schcpka 2003,[778] Song 2000,[825] Chen 1998,[163] De 1999,[222] Sarin 1999,[773] De la Mora 2000,[217] Lui 2002,[542] Abulfutuh 2003,[15] Schepke 2004,[779] Jutabha 2005,[443] Thuluvath 2005,[872] Anon 2005,[3] Lay 2006,[503] Abdelfattah 2006,[9] Lo 2004,[531] Norberto 2007,[639] Perez-Ayuso 2010,[685] Psilopoulos 2005,[712] Sarin 1997,[776] Tripathi 2009[885])**
	medication/care: not stated.
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BAND LIGATION versus NON-SELECTIVE BETA-BLOCKERS

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): mortality at range of average follow-up times (10-55 months); Group 1: 176/731, Group 2: 178/773; risk of bias: high; indirectness of outcome: serious indirectness
- Actual outcome for Drastich 2011[239] and size of varices (medium/large): overall survival at median 11 months; HR 0.81 (95%CI 0.11 to 5.77) calculated – from logrank P-value; Indirectness of outcome: no indirectness
- Actual outcome for Lo 2004[531] and size of varices (medium/large): overall survival at median 21.8 months; HR 0.81 (95%CI 0.36 to 1.84) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Perez-ayuso 2010[685] and size of varices (medium/large): overall survival at median 55 months; HR 1.48 (95%CI 0.74 to 2.96) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Lui 2002[542] and size of varices (medium/large): overall survival at mean 19.7 months; HR 1.09 (95%CI 0.5 to 2.36) calculated – from curve and numbers at risk; indirectness of outcome: no indirectness
- Actual outcome for Psilopoulos 2005[712] and size of varices (medium/large): overall survival (censored when have variceal bleeding event) at mean 27.5 months; HR 0.79 (95%CI 0.34 to 1.84) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Schepke 2004[779] and size of varices (medium/large): overall survival at mean 34.3 months; HR 1.24 (95%CI 0.77 to 2.01) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Tripathi 2009[885] and size of varices (medium/large): overall survival at mean 25.5 months; HR 0.9 (95%CI 0.53 to 1.55) calculated – from logrank P-value; indirectness of outcome: no indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (medium/large): variceal bleeding at range of average follow-up times (10-55 months); Group 1: 75/590, Group 2: 112/611; risk of bias: high; indirectness of outcome: serious indirectness
- Actual outcome for Drastich 2011[239] and size of varices (medium/large): without variceal bleeding at median 11 months; HR 0.64 (95%CI 0.09 to 4.6) calculated – from logrank P-value; ndirectness of outcome: no indirectness
- Actual outcome for Lo 2004[531] and size of varices (medium/large): free from first bleeding of oesophageal varices at median 21.8 months; HR 0.57 (95%CI 0.19 to 1.69) reported; indirectness of outcome: no indirectness

Study (subsidiary papers)	Gluud 2012[340] (Drastich 2011,[239] Gheorghe 2002,[324] Jutabha 2000,[444] Schcpka 2003,[778] Song 2000,[825] Chen 1998,[163] De 1999,[222] Sarin 1999,[773] De la Mora 2000,[217] Lui 2002,[542] Abulfutuh 2003,[15] Schepke 2004,[779] Jutabha 2005,[443] Thuluvath 2005,[872] Anon 2005,[3] Lay 2006,[503] Abdelfattah 2006,[9] Lo 2004,[531] Norberto 2007,[639] Perez-Ayuso 2010,[685] Psilopoulos 2005,[712] Sarin 1997,[776] Tripathi 2009[885])
- Actual outcome for Lui 2002[542] and size of varices (medium/large): free from variceal bleeding at mean 19.7 months; HR 0.46 (95%CI 0.15 to 1.47) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Psilopoulos 2005[712] and size of varices (medium/large): free from variceal bleeding at mean 27.5 months; HR 0.21 (95%CI 0.04 to 0.95) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Sarin 1997[776] and size of varices (medium/large): free from variceal bleeding at mean 13 months; HR 0.33 (95%CI 0.11 to 0.77) reported; indirectness of outcome: no indirectness - Actual outcome for Schepke 2004[779] and size of varices (medium/large): without first variceal bleed at mean 34.3 months; HR 1.05 (95%CI 0.57 to 1.94) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Tripathi 2009[885] and size of varices (medium/large): free from variceal bleeding at mean 25.5 months; HR 2.4 (95%CI 1.03 to 5.55) reported; indirectness of outcome: no indirectness Protocol outcome 3: hospital admission at end of study - Actual outcome for Sarin 1997[776] and size of varices (medium/large): hospitalisations at mean 13 months; Group 1: 5/45, Group 2: 12/44; indirectness of outcome: no indirectness Protocol outcome 4: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at range of average follow-up times (10-55 months); Group 1: 103/731, Group 2: 157/773; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 5: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): bleeding related mortality at range of average follow-up times (10-55 months); Group 1: 29/567, Group 2: 37/585; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 6: adverse events: fatigue at end of study - Actual outcome for size of varices (medium/large): lethargy at range of average follow-up times (10-55 months); Group 1: 0/86, Group 2: 22/77; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital length of stay at end of study

Study	Lay 1997[504]

Study	Lay 1997[504]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in China; setting: general hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: mean (SD) months: EVL: 13 (11), control: 14 (10)
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: cirrhosis with no other disease (for example cancer) reducing the life expectancy
Stratum	Size of varices (medium/large): all patients had oesophageal varices at high risk of bleeding of F2 or F3 size
Subgroup analysis within study	Unclear: Child-Pugh classification (subgroup analysis for first oesophageal bleeding episode but data inconsistent with total number reported in the text and at an unknown timepoint)
Inclusion criteria	1) No known previous bleeding from the upper gastrointestinal tract; 2) Oesophageal varices at high risk of bleeding, as defined below; and 3) Cirrhosis with no other disease (for example cancer) reducing the life expectancy. Oesophageal varices at high risk of bleeding (score <-0.38 resulting from the total sum of the category scores (fundamental colour, red colour sign, form, and esophagitis). Therefore, all patients had blue varices of F2 or F3 size with at least 1 of the following: red wale markings (++, +++), cherry-red spots (++, +++), or hematocystic spots (+).
Exclusion criteria	Presence of gastric or ectopic varices were excluded
Recruitment/selection of patients	January 1993 to December 1995
Age, gender and ethnicity	Age - mean (SD): endoscopic variceal ligation (EVL): 56 (11); control: 55 (10). Gender (M:F): 101/25. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (mean for each arm <65 years. EVL: 56 (11); control: 55 (10)). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 26.2%; Child-Pugh B: 35.7%; Child-Pugh C: 38.1%% [Overall 73.8% Child Pugh B or C]).
Extra comments	Aetiology (alcohol/hepatitis/other): EVL: 12/47/3; control: 11/49/4. Child-Pugh classification (A/B/C): EVL: 17/22/23; control: 16/23/25. Ascites: EVL: 33; control: 32.
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: band ligation - conventional. Each varix was ligated with 1 to 3 rubber bands (adapted endoscopic ligating device, Bard Interventional Products, Billerica, MA). Ligation was performed by 2 experienced endoscopists who had performed more than 10 sessions. During elective sessions, individual ligation sites were gradually reduced until the varices were too small to ligate. The total did not exceed 10 rubber bands per treatment session. Endoscopic treatment was performed weekly for the first 3 weeks, when possible, unless extensive

Study	Lay 1997[504]
	oesophageal ulcers occurred or delays resulted from complications; then, treatment was performed every 2 weeks until the oesophageal varices were eradicated. Duration mean 13 months. Concurrent medication/care: follow-up endoscopic examination was performed later on a 3-month basis. Patients were instructed to identify any symptoms or signs suggestive of complications and bleeding, and to visit the hospital immediately. (n=64) Intervention 2: no intervention. No details reported. Duration mean 14 months. Concurrent medication/care: no details reported.
Funding	Academic or government funding (supported by grant NSC 83-0412-B-075A-011 from the National Science Council)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONVENTIONAL versus NO INTERVENTION Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): overall survival at up to 2 years (mean 13 months); HR 0.41 (95%CI 0.24 to 0.7) calculated – from logrank P-value; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): active variceal bleeding was diagnosed when blood was seen directly by endoscopy to issue from a varix, or when fresh blood was seen in the oesophagus of patients with cherry-red spots on large varices and no other potential site of bleeding was discovered. Clinical signs were defined as new onset of hematemesis, coffee ground vomitus, hematochezia, or melena with increasing pulse rate over 110 beats per minute and decreasing blood pressure below 90 mm Hg at up to 2 years (mean 13 months); HR 0.33 (95%CI 0.19 to 0.58) calculated – from logrank P-value; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at up to 2 years (mean 13 months); Group 1: 12/62, Group 2: 38/64; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; bleeding related mortality at end of study; adverse events: fatigue at end of study

Study	Lo 1999[532]
Study type	RCT (patient randomised; parallel)

Study	Lo 1999[532]
Number of studies (number of participants)	1 (n=133)
Countries and setting	Conducted in Taiwan; setting: general hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: median 29 months
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: cause of portal hypertension was cirrhosis
Stratum	Size of varices (medium/large): endoscopically assessed high risk oesophageal varices (F2 or F3 , associated with a moderate degree of red colour signs)
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	January 1992 to March 1995
Age, gender and ethnicity	Age - mean (SD): endoscopic variceal ligation (EVL): 55 (12); control: 57 (11). Gender (M:F): define. Ethnicity: not stated.
Further population details	1. Age of patient: 65 years and under (range for study 20-70 years. Mean for each arm <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 28.3%; Child-Pugh B: 43.3%; Child-Pugh C: 28.3% [Overall 71.7% Child Pugh B or C]).
Extra comments	Aetiology of cirrhosis (alcohol/hep B/hep C/ cryptogenic) EVL: 18/23/19/4; control: 20/18/22/3. Ascites EVL: 21; control: 22. Child-Pugh class (A/B/C) EVL: 16/30/18; control: 20/25/17. Variceal size (F2/F3): EVL: 27/37; control: 30/33. Red colour signs (moderate/severe): EVL: 33/31; control: 36/27.
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: band ligation - conventional. Performed under premeditation with 20 mg of buscopan intramuscularly. Performed by 2 experienced endoscopists. Each varix ligated with 1 to 2 rubber bands (Bard Interventional Products, Billerica, MA, USA). Performed at intervals of 3 weeks until all varices were obliterated or too small to be ligated. Duration median 28 months. Concurrent medication/care: sucralfate granules 1 g four times per day were administered to patients during the course of EVL treatment. After obliteration, patients in the treatment group underwent follow-up endoscopy every 3 months. Repeat EVL was performed in case of variceal recurrence. Patients in both groups were advised to receive follow-up consisting of abdominal sonogram, serum alpha-fetoprotein and biochemistry at 3-month intervals. Patients in both groups were advised to abstain from alcohol. (n=67) Intervention 2: no intervention. Control group, no intervention. Duration median 30 months. Concurrent

Study	Lo 1999[532]
	medication/care: in the control group, endoscopy was carried out every 6 months. Patients in both groups were advised to receive follow-up consisting of abdominal sonogram, serum alpha-fetoprotein and biochemistry at 3-month intervals. Patients in both groups were advised to abstain from alcohol.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONVENTIONAL BAND LIGATION versus NO INTERVENTION Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): survival at mean 29 months; HR 0.66 (95%CI 0.35 to 1.23) calculated – from MH P-value; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): oesophageal variceal bleeding (appearance of haematemesis or melena, together with a decrease of haemoglobin and a requirement for blood transfusion of 2 or more units, and the bleeding source proven by emergency endoscopy) at mean 29 months; HR 0.59 (95%CI 0.26 to 1.37) calculated – from MH P-value; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): upper gastrointestinal haemorrhage at mean 29 months; Group 1: 14/64, Group 2: 22/63; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): death due to variceal bleeding or ulcer bleeding at mean 29 months; Group 1: 4/64, Group 2: 9/63; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Pagliaro 1989[657] (Pagliaro 1988,[658] Pagliaro 1989[661])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=174)

Study (subsidiary papers)	Pagliaro 1989[657] (Pagliaro 1988,[658] Pagliaro 1989[661])
Countries and setting	Conducted in Italy; setting: multicentre (4 hospitals)
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: cirrhosis biopsy proven in 43%
Stratum	Size of varices (medium/large): large oesophageal varices endoscopically assessed (F3 according to the Japanese Research Society for Portal Hypertension, that is, varices occupying more than one-third of the oesophageal lumen)
Subgroup analysis within study	Post-hoc subgroup analysis: Child-Pugh classification
Inclusion criteria	All patients with liver cirrhosis and 1) Large oesophageal varices (F3 according to the Japanese Research Society for Portal Hypertension, that is, varices occupying more than one third of the oesophageal lumen); 2) No previous upper gastrointestinal bleeding.
Exclusion criteria	1) Hepatocellular carcinoma; 2) Tense ascites, resistant to in-hospital diuretic treatment, or chronic or recurrent (>3 episodes per year) encephalopathy; 3) Bilirubin >3mg/dl; 4) Heart failure or obstructive lung disease.
Recruitment/selection of patients	Consecutive patients from July 1982 to Jan 1984
Age, gender and ethnicity	Age - mean (SD): propranolol: 55 (11), placebo: 53 (11). Gender (M:F): 122/52. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (propranolol: 55 (11), placebo: 53 (11). Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score A (Child-Pugh A: 59.2%, Child-Pugh B: 34.5%, Child-Pugh C: 6.3%. Overall Child-Pugh A 59.2%).
Extra comments	Child-Pugh classification (A/B/C): propranolol 47/32/6, placebo 56/28/5. Ascites: propranolol 39, placebo 38.
Indirectness of population	No indirectness
Interventions	(n=85) Intervention 1: oral non-selective beta-blockers - propranolol. Oral propranolol twice daily at a dose reducing the resting heart rate by 25%. Dose ranged from 10-480mg. Follow-up every 3 months. Duration 2 years. Concurrent medication/care: same treatment protocol in patients who bled. (n=89) Intervention 2: placebo. Oral vitamin K tablets (10mg) twice daily (not identical to propranolol but stated that patients did not know what treatment they were receiving in unlabelled bottles). Follow-up every 3 months. Duration 2 years. Concurrent medication/care: same treatment protocol in patients who bled.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO	

Study (subsidiary papers)	Pagliaro 1989[657] (Pagliaro 1988,[658] Pagliaro 1989[661])
Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): survival at 2 years (mean 28 months); HR 1.49 (95%CI 0.91 to 2.42) calculated – from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): bleeding cause varices (haematemesis and/or fresh melena) at 2 years (mean 28 months); Group 1: 13/83, Group 2: 18/88; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): patients who bled (varices, erosions or undetermined). Haematemesis and/or fresh melena at 2 years (mean 28 months); Group 1: 18/83, Group 2: 31/88; risk of bias: low; indirectness of outcome: no indirectness. - Actual outcome for size of varices (medium/large): Child-Pugh A. Patients who bled (varices, erosions or undetermined). Haematemesis and/or fresh melena at 2 years (mean 28 months); Group 1: 6/47, Group 2: 18/56; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for size of varices (medium/large): Child-Pugh B & C. Patients who bled (varices, erosions or undetermined). Haematemesis and/or fresh melena at 2 years (mean 28 months); Group 1: 12/38, Group 2: 13/33; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): death due to bleeding at 2 years (mean 28 months); Group 1: 10/83, Group 2: 12/88; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Pascal 1989[675] (Pascal 1987[674])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=230)
Countries and setting	Conducted in France; setting: multicentre
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 1.2 years
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: cirrhosis confirmed by liver biopsy or biochemical and clinical data

Study (subsidiary papers)	Pascal 1989[675] (Pascal 1987[674])
Stratum	Size of varices (medium/large): grade II or II (medium or large) oesophageal varices at endoscopy (Italian Liver Cirrhosis Project, Witzel et al 1987). Grade II: not flattened by insufflation and separated by areas of normal mucosa; grade III: confluent and not flattened by insufflation.
Subgroup analysis within study	Stratified then randomised: stratified by Child-Pugh score <9 and 9-13
Inclusion criteria	Aged under 75 years; cirrhosis and Child-Pugh score <14; grade II or II (medium or large) oesophageal varices at endoscopy (Italian Liver Cirrhosis Project, Witzel et al 1987)
Exclusion criteria	Contraindication to beta-blockers; a past history of upper gastrointestinal bleeding; evidence of gastroduodenal ulcer or hepatic carcinoma, receiving treatment that altered portal haemodynamics.
Recruitment/selection of patients	Every patient with cirrhosis and no history of bleeding and none of the exclusion criteria had an endoscopy
Age, gender and ethnicity	Age - range of means: 51.5 - 55.5 years. Gender (M:F): not reported. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Overall Child-Pugh classification % A/B/C: 17%/37%/46%).
Extra comments	Overall Child-Pugh classification % A/B/C: 17%/37%/46%; varices (grade II/III): propranolol 86/27, placebo 85/25. Violations of inclusion: patients with non-cirrhotic liver: propranolol 0, placebo 1; previous haemorrhage: propranolol 3, placebo 2; small varices: propranolol 2, placebo 2; aged >75: propranolol 0, placebo 2; hepatic carcinoma: propranolol 2, placebo 0.
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: oral non-selective beta-blockers - propranolol. Starting dose 20mg of conventional formulation twice daily. Titrated up to 160mg or 320mg of long-acting once daily to achieve a 20-25% reduction in resting heart rate or until maximum dose permitted (320mg of long acting once daily). Patients evaluated every 2 months. Duration mean 1.2 years. Concurrent medication/care: not reported. (n=112) Intervention 2: placebo. Identical placebo tablet once daily. Duration mean 1.2 years. Concurrent medication/care: not reported.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO Protocol outcome 1: survival (with or without transplant) at end of study	

Study (subsidiary papers)	Pascal 1989[675] (Pascal 1987[674])
- Actual outcome for size of varices (medium/large): survival at mean 1.2 years; HR 0.96 (95%CI 0.59 to 1.56) calculated – from Cox SE/variance; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at mean 1.2 years; Group 1: 20/116, Group 2: 30/111; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 3: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): cause of death bleeding at mean 1.2 years; Group 1: 10/116, Group 2: 18/111; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; primary variceal bleeding at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Sarin 1996[772]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in India; setting: hospital based
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 14 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: all patients had portal hypertension, 6/68 had causes other than cirrhosis.
Stratum	Size of varices (medium/large): patients had blue varices of F2 or F3 size with at least 1 of the red colour signs
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Portal hypertension; 2) Without previous history of upper or lower gastrointestinal bleeding (including bleeding from portal hypertensive gastropathy or ulcer; 3) High risk varices (see below); 4) Presence of 1 of more red colour signs on the varices; no previous sclerotherapy or banding; available for informed consent. High-risk varices assessed endoscopically: patients with large varices >5mm assessed for risk of bleeding according to Beppu (score <0 defined high-risk). This included blue varices of F2 or F3 size with at least 1 of the red colour signs.
Exclusion criteria	Hepatorenal syndrome or hepatic encephalopathy

Study	Sarin 1996[772]
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - mean (SD): endoscopic variceal ligation (EVL): 41.8 (13.7), control: 39.3 (11.9). Gender (M:F): 54/14. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (EVL: 41.8 (13.7), control: 39.3 (11.9). Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 27.9%; Child-Pugh B: 27.9%; Child-Pugh C: 30.9%%. Overall Child-Pugh B and C 58.8%).
Extra comments	Aetiology (alcohol related cirrhosis/non-alcoholrelated cirrhosis/non-cirrhotic portal fibrosis/extrahepatic portal vein obstruction): EVL 14/18/1/2, control 11/19/2/1. Ascites: EVL 30, control 26. Child-Pugh classification (A/B/C): EVL 9/16/11, control 10/13/10.
Indirectness of population	Serious indirectness: portal hypertension was due to cirrhosis in 62 of the patients and non-cirrhotic portal hypertension in 6 patients
Interventions	(n=35) Intervention 1: band ligation - conventional. Varices ligated about 1-2cm above the gastro-oesophageal junction. One or two bands applied at each variceal column between the lower 4-5cm of the oesophagus. EVL done at regular 7-10 day intervals until total variceal obliteration achieved (no variceal column visible) or it was not possible to suck in a varix for band ligation (grade 1 varices). Endoscopy performed every 3 months after the eradication of varices. Duration mean 14 months. Concurrent medication/care: asked to refrain from the use of alcohol and NSAIDs. (n=33) Intervention 2: no intervention. Carefully followed up clinically every 4 weeks. Duration mean 14 months. Concurrent medication/care: asked to refrain from the use of alcohol and NSAIDs.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONVENTIONAL BAND LIGATION versus NO INTERVENTION

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): mortality at mean 14 months; Group 1: 4/35, Group 2: 8/33; risk of bias: very high; indirectness of outcome: serious indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (medium/large): variceal bleeding defined as active bleeding identified from the varix, or if a clot was seen adherent to a varix and no other cause of bleeding from the gastrointestinal tract was evident at mean 14 months; Group 1: 3/35, Group 2: 13/33; risk of bias: very high; indirectness of outcome: serious indirectness

Study	Sarin 1996[772]
Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at mean 14 months; Group 1: 3/35, Group 2: 13/33; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): death due to variceal bleeding at mean 14 months; Group 1: 1/35, Group 2: 5/33; risk of bias: very high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Sarin 2013[775]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in India, unknown; setting: single-centre, hospital liver clinic
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 25 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical, radiological or histological diagnosis of cirrhosis
Stratum	Size of varices (small): small (grade 1 or 2 by Conn's classification or small as per Baveno).
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Clinical, radiological or histological diagnosis of cirrhosis; 2) Aged between 18 and 70 years; 3) Oesophageal varices were small (grade 1 or 2 by Conn's classification or small as per Baveno); 4) No history of variceal bleeding.
Exclusion criteria	Previous medical, surgical or endoscopic treatment of portal hypertension; a Child-Pugh score >13; neoplastic disease of any site; splenic or portal vein thrombosis; concurrent illnesses expected to decrease life expectancy to less than 1 year; pregnancy; contraindication to beta-blockers (second or higher degree of atrio-ventricular block, sinus bradycardia with a heart rate < 50 BPM, atrial hypotension with a systolic BP <90mmHg, heart failure, peripheral arterial disease, diabetes needing insulin treatment or bronchial asthma); concurrent antiviral treatment during the study period; concurrent treatment with any drug having an effect on portal hypertension; inability to comply with follow-up protocol; failure to give consent.

Study	Sarin 2013[775]
Recruitment/selection of patients	Consecutive patients (October 2004 - June 2007)
Age, gender and ethnicity	Age - mean (SD): propranolol: 42 (13); placebo: 44 (13). Gender (M:F): 120/30. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (propranolol: 42 (13); placebo: 44 (13). Age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): not applicable/not stated/ unclear
Extra comments	Aetiology (viral/alcoholic/other): propranolol 42/27/8; placebo 38/26/9. Ascites: propranolol 33; placebo 35. Child-Pugh score: propranolol 7.4 (1.9); placebo 7.7 (2.3). Gastric varices: propranolol 5; placebo 6.
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: oral non-selective beta-blockers - propranolol. Starting dose 20mg twice daily. Incremental dosing used to achieve target heart rate (dose increased every alternate day to achieve a target heart rate of 55/min or to the maximum dose of 360mg/day if the medication was well tolerated and the systolic BP remained above 90mmHg). Dose decreased stepwise on occurrence of intolerable adverse effects, systolic BP <90mmHg or pulse rate <55/min). Patients seen in the liver clinic every alternate day for dose titration and follow-up at the clinic at a 1-month interval for 3 months then every 6 months. Biochemical assessment and endoscopy done every 3-6 months. Patients further randomised to undergo no HVPG measurements, HVPG measurements at baseline or serial HVPG measurements. Duration mean 25 months. Concurrent medication/care: patients developing large varices were treated with either propranolol or EVL according to the clinical decisions of the attending physician. (n=73) Intervention 2: placebo. No details of placebo given. Unclear if patients seen in the liver clinic every alternate day (as with intervention arm). Follow-up at the clinic at a 1-month interval for 3 months then every 6 months. Biochemical assessment and endoscopy done every 3-6 months. Patients further randomised to undergo no HVPG measurements, HVPG measurements at baseline or serial HVPG measurements. Duration mean 25 months. Concurrent medication/care: patients developing large varices were treated with either propranolol or EVL according to the clinical decisions of the attending physician.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (small): mortality at mean 25 months; Group 1: 3/77, Group 2: 2/73; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 2: primary variceal bleeding at end of study

Study	Sarin 2013[775]
- Actual outcome for size of varices (small): variceal bleeding defined as any haematemesis or melena and endoscopy showed active bleeding from varices, varices with an adherent clot or no other sources of bleeding at mean 25 months; Group 1: 4/77, Group 2: 1/73; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (small): upper gastrointestinal bleeding at mean 25 months; Group 1: 4/77, Group 2: 1/73; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; bleeding related mortality at end of study; adverse events: fatigue at end of study

Study	Shah 2014[793]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in Pakistan; setting: multicentre (3 tertiary care hospitals)
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 13.2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of cirrhosis made on the basis of clinical, radiological, biochemical features and liver histology where available
Stratum	Size of varices (medium/large): medium or large sized oesophageal varices (grade II-IV)
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis (made on the basis of clinical, radiological, biochemical features and liver histology where available); without history of variceal bleed; male and female between 18 and 75 years; medium or large sized oesophageal varices (grade II-IV).
Exclusion criteria	Pregnant or lactating; allergy to carvedilol or reactive airway disease; already on beta-blocker treatment; presence of hepatic or other malignancy, which could impair longevity of life or presence of severe systemic illness which could impair the subject's ability to participate in the trial; psychiatric or mentally handicapped people; gastric varices alone.
Recruitment/selection of patients	May 2007 to September 2011
Age, gender and ethnicity	Age - mean (SD): EVL: 47.2 (13.2); carvedilol 48.3 (11.3). Gender (M:F): define. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (EVL: 47.2 (13.2); carvedilol 48.3 (11.3). Mean age in both arms <65 years). 2.

Study	Shah 2014[793]
	Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A 44.0%, Child-Pugh B & C 56.0%).
Extra comments	Aetiology (viral/alcohol related/other): EVL 77/3/6, carvedilol 74/0/8 Child-Pugh (A/B/C): EVL 37/37/12, carvedilol 37/35/10. Varices size (medium/large): EVL 42/44, carvedilol 49/33. Ascites: EVL 32, carvedilol 33.
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: band ligation - multiband. EVL performed using Saeed Six Shooter Multiband ligator (Wilson-Cook Medical, USA). Performed by gastroenterologists with at least 5 years' experience. Repeated every 3 weeks until obliteration of varices achieved (no varices or only small varices which were flattened on air insufflations). Endoscopy performed every 6 months and procedure repeated if varices recurred. Follow-up at 3 monthly intervals. Duration mean 13.4 months. Concurrent medication/care: not reported. (n=82) Intervention 2: oral non-selective beta-blockers - Carvedilol. Carvedilol (Carvida, Ferozsons Laboratories, Pakistan) initial dose 6.25mg once a day increased to twice a day after a period of 1 week. Follow-up at 2 weeks, 6 weeks and then 3 monthly intervals. Duration mean 13.2 months. Concurrent medication/care: not reported.
Funding	Study funded by industry (Ferozsons Laboratories (BF Biosciences), Pakistan (drug costs, clinical research associate honorarium and pharmacy charges - no role in study design, collection or analysis of data).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND LIGATION versus CARVEDILOL

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): survival at 2 years; HR 0.65 (95%CI 0.3 to 1.41) reported; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (medium/large): free of variceal bleeding (overt haematemesis and/or melena with endoscopic evidence of variceal bleeding or signs of recent bleed and at least 2g/dl drop in haemoglobin within 24 hours of admission) at 2 years; HR 0.63 (95%CI 0.1 to 3.7) reported; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study
- Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at 2 years; Group 1: 6/86, Group 2: 7/82; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 4: bleeding related mortality at end of study

Study	Shah 2014[793]
- Actual outcome for size of varices (medium/large): death due to variceal bleeding (overt haematemesis and/or melena with endoscopic evidence of variceal bleeding or signs of recent bleed and at least 2g/dl drop in haemoglobin within 24 hours of admission) at 2 years; Group 1: 4/86, Group 2: 4/82; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Singh 2012[811]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in India
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eligibility criteria does not specify cirrhosis but results report all patients had cirrhosis and cirrhosis was diagnosed on the basis of clinical biochemical, histologic, or ultrasonographic evidence.
Stratum	Size of varices (medium/large): large, grade 3 or 4 varices at high-risk (Conn's criteria: grade 3, varices of 3 to 6 mm; grade 4, varices of > 6 mm).
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with portal hypertension and oesophageal varices at high risk of bleeding, who had never had bleeding from varices. Large, grade 3 or 4 varices at high-risk (Conn's criteria: grade 3, varices of 3 to 6 mm; grade 4, varices of > 6 mm). The risk of bleeding in large varices (> 5 mm) was assessed by looking for the presence of at least 1 “red sign,” such as a cherry-red spot, a red wale, or a haematocystic spot.
Exclusion criteria	Receiving antiviral therapy or if they had concomitant hepatoma or another tumour, severe cardio-pulmonary or renal disease, bradycardia (basal heart rate < 55 beats per minute), bronchial asthma, diabetes mellitus, heart failure, peripheral vascular disease, a psychiatric disorder, glaucoma, or prostatic hypertrophy.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - other: not reported. Gender (M:F): not reported. Ethnicity: not reported
Further population details	1. Age of patient: not applicable/not stated/unclear. 2. Severity of underlying liver disease at the time of intervention (measured by MELD): not applicable/not stated/unclear

Study	Singh 2012[811]
Extra comments	Aetiology (alcohol related/hep B/hep C/autoimmune/other): EVL 8/5/2/1/2, propranolol 11/6/2/0/1. Ascites: EVL 11, propranolol 12
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: band ligation - multiband. Ligation carried out by placing multiple rubber bands (PentaGun Multiband Ligator, Hospiline Medi-Devices, India) - as many bands as possible, 3-6 bands (with fewer in later sessions) were placed in the lower 5-7cm of all variceal columns. Performed weekly until varices obliterated or reduced to size grade 1 and it was not possible to apply any more bands because of the small size of the varices. If varices recurred or became grade 2 or larger in size, ligation was repeated to obliterate them. Duration 12 months. Concurrent medication/care: underwent endoscopy for monthly for the first 3 months and then once every 3 months. (n=20) Intervention 2: oral non-selective beta-blockers - propranolol. Treatment started with 40mg oral propranolol. Dose increased by increments of 20-40mg/day until a 25% decrease in the resting heart rate was achieved. Treatment stopped if systolic BP below 90mmHg, HR less than 55bpm or serious side effects. Duration 12 months. Concurrent medication/care: underwent endoscopy for monthly for the first 3 months and then once every 3 months.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND LIGATION versus PROPRANOLOL

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): mortality at 12 months; Group 1: 2/18, Group 2: 3/20; indirectness of outcome: serious indirectness

Protocol outcome 2: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study
- Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at 12 months; Group 1: 3/18, Group 2: 5/20; indirectness of outcome: no indirectness

Protocol outcome 3: bleeding related mortality at end of study
- Actual outcome for size of varices (medium/large): death due to bleeding at 12 months; Group 1: 1/18, Group 2: 2/20; indirectness of outcome: no indirectness

Protocol outcomes not reported by the study	Health-related quality of life at end of study; primary variceal bleeding at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Svoboda 1999[853]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=186)
Countries and setting	Conducted in Czech Republic; setting: referral from district gastroenterologists
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 25 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: liver cirrhosis with no other serious disease
Stratum	Size of varices (medium/large): oesophageal varices of grades III and IV; oesophageal varices of grade II with signs of high risk (Paquet's classification)
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Referral of all suitable patients between August 1994 and September 1994
Age, gender and ethnicity	Age - mean (SD): LI: 48 (12); control: 47 (11). Gender (M:F): define. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (LI: 48 (12); control: 47 (11). Mean for both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score A (Child-Pugh A: 58.8%; Child-Pugh B: 29.4%; Child-Pugh C: 11.8% [overall: 58.8% Child-Pugh A]).
Extra comments	Aetiology (alcohol/infection): LI 35/17; control 34/16. Child-Pugh (A/B/C): LI 32/14/6; control 28/16/6. Varices (II/III/IV): LI: 2/36/14; control: 1/38/11. Study is a 3-arm trial including n=55 patients receiving sclerotherapy intervention.
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: band ligation - multiband. Three sessions at 2-week intervals, and then every month until the varices were too small to treat. Repeated if recurrence of varices occurred. Ligation performed using an endoscopic ligation device (suction oesophageal varices ligator, Pauldrach Medical, Germany). Later multiband ligators were also used (Wilson-Cook medical, USA or Microvasive, USA). Endoscopies performed by 2 experienced endoscopists who had performed >300 EIL or EVS procedures. In each session the largest number possible (up to 6) of elastic bands were positioned in the distal oesophagus. Duration mean 25 months. Concurrent medication/care: all patients given ACE inhibitor enalapril (later quinapril) 2x 5-10mg orally to decrease portal pressure. Regular endoscopy every 3 months. Comments: 29 lost to follow-up, trial arm not specified.

Study	Svoboda 1999[853]
	(n=50) Intervention 2: no intervention. Duration mean 26 months. Concurrent medication/care: all patients given ACE inhibitor enalapril (later quinapril) 2x 5-10mg orally to decrease portal pressure. Regular clinical examination and endoscopy every 3 months. Comments: 29 lost to follow-up, trial arm not specified.
Funding	Academic or government funding (supported by grant IGA MZ CR 5187 of Internal Grant Agency of Ministry of Health of the Czech Republic)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND OR CONVENTIONAL BAND LIGATION (LI) versus NO INTERVENTION Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): mortality at mean 25 months; Group 1: 12/52, Group 2: 19/50; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at mean 25 months; Group 1: 15/52, Group 2: 27/50; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at mean 25 months; Group 1: 15/52, Group 2: 27/50; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): death due to bleeding from oesophageal varices at mean 25 months; Group 1: 5/52, Group 2: 13/50; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Triantos 2005[882]
Study type	RCT (patient randomised; parallel)

Study	Triantos 2005[882]
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Greece; setting: multicentre: 1 tertiary referral centre for liver diseases and 1 general hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: mean 20.6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: patients with cirrhosis
Stratum	Size of varices (overall): small varices: <5mm diameter (patients with large and small varices reported separately in study)
Subgroup analysis within study	Post-hoc subgroup analysis: small and large varices
Inclusion criteria	Age >18 and <76 years; varices of any size (assessed endoscopically by 2 independent observers; large varices: diameter of large varix >5mm - measured with open forceps and not disappearing on oesophageal insufflation; small varices: <5mm diameter); contraindication or intolerance to beta-blocker therapy; no prior bleeding from portal hypertensive sources; no previous prophylactic sclerotherapy or banding; absence of terminal disease (likelihood of dying within 6 months); ability to give consent; no contraindication to banding.
Exclusion criteria	Not reported
Recruitment/selection of patients	December 1999 to November 2003
Age, gender and ethnicity	Age - mean (SD): endoscopic banding ligation (EBL): 60 (9.4), control: 63 (10.3). Gender (M:F): 38/14. Ethnicity: not reported
Further population details	1. Age of patient: 65 years and under (EBL: 60 (9.4), control: 63 (10.3). Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 32.7%; Child-Pugh B: 25%; Child-Pugh C: 42.3%. Overall Child-Pugh B and C 67.3%).
Extra comments	Aetiology (Alcohol/viral/other): EBL 9/11/5, control: 9/7/11; Child-Pugh (A/B/C): EBL 9/6/10, control: 8/7/12; Ascites: EBL 11, control: 19; Varices size (small/large): EBL 14/11, control 17/10. Trial stopped early due to interim analysis and twice as much bleeding than expected in the EBL group.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: band ligation - multiband. Bands were placed starting at the gastro-oesophageal junction and then proximally in a helical fashion for approximately 5 cm, putting at least 1 band on each varix (Multiband ligator 6 shooter, Wilson-Cook, Ireland). Subsequent sessions at 14-day intervals until the varices were too small to ligate (no effect of suction). Banding performed by 4 experienced endoscopists. Duration mean 20.6 months. Concurrent medication/care: not reported.

Study	Triantos 2005[882]
	(n=27) Intervention 2: no intervention. Yearly endoscopy and staging of liver disease. Duration mean 18.3 months. Concurrent medication/care: not reported.
Funding	Other (principle author funded by the Hellenic Association for the Study of the Liver)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND BAND LIGATION versus NO INTERVENTION Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (overall): survival at mean 18.3 - 20.6 months; HR 0.72 (95%CI 0.29 to 1.82) calculated – from logrank P-value; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (overall): bleeding from varix at mean 18.3 - 20.6 months; Group 1: 3/25, Group 2: 2/27; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (small): portal hypertensive bleeding (haematemesis or melaena, either from a bleeding varix or a clot adherent to a varix, a variceal ulceration, portal hypertensive gastropathy, or presumed to be from these sources when there were no other visible lesions at endoscopy) at mean 18.3 - 20.6 months; Group 1: 1/14, Group 2: 0/17; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for size of varices (medium/large): portal hypertensive bleeding (haematemesis or melaena, either from a bleeding varix or a clot adherent to a varix, a variceal ulceration, portal hypertensive gastropathy, or presumed to be from these sources when there were no other visible lesions at endoscopy) at mean 18.3 - 20.6 months; Group 1: 4/11, Group 2: 2/10; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (overall): cause of death variceal bleeding at mean 18.3 - 20.6 months; Group 1: 3/25, Group 2: 0/27; risk of bias: high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

H.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Study (subsidiary papers)	Chavez-tapia 2010[161] (Chavez-tapia 2011[160], Fernandez 2006[273], Sabat 1998[751], Spanish group for the study of bacterial infections in cirrhosis 1998[832])
Study type	Systematic review
Number of studies (number of participants)	3 (n=532)
Countries and setting	Conducted in Spain; setting: usually hospital
Line of therapy	1st line
Duration of study	Other: from 10 days to 3 weeks
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: review did not define
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with cirrhosis and upper gastrointestinal bleeding, regardless of aetiology of cirrhosis or severity of the disease
Exclusion criteria	Not specified
Recruitment/selection of patients	Appears to be consecutive patients in 2 studies (not stated in others); Fernandez 2006: between February 2000 and April 2004; Sabat 1998: from June 1993 to 1995; Spanish Group 1998 – no further details from abstract.
Age, gender and ethnicity	Age – mean (SD): Fernandez 2006: 57(12) norfloxacin and 58(12) ceftriaxone; Sabat 1998: 65(10) norfloxacin and 61(13) norflocaxin+ceftriaxone; Spanish Group 1998 - no further details from abstract. Gender (M:F): Fernandez 2006: 85/26; Sabat 1998: 25/21; Spanish Group 1998 - no further details from abstract. Ethnicity: not reported in systematic review.
Further population details	1. Severity of the underlying liver disease: systematic review: mixed (Fernandez 2006: 52 CP-B, 59 CP-C; Sabat 1998: 4 CP-A, 31 CP-B, 11 CP-C; Spanish Group 1998 – not provided).
Extra comments	Aetiology of infection/treatment: Fernandez 2006: 77% portal hypertension/sclerotherapy or banding; Sabat 1998: no details/emergency sclerotherapy; Spanish Group 1998 – no further details.
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: IV: 3rd generation Cephalosporins (beta-lactams) – Ceftriaxone. 1 g/day for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: IV administration Comments: Fernandez 2006

Study (subsidiary papers)	Chavez-tapia 2010[161] (Chavez-tapia 2011[160], Fernandez 2006[273], Sabat 1998[751], Spanish group for the study of bacterial infections in cirrhosis 1998[832])
	(n=63) Intervention 2: Oral: Quinolones – Norfloxacin. 400 mg twice daily for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Fernandez 2006 (n=42) Intervention 3: IV: 3rd generation Cephalosporins (beta-lactams) – Ceftriaxone. 2 g single dose after TIPS. Duration not specified. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: IV administration Comments: Gulberg 1999 (n=40) Intervention 4: IV: 3rd generation Cephalosporins (beta-lactams) – Ceftriaxone. 1 g, single dose before TIPS. Duration not specified. Concurrent medication/care: not reported Further details: 1. Different modes of administration: IV administration Comments: Gulberg 1999 (n=21) Intervention 5: IV: Penicillin (beta-lactams) – Ampicillin/sulbactam. 1.5 g twice daily for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: IV administration Comments: Lata 2005 (n=25) Intervention 6: Oral: Quinolones – Norfloxacin. Oral or through nasogastric tube 400 mg twice daily for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: other (oral or through nasogastric tube). Comments: Lata 2005 (n=28) Intervention 7: Combinations – Ceftriaxone (IV) and norfloxacin (oral). 800 mg/day norfloxacin orally for 7 days including 2 g/day of IV ceftriaxone for the first 3 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: other (oral for full 7 days and IV for 3 of these days). Comments: Sabat 1998 (n=28) Intervention 8: Oral: Quinolones – Norfloxacin. 800 mg/day for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Sabat 1998

Study (subsidiary papers)	Chavez-tapia 2010[161] (Chavez-tapia 2011[160], Fernandez 2006[273], Sabat 1998[751], Spanish group for the study of bacterial infections in cirrhosis 1998[832])
	(n=183) Intervention 9: Oral: Quinolones – Norfloxacin. 800 mg/day for 5 days. Duration 5 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Spanish Group 1998 (n=182) Intervention 10: Oral: Quinolones – Ofloxacin. 400 mg/day for 5 days. Duration 5 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Spanish Group 1998
Funding	Other (systematic review: Medica Sur Clinic & Foundation, Mexico; individual studies – Fernandez 2006: supported by grants from the Fondo de Investigacion Santaria and the Instituto de Salud Carlos III; not reported for Sabat 1998 or Spanish Group 1998.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE (1 G FOR 7DAYS) (IV) versus NORFLOXACIN (400 MG TWICE DAILY FOR 7 DAYS) (ORAL)

Protocol outcome 1: Occurrence of bacterial infections at end of study
- Actual outcome for Fernandez 2006[273]: bacterial infection at 10 days; group 1: 6/54, group 2: 15/57; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: All-cause mortality
- Actual outcome for Fernandez 2006[273]: mortality at 10 days; group 1: 8/54, group 2: 6/57; risk of bias: very high; indirectness of outcome: serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE (2 G FOR 3DAYS) (IV) AND NORFLOXACIN (800 MG FOR ALL 7 DAYS) (ORAL) versus NORFLOXACIN (800 MG FOR 7 DAYS) (ORAL)

Protocol outcome 1: Occurrence of bacterial infections at end of study
- Actual outcome for Sabat 1998[751]: bacterial infections at up to 3 weeks; group 1: 3/24, group 2: 4/22; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: All-cause mortality
- Actual outcome for Sabat 1998[751]: mortality at up to 3 weeks; group 1: 1/24, group 2: 2/22; risk of bias: very high; indirectness of outcome: serious indirectness

Study (subsidiary papers)	Chavez-tapia 2010[161] (Chavez-tapia 2011[160], Fernandez 2006[273], Sabat 1998[751], Spanish group for the study of bacterial infections in cirrhosis 1998[832])
Protocol outcome 3: Length of hospital stay at end of study - Actual outcome for Sabat 1998[751]: length of hospital stay at up to 3 weeks; group 1: mean 12 days (SD 8); n=24, group 2: mean 12 days (SD 6); n=22; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (800 MG FOR 5 DAYS) (ORAL) versus OFLOXACIN (400 G FOR 5 DAYS) (ORAL) Protocol outcome 1: Occurrence of bacterial infections at end of study - Actual outcome for Spanish group for the study of bacterial infections in cirrhosis 1998[832]: bacterial infections at during the first 10 days of the bleeding episode; group 1: 26/183, group 2: 27/182; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; renal failure at end of study; re-admission rate at end of study, antibiotic complications at end of study

Study	Kim 2011[465]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=113)
Countries and setting	Conducted in South Korea
Line of therapy	1st line
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis diagnosis based on clinical, laboratory and ultrsonographic data or histological assessment
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 18 and 80 years old, had active gastrointestinal haemorrhage (haematemesis [vomiting of blood] and/or melena [black or tarry faeces]) within 24 hours prior to inclusion, had decompensated liver cirrhosis as defined by the Child-Turcotte-Pugh score of 7 or greater.
Exclusion criteria	Allergy to cephalosporins or quinolones, presence of any of the following signs of infection (fever >37.5 degreed celsius, white blood count >15 000/mm^3, immature neutrophils >500/mm^3, polymorphonuclear cell count in ascitic fluid >250/mm^3, 15 or more leuckocytes/field in the fresh urine sedement, or data compatible with pneumonia on the

Study	Kim 2011[465]
	chest X-ray), treatment of antibiotics within 2 weeks before haemorrhage, previously diagnosed advanced hepatocellular carcinoma (one nodule greater than 5 cm, 3 nodules with 1 greater than 3 cm, or more than 3 nodules), and HIV infection.
Recruitment/selection of patients	From 172 patients admitted to 3 Korean hospitals for the treatment of gastrointestinal haemorrhage between May 2007 and April 2009
Age, gender and ethnicity	Age – mean (SD): 53.9 (9.7). Gender (M:F): 93/20. Ethnicity: not explicitly reported.
Further population details	1. Severity of the underlying liver disease: Child-Pugh mixed categories (study inclusion of decompensated liver cirrhosis only and defined this as Child-Pugh 7 or greater; 77% had grade B and 23% grade C)
Extra comments	58.4% had cirrhosis due to alcoholism (but other causes included HBV and HCV and cryptogenic cirrhosis), mean Child-Turcotte-Pugh score: 8.6 (SD1.7), mean MELD score 14.8 (SD 5.7), 77% had ascites and 24% had hepatic encephalopathy, 6% had hepatocellular carcinoma. Authors state that there may be some resistance of certain bacteria to quinolones in Korea and that this may affect the performance of ciprofloxacin, making it appear worse than it may in areas with less resistance.
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Oral: Quinolones – Ciprofloxacin. 500 mg every 12 hours for 7 days, initiated immediately after enrolment and within first 6 hours after admission to hospital. Duration 7 days. Concurrent medication/care: gastrointestinal haemorrhage treatment included emergency endoscopy & endoscopic treatment (variceal ligation and/or N-butyl-2-cyanoacrylate injection or haemoclipping and/or injection haemostasis with hypertonic saline-epinephrine) within 24 hours of bleed onset; terlipressin given if oesophageal or gastric varices bleeding or portal hypertensive gastropathy; PPI if from peptic ulcer; blood transfusions to maintain haematocrit levels 25–30%. Further details: 1. Different modes of administration: not applicable/not stated/unclear (no details given). (n=66) Intervention 2: IV: 3rd generation Cephalosporins (beta-lactams) – Ceftriaxone. 2 g per day for 7 days, initiated immediately after enrolment and within first 6 hours after admission to hospital. Duration 7 days. Concurrent medication/care: gastrointestinal haemorrhage treatment included emergency endoscopy & endoscopic treatment (variceal ligation and/or N-butyl-2-cyanoacrylate injection or haemoclipping and/or injection haemostasis with hypertonic saline-epinephrine) within 24 hours of bleed onset; terlipressin given if oesophageal or gastric varices bleeding or portal hypertensive gastropathy; PPI if from peptic ulcer; blood transfusions to maintain haematocrit levels 25–30%. Further details: 1. Different modes of administration: IV administration.
Funding	Academic or government funding (Korea Association of Study for Liver Disease)

Study	Kim 2011[465]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN versus CEFTRIAXONE Protocol outcome 1: Occurrence of bacterial infections at end of study - Actual outcome: Occurrence of bacterial infections at 7 days; group 1: 13/57, group 2: 2/66; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	All-cause mortality; quality of life at end of study; renal failure at end of study; length of hospital stay at end of study; re-admission rate at end of study; antibiotic complications at end of study

H.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large volume paracentesis (LVP) for ascites

Study	Narahara 2011[622]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Japan; setting: enrolled from authors department
Line of therapy	2nd line
Duration of study	Follow-up (post-intervention): reported up to 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of cirrhosis made on basis of laboratory and ultrasonographic findings or transjugular liver biopsy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with cirrhosis and refractory ascites who presented with a Child-Pugh score of <11, serum bilirubin of <3 mg/dl and creatinine of <1.9 mg/dl were admitted to the department and considered for inclusion in this study
Exclusion criteria	Age greater than 70 years, episodes of chronic hepatic encephalopathy, hepatocellular carcinoma or other malignancy, complete portal vein thrombosis with cavernomatous transformation, active infection, severe cardiac or pulmonary disease, and organic renal disease (urine protein level >500 mg/24 h, active sediment, or small kidneys on ultrasonography)
Recruitment/selection of patients	Between September 2000 and December 2007 consecutive Japanese patients with cirrhosis and refractory ascites were enrolled

Study	Narahara 2011[622]
Age, gender and ethnicity	Age – mean (SD): TIPS: 57.9 (8.6) and LVP: 61.1 (8.1) years. Gender (M:F): 44/16. Ethnicity: Japanese.
Further population details	1. Age of patient: mean under 65 years. 2. Current or past encephalopathy: excluded patients with episodes of chronic 3. Severity of underlying liver disease at the time of intervention (measured by MELD): mean score below 15.
Extra comments	The aim of this study was to include cirrhotic patients with good hepatic and renal function. The model for end stage liver disease (MELD) score was not used as an inclusion criterion because the cut-off value for predicting good survival of patients undergoing TIPS was not clearly indicated when this study was initiated.
Indirectness of population	No indirectness: none
Interventions	(n=30) Intervention 1: TIPS. After the TIPS tract was created, an expandable stent was placed and dilated to obtain a portosystemic pressure gradient of below 12 mmHg. The stent was initially dilated to 6 or 8 mm in diameter. If the portosystemic pressure gradient remained above 12 mmHg, the stent was further dilated to 8 or 10 mm. Did not use a covered stent as not available in Japan. Patients received lactulose to ensure a few soft bowel movements per day in order to prevent hepatic encephalopathy. Duration median follow-up of 598 days. Concurrent medication/care: diuretics were given before and after randomisation in both groups, but the doses were adjusted according to clinical need. Patients were discharged when their hepatic and renal functions were stable or improved. All patients were followed up monthly at the outpatient clinic after discharge. All patients were instructed not to drink alcohol. Further details: 1. Type of TIPS stent: uncovered Comments: none (n=30) Intervention 2: LVP – LVP with albumin infusion. Patients received sodium restriction (85 mEq/day) and treatment with diuretics. Large volume paracentesis (4 or more litres) was performed along with intravenous infusion of albumin (6 g/l ascites removed). Recurrent ascites was treated with repeated paracentesis plus albumin if necessary. Duration: median follow-up 227 days. Concurrent medication/care: diuretics were given before and after randomisation in both groups, but the doses were adjusted according to clinical need. Patients were discharged when their hepatic and renal functions were stable or improved. All patients were followed up monthly at the outpatient clinic after discharge. All patients were instructed not to drink alcohol. Further details: 1. Type of TIPS stent: N/A Comments: none
Funding	Funding not stated (not stated)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TIPS versus LVP WITH ALBUMIN INFUSION

Protocol outcome 1: Re-accumulation of ascites at end of study

Study	Narahara 2011[622]
- Actual outcome: re-accumulation of ascites at 24 months; group 1: 22/30, group 2: 27/30; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: Transplant-free survival at 12 months - Actual outcome: survival at 24 months; HR 0.35 (95% CI 0.17 to 0.7) reported; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 3: Hepatic encephalopathy at end of study - Actual outcome: hepatic encephalopathy at end of study; group 1: 20/30, group 2: 5/30; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; spontaneous bacterial peritonitis at end of study; renal failure at end of study; length of stay at end of study; re-admission rate at end of study

Study (subsidiary papers)	Saab 2006[749] (Gines 2002[335], Rossle 2000[744], Salerno 2004[759], Sanyal 2003[770])
Study type	Systematic review
Number of studies (number of participants)	5 (n=330)
Countries and setting	Conducted in Canada, France, Germany, Italy, Spain, USA; setting: not reported in systematic review
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12–60 months after inclusion
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of liver disease could be made via a combination of biochemical and clinical data. The definition of refractory ascites in the individual trial was assessed by set criteria.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with refractory ascites due to cirrhosis and portal hypertension
Exclusion criteria	Patients without portal hypertension such as those with malignant ascites were excluded
Recruitment/selection of patients	Consecutive patients with cirrhosis and refractory ascites
Age, gender and ethnicity	Age – range: not reported. Gender (M:F): 69% /31%. Ethnicity: systematic review – not reported
Further population details	1. Age of patient: mean under 65 years for all studies. 2. Current or past encephalopathy: Sanyal: excluded patients with active hepatic encephalopathy (grade 2 or higher), Rossle: excluded patients with hepatic encephalopathy grade 2 or higher, Gines: excluded patients with chronic hepatic encephalopathy, Salerno: excluded patients who had a history of recurrent episodes of hepatic encephalopathy. 3. Severity of underlying liver disease at the time of

	intervention (measured by MELD): Salerno: mean score below 15; all other studies not reported.
Extra comments	None
Indirectness of population	No indirectness
Interventions	(n=162) Intervention 1: TIPS. Prescribed diuretics and sodium intake restriction, and underwent an initial paracentesis before the TIPS procedure with repeat paracentesis as needed. Duration: not reported. Concurrent medication/care: medical management (diuretics and sodium restriction) and any co-interventions were allowed if used in both groups of the study. Further details: 1. Type of TIPS stent: Sanyal: not reported; Gines: not reported; Rossle: not reported; Salerno: not reported. Comments: none (n=168) Intervention 2: LVP – LVP with albumin infusion. Treated with diuretics, dietary sodium restriction, and large volume paracentesis as indicated. Paracentesis with infusion of 8 g of albumin per litre of ascitic fluid removed was performed in 4 of the studies. Duration: outpatient procedure. Concurrent medication/care: medical management (diuretics and sodium restriction) and co-interventions were allowed if used in both groups of the study. Further details: 1. Type of TIPS stent: N/A Comments: none
Funding	Academic or government funding (Cochrane Review – external funding from (1) The Danish Medical Research Council's Grant on Getting Research into Practice, Denmark and (2) the Copenhagen Hospital Corporation Medical Research Council's Grant on Getting Research in to Practice (GRIP), Denmark.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TIPS versus LVP WITH ALBUMIN INFUSION

Protocol outcome 1: Re-accumulation of ascites at end of study
- Actual outcome: re-accumulation of ascites at 12 months at 12 months; group 1: 60/133, group 2: 111/137; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 2: Health-related quality of life at end of study
- Actual outcome for Sanyal 2003[770]: quality of life – physical score (SF-36 score used to calculate physical component scale) at 12 months; group 1: mean 2.33 (SD 12); n=52, group 2: mean 5.69 (SD 10); n=57; SF-36 physical component scale not reported. High score=poor outcome; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for Sanyal 2003[770]: quality of life – mental score (SF-36 score used to calculate physical component scale) at 12 months; group 1: mean 1.83 (SD 7.6); n=52, group 2: mean 3.96 (SD 10); n=57; SF-36 mental component scale not reported. High score=poor outcome; risk of bias: very high; indirectness of outcome: no indirectness

	Protocol outcome 3: Transplant-free survival at 12 months - Actual outcome for Rossle 2000[744]: survival without the need for transplantation at end of study; HR 0.44 (95% CI 0.22 to 0.87) reported; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for Sanyal 2003[770]: transplant-free survival at end of study; HR 0.91 (95% CI 0.48 to 1.73) calculated – from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome for Gines 2002[335]: survival without liver transplantation at end of study; HR 1.12 (95% CI 0.65 to 1.93) calculated – from curve + numbers at risk; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome for Salerno 2004[759]: survival without liver transplantation at end of study; HR 0.34 (95% CI 0.15 to 0.78) reported; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 4: Spontaneous bacterial peritonitis at end of study - Actual outcome for Gines 2002[335]: SBP at end of study; group 1: 2/35, group 2: 4/35; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome for Sanyal 2003[770]: SBP at end of study; group 1: 4/52, group 2: 2/57; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 5: Renal failure at end of study - Actual outcome: acute renal failure at end of study; group 1: 12/87, group 2: 19/92; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 6: Hepatic encephalopathy at end of study - Actual outcome: hepatic encephalopathy at end of study; group 1: 87/162, group 2: 60/168; risk of bias: low; indirectness of outcome: no indirectness
Protocol outcomes not reported by the study	Length of stay at end of study; re-admission rate at end of study

H.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Study (subsidiary papers)	**Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])**
Study type	Systematic review
Number of studies (number of participants)	5 (n=404)
Countries and setting	Conducted in Argentina, France, Spain; setting: usually hospital
Line of therapy	1st line
Duration of study	Other: from 6 months to 1 year treatment period (and up to 32 months follow-up)
Method of assessment of guideline condition	Systematic review: method of assessment mixed: all studies used a combination of clinical, laboratory, and

Study (subsidiary papers)	Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])
	ultrasonographic data or histology to confirm cirrhosis (method not described in Soriano 1991)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with ascites (diagnosed with any method) due to cirrhosis and without overt signs of bacterial infections in any setting, regardless of the aetiology of cirrhosis or severity of disease
Exclusion criteria	Not reported in systematic review. Fernandez 2007 - previous norfloxacin prophylaxis, quinolone allergy, HCC, organic renal failure (ultrasonography showing obstructure uropathy/parenchymal renal disease/haematuria and/or proteinuria), HIV infection; Grange 1998 - active GI bleeding, HCC, other life-threatening disease; Rolachon 1995 - quinolone allergy, recent GI bleeding, hepatic encephalopathy grade II-III, renal failure, HCC; Soriano 1991 - community-acquired infection, active GI bleeding at admission and those undergoing antibiotic therapy in the week before admission; Terg 2008 - AB in previous 30d, pregnancy, active GI bleeding, encephalopathy > grade 2, HCC, quinolone allergy, creatinin > 3 mg/dl, bilirubin > 3.2 mg/dl, platelet <98,000, bacterial infection
Recruitment/selection of patients	Fernandez 2007: September 2000 to June 2004, Grange 1998: February 1991 to February 1993 (consecutive), Rolachon 1995: November 1991 to August 1993, Terg 2008: March 2000 to December 2005 (no further details; no details for Soriano 1991).
Age, gender and ethnicity	Age - mean (SD): Fernandez 2007: 62(11) versus 61(12), Grange 1998: 55 (35-70) versus 55 (31-70), Rolachon 1995: 57 (9.6) versus 55 (9.4), Soriano 1991: 62 (11) versus 61 (11), Terg 2008: 56 (10) versus 58 (11). Gender (M:F): Fernandez 2007: 22/13 versus 23/10, Grange 1998: 36/17 versus 32/21, Rolachon 1995: 15/13 versus versus/15, Soriano 1991: 18/14 versus 20/11, Terg 2008: not reported. Ethnicity: not explicitly reported.
Further population details	1. Risk of SBP: systematic review: mixed (ascitic level in Fernandez 2007: <15 g/L or impaired renal function were inclusion criteria (mean 9(4) versus 9(3)), Grange 1998: <15 g/L (mean 10.4 versus 9.3 g/l), Rolachon 1995: <15 g/L, Soriano 1991: <15 g/L, Terg 2008: < 1.5 g/dl (0.84 (0.31) versus 0.85 (0.36)). 2. Severity of the underlying liver disease: systematic review: mixed (Fernandez 2007: Child Pugh=/>9 only, Grange 1998: not specified (but most advanced with history of complications), Rolachon 1995: A/B/C - 0/17/11 versus 1/18/13, Soriano 1991: A/B/C - 2/13/17 versus 1/14/16, Terg 2008: mean 8.5 (1.5) versus 8.3 (1.3)).
Extra comments	Inclusion criteria: Fernandez 2007 - protein <15 g/L, impaired renal function (serum creatine level =/>1.2 mg/dl, BUN =/>25 mg/dl or serum Na+=/< 130 mEq/l) or severe liver failure (CP score =/>9 with serum bilirubin =/>3 mg/dl); Grange 1998 - low protein ascites (< 15 g/l), negative ascitic cultures, <250 neutrophils/ul; Soriano 1991 - total ascitic protein <1.5 g/dl; Terg 2008 - low ascitic total protein concentration (1.5 g/dl)
Indirectness of population	No indirectness: Rolachon 1995 and Soriano 1991 had small proportions of patients with prior SBP (11% and 6% respectively).
Interventions	(n=38) Intervention 1: oral: quinolones - norfloxacin. 400 mg/day tablet (identical tablets prepared by Madaus S.A.,

Study (subsidiary papers)	Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])
	Barcelona, Spain). Duration 1 year. Concurrent medication/care: SBP was treated with ceftriaxone and received intravenous albumin to prevent HRS. Norfloxacin 400 mg/12 hours for 7 days was given to patients who developed upper GI haemorrhage to prevent bacterial infections (HRS was not treated with vasoconstrictors as there were very few data on this treatment at the time of protocol approval). Further details: 1. Antibiotic class: quinolones (norfloxacin). Comments: Fernandez 2007 (n=36) Intervention 2: placebo. 1 tablet (identical tablets prepared by Madaus S.A., Barcelona, Spain). Duration 1 year. Concurrent medication/care: SBP was treated with ceftriaxone and received intravenous albumin to prevent HRS. Norfloxacin 400 mg/12 hours for 7 days was given to patients who developed upper GI haemorrhage to prevent bacterial infections (HRS was not treated with vasoconstrictors as there were very few data on this treatment at the time of protocol approval). Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Fernandez 2007 (n=53) Intervention 3: oral: quinolones - norfloxacin. 400 mg/day every 24 hours (Noroxine, Merck Sharp and Dohme, Paris, France). Treatment was discontinued if SBP occurred but continued if GI haemorrhage, HCC or hepatic encephalopathy occurred). Duration 6 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: quinolones Comments: Grange 1998 (n=54) Intervention 4: placebo. Daily oral tablet (identical to active tablets; prepared by Merck Sharp and Dohme, Paris, France). Treatment was discontinued if SBP occurred but continued if GI haemorrhage, HCC or hepatic encephalopathy occurred). Duration 6 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Grange 1998 (n=50) Intervention 5: oral: quinolones - ciprofloxacin. 500 mg/d (Ciriax, Laboratorios Roemmers, Buenos Aires, Argentina). Study medication withdrawn if SBP occurred and transitorily if patients had other complications like GI bleeding or encephalopathy (patients were withdrawn from the study if they were off study medications for more than 2 weeks). Duration 12 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: quinolones Comments: Terg 2008 (n=50) Intervention 6: placebo. No details provided. Study medication withdrawn if SBP occurred and transitorily if

Study (subsidiary papers)	Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])
	patients had other complications like GI bleeding or encephalopathy (patients were withdrawn from the study if they were off study medications for more than 2 weeks). Duration 12 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Terg 2008 (n=28) Intervention 7: oral: quinolones - ciprofloxacin. 750 mg/week (Bayer Pharma, Germany). Duration 6 months. Concurrent medication/care: 6 patients also were receiving diuretics and were transitorily free of ascites so the diuretics were withdrawn in these patients and recommenced when ascites recurred (none of these patients had SBP). Further details: 1. Antibiotic class: quinolones Comments: Rolachon 1995 (n=32) Intervention 8: placebo. Identical pills prepared by Bayer Pharma (Germany). Duration 6 months. Concurrent medication/care: 9 patients also were receiving diuretics and were transitorily free of ascites so the diuretics were withdrawn in these patients and recommenced when ascites recurred (none of these patients had SBP). Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Rolachon 1995 (n=32) Intervention 9: oral: quinolones - norfloxacin. 400 mg/d started in the first 8 hours of hospitalisation and for the length of hospitalisation. Duration: mean 27 (SD 15) versus 24 (SD 13) days. Concurrent medication/care: 23 were treated with diuretics during hospitalisation. Further details: 1. Antibiotic class: quinolones Comments: Soriano 1991 (n=31) Intervention 10: placebo. No details provided except that it was started within the first 8 hours of hospitalisation and provided for the length of hospitalisation. Duration: mean 27 (SD 15) versus 24 (SD 13) days. Concurrent medication/care: 22 were treated with diuretics during hospitalisation. Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Soriano 1991
Funding	Funding for systematic review: not stated (Individual papers: Fernandez 2007 had grants from Fondo de Investigacion Sanitaria and Instituto de Salud Carlos III; Grange 1998 was supported from a grant from Merck Sharp and Dohme, Paris, France; Terg 2008 study was supported from a grant from the Consejo de Investigacion en Salud del Gobierno

Study (subsidiary papers)	Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])
	de la Ciudad de Buenos Aires; no details of funding for Rolachon 1995 or Soriano 1991)).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (400MG/D) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Fernandez 2007[272]: occurrence of SBP at 12 months; group 1: 2/35, group 2: 10/33; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Fernandez 2007[272]: mortality (dichotomous) at 12 months; group 1: 10/35, group 2: 13/33; risk of bias: high; indirectness of outcome: serious indirectness
- Actual outcome for Fernandez 2007[272]: mortality (time-to-event) at 12 months; HR 0.44 (95%CI 0.19 to 1) calculated from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: incidence of resistant organisms at end of study
- Actual outcome for Fernandez 2007[272]: incidence of SBP caused by quinolone-resistant bacteria at 12 months; group 1: 0/2, group 2: 0/10; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: renal failure at end of study
- Actual outcome for Fernandez 2007[272]: renal failure at 12 months; group 1: 7/35, group 2: 16/33; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 5: liver failure at end of study
- Actual outcome for Fernandez 2007[272]: liver failure leading to death at 12 months; group 1: 4/35, group 2: 1/33; risk of bias: high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (400 MG/D) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Grange 1998[356]: occurrence of SBP at mean 128 (SD 71) days for norfloxacin versus 136 (SD69) days for placebo; group 1: 0/53, group 2: 5/54; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Grange 1998[356]: mortality (dichotomous) at mean 128 (SD 71) days for norfloxacin versus 136 (SD69) days for placebo; group 1: 8/53, group 2: 10/54; risk of bias: very high; indirectness of outcome: serious indirectness

Study (subsidiary papers)	Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])

Protocol outcome 3: incidence of resistant organisms at end of study
- Actual outcome for Grange 1998[356]: incidence of resistant organisms not present at baseline at mean 128 (SD 71) days for norfloxacin versus 136 (SD69) days for placebo; group 1: 10/24, group 2: 3/22; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: liver failure at end of study
- Actual outcome for Grange 1998[356]: liver failure leading to death at mean 128 (SD 71) days for norfloxacin versus 136 (SD69) days for placebo; group 1: 4/53, group 2: 1/54; risk of bias: very high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN (500MG/D) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Terg 2008[864]: occurrence of SBP at 12 months; group 1: 2/50, group 2: 7/50; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Terg 2008[864]: mortality (dichotomous) at 12 months; group 1: 6/50, group 2: 14/50; risk of bias: very high; indirectness of outcome: serious indirectness
- Actual outcome for Terg 2008[864]: mortality (time-to-event) at 12 months; HR 0.37 (95%CI 0.14 to 0.96) calculated –from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: renal failure at end of study
- Actual outcome for Terg 2008[864]: renal failure at 12 months; group 1: 7/50, group 2: 9/50; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: liver failure at end of study
- Actual outcome for Terg 2008[864]: liver failure leading to death at 12 months; group 1: 2/50, group 2: 2/50; risk of bias: high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN (750 MG/WK) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Rolachon 1995[738]: occurrence of SBP at 6 months; group 1: 1/28, group 2: 7/32; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Rolachon 1995[738]: mortality (dichotomous) at 6 months; group 1: 4/28, group 2: 6/32; risk of bias: very high; indirectness of outcome: serious indirectness

Protocol outcome 3: incidence of resistant organisms at end of study

Study (subsidiary papers)	Cohen 2009[187] (Terg 2008,[864] Fernandez 2007,[272] Grange 1998,[356] Rolachon 1995,[738] Soriano 1991[829])
- Actual outcome for Rolachon 1995[738]: incidence of acquired resistance to ciprofloxacin or modifications of faecal flora gram-positive cocci at 6 months; group 1: 0/28, group 2: 0/32; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 4: liver failure at end of study - Actual outcome for Rolachon 1995[738]: liver failure leading to death at 6 months; group 1: 2/28, group 2: 4/32; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 5: length of hospital stay at end of study - Actual outcome for Rolachon 1995[738]: length of hospital stay at n/a; group 1: mean 9.3 length of hospital stay (SD 4.5); n=28, group 2: mean 17.6 length of hospital stay (SD 6.2); n=32; risk of bias: high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (400 MG/D) versus PLACEBO Protocol outcome 1: occurrence of SBP at end of study - Actual outcome for Soriano 1991[829]: occurrence of SBP at mean 27 (SD 15) versus 24 (SD 13) days; group 1: 0/32, group 2: 7/31; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: all-cause mortality - Actual outcome for Soriano 1991[829]: mortality (dichotomous) at mean 27 (SD 15) versus 24 (SD 13) days; group 1: 2/32, group 2: 5/31; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: length of hospital stay at end of study - Actual outcome for Soriano 1991[829]: length of hospital stay at n/a; group 1: mean 27 length of hospital stay (SD 15); n=32, group 2: mean 24 length of hospital stay (SD 13); n=31; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; re-admission rate at end of study

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[861]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Mexico
Line of therapy	1st line

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[861]
Duration of study	Intervention + follow up: 4-week treatment + 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Included were patients aged from 19 to 79 years, who were able to give written informed consent and who had cirrhosis of the liver and ascites.
Exclusion criteria	Patients were excluded if cirrhosis was due to autoimmune disease, history of SBP, active gastrointestinal bleeding, total protein in ascitic fluid < 1.5g/dL, use of antibiotics within the last 30 days, pregnancy, encephalopathy ≥ grade 2, immune-related comorbidities, immunosuppressive therapy, hepatocarcinoma or other malignancies, allergy to fluoroquinolones, and bacterial infection at the time of enrolment.
Recruitment/selection of patients	Diagnosis of cirrhosis was supported by means of clinical (jaundice, ascites, hepatic encephalopathy, evidence of portal hypertension, variceal haemorrhage), laboratory (abnormal liver function test as decreased serum albumin, elevated serum bilirubin, elevated serum aminotransferases), ultrasound (hyperechoic hepatic parenchyma, heterogeneous liver, nodularity of the liver surface, and selective enlargement of the caudate lobe) and/or histologic data (diffuse involvement of the liver with progressive fibrosis with nodule formation and distortion of the hepatic architecture).Upon enrolment, physical examination and laboratory tests (liver and renal function tests, red and white cell counts, platelet count, and pro-thrombin time) were performed.
Age, gender and ethnicity	Age - Mean (SD): intervention: 56.7 (13.2); placebo: 56.3 (11.7). Gender (M:F): Define. Ethnicity: unknown (Mexican?)
Further population details	1. Risk of SBP: low risk total protein in ascitic fluid ≥ 1.5g/dL 2. Severity of the underlying liver disease: Child-Pugh A 14/95, Child-Pugh B 62/95, Child-Pugh C 19/95.
Extra comments	The same (as baseline) assessment was repeated 4, 6, 12, 18, and 24 weeks afterwards, or whenever a primary end point occurred. Enrolled patients continued with their regular baseline medications during the 6 month follow-up of the trial. Patients taking the study medication for less than 2 weeks were considered as non-compliers and were withdrawn from the per-protocol analysis.
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Oral: Quinolones - Ciprofloxacin. oral ciprofloxacin 500 mg/day (Ciproflox, Laboratorios Senosiain, S.A. de C.V., Mexico). Duration 4 week intervention + 6 month follow-up. Concurrent medication/care: Enrolled patients continued with their regular baseline medications during the 6 month follow-up of the trial. Further details: 1. Antibiotic class: quinolones (n=46) Intervention 2: Placebo. 500mg/day of an equally appearing placebo. Duration 4 week intervention + 6 month

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[861]
	follow-up. Concurrent medication/care: Enrolled patients continued with their regular baseline medications during the 6 month follow-up of the trial. Further details: 1. Antibiotic class: n/a
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN versus PLACEBO Protocol outcome 1: Occurrence of SBP at End of study - Actual outcome: Incidence of SBP at follow-up (6 months); Group 1: 2/49, Group 2: 0/46; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: all cause mortality - Actual outcome: Mortality (time-to-event) at 6 months; HR 0.34 (95%CI 0.05 to 2.41) was estimated from the P value; Total number of deaths during study period: ciprofloxacin 1/49; placebo 3/46. Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Incidence of resistant organisms at End of study; Renal failure at End of study; Liver failure at End of study; Length of hospital stay at End of study; Re-admission rate at End of study

H.10 Volume replacers in hepatorenal syndrome

None

H.11 Management of an episode of acute hepatic encephalopathy

Study	Abid 2011[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=120)
Countries and setting	Conducted in Pakistan; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Until discharge or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis diagnosed on the basis of clinical findings, ultrasonic and/or

Study	Abid 2011[13]
	histologic basis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Diagnosis of cirrhosis. (2) Aged > 18 years with hepatic encephalopathy grades 1 to 4. (3) Patients were grouped as minimal hepatic encephalopathy if NCT-A completion took > 30 seconds and no other sign of encephalopathy. (4) Hyperammonaemia. (5) With/Without a single reversible precipitating factor of hepatic encephalopathy (for example constipation, hypokalaemia, urinary tract infection, respiratory tract infection, spontaneous bacterial peritonitis, dehydration)
Exclusion criteria	Hepatocellular carcinoma; severe septicaemia with compromised haemodynamic status; active GI bleeding; hepatorenal syndrome; acute superimposed liver injury; advanced cardiac/pulmonary disease; end-stage renal failure; patients taking sedatives / anti-depressants / benzodiazepines; patients with chronic hepatic encephalopathy on metronidazole/lactulose prior to admission
Recruitment/selection of patients	Patients admitted to the hospital via outpatient clinic or emergency room were assessed at randomisation.
Age, gender and ethnicity	Age - Mean (SD): 57 (11). Gender (M:F): 62/58. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Child-Pugh B or C
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: l-Ornithine-l-aspartate (LOLA) . IV administration of 20g (4 ampoules of 10ml each) mixed in 250ml of 5% dextrose, daily over 4 hours for 3 consecutive days. Duration 3 days. Concurrent medication/care: Lactulose + Metronidazole + Any necessary concomitant medications for the treatment of precipitating factor(s) (n=60) Intervention 2: Placebo. IV administration of 20g (4 ampoules of 10ml distilled water) mixed in 250ml of 5% dextrose, appearance indistinguishable from LOLA, daily over 4 hours for 3 consecutive days. Duration 3 days. Concurrent medication/care: Lactulose + Metronidazole + Any necessary concomitant medications for the treatment of precipitating factor(s)
Funding	Study funded by industry (Unrestricted grant from Brookes Pharmaceutical Pakistan)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: L-ORNITHINE-L-ASPARTATE (LOLA) versus PLACEBO Protocol outcome 1: Survival at End of study	

Study	Abid 2011[13]
- Actual outcome: Mortality (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm) at During inpatient stay; Group 1: 4/60, Group 2: 7/60; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Complete improvement defined as improvement of 2 grades from baseline (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 45/54, Group 2: 25/54; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Partial improvement defined as improvement of 1 grade from baseline (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 4/54, Group 2: 19/54; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: No improvement/deterioration in hepatic encephalopathy grade (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 5/54, Group 2: 10/54; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SUBGROUP DATA (Grade I and II). Complete improvement defined as improvement of 2 grades from baseline (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 25/29, Group 2: 10/27; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SUBGROUP DATA (Grade III and IV). Complete improvement defined as improvement of 2 grades from baseline (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 20/25, Group 2: 15/27; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SUBGROUP DATA (Grade I and II). Partial improvement defined as improvement of 1 grade from baseline (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 2/29, Group 2: 14/27; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SUBGROUP DATA (Grade III and IV). Partial improvement defined as improvement of 1 grade from baseline (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 2/25, Group 2: 5/27; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SUBGROUP DATA (Grade I and II) No improvement/deterioration in hepatic encephalopathy grade (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 2/29, Group 2: 3/27; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SUBGROUP DATA (Grade III and IV) No improvement/deterioration in hepatic encephalopathy grade (West Haven Grade I - IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 3/25, Group 2: 7/27; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Discharge from hospital at End of study - Actual outcome: Median duration of hospitalisation (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm) at N/A; Other: Median (range). LOLA = 96 hours (range 48 - 574) versus. Placebo = 96 hours (range 90 - 240); p = 0.025; Risk of bias: Low; Indirectness of outcome: Serious indirectness	

Study	Abid 2011[13]
Protocol outcome 4: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Adverse drug reactions (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm) at 3 days; Group 1: 0/60, Group 2: 0/60; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study

Study	Ahmad 2008[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=80)
Countries and setting	Conducted in Pakistan; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was diagnosed on the basis of clinical, laboratory and ultrasonographic features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Adult with diagnosis of cirrhosis. (2) Clinically overt encephalopathy (West Haven 1 - 4) developed spontaneously without any precipitating factor. (3) Hyperammonaemia.
Exclusion criteria	Existence of specified precipitating factors; mental state grade IV hepatic encephalopathy; active & major complications of portal hypertension; acute superimposed liver injury; hepatocellular carcinoma; serious non-hepatic diseases (e.g. heart/respiratory/renal failure); presence of infections other than spontaneous bacterial peritonitis necessitating antibiotic therapy
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Intervention 51.7 (10.8) versus Control 52.0 (11.7). Gender (M:F): 59/21. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Grade 1-2 (82.5% grade I or II; 17.5% grade III). 2. Severity of the underlying liver disease : Child-Pugh B or C (only 2.5% were Child Pugh A).
Extra comments	The participants had hepatic encephalopathy of I to III.
Indirectness of population	No indirectness

Study	Ahmad 2008[21]
Interventions	(n=40) Intervention 1: l-Ornithine-l-aspartate (LOLA) . IV of 20g (4 ampoules of 10ml each) in 250ml of 5% dextrose; administered daily over 4 hours for 5 consecutive days. Duration 5 days. Concurrent medication/care: Lactulose + Metronidazole (n=40) Intervention 2: Placebo. IV of 20g (4 ampoules of 10ml distilled water) in 250ml of 5% dextrose; administered daily over 4 hours for 5 consecutive days. Duration 5 days. Concurrent medication/care: Lactulose + Metronidazole
Funding	Equipment / drugs provided by industry (Brookes Pharmaceutical Pakistan provided the intervention medication.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: L-ORNITHINE-L-ASPARTATE (LOLA) versus PLACEBO Protocol outcome 1: Survival at End of study - Actual outcome: In-hospital mortality at 5 days; Group 1: 2/40, Group 2: 4/40; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Number of participants who achieved hepatic encephalopathy grade 0 at 5 days; Group 1: 37/40, Group 2: 31/40; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Adverse reactions to medicine (nausea/vomiting) at 5 days; Group 1: 1/40, Group 2: 0/40; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Cerra 1983[152]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in USA; Setting: Department of Surgery, University of Minnesota Hospital, Minneapolis.
Line of therapy	1st line

Study	Cerra 1983[152]
Duration of study	Intervention + follow up: 4-14 days with a follow-up period of at least 7 days after study or until death or discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis proven by clinical evaluation or biopsy studies. Patients were screened by means of a history, physical examination, mental status exam, EEG and metabolic and laboratory data.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 18-85 with chronic hepatic disease and at least acute grade 2 encephalopathy who were judged to require parenteral nutritional support.
Exclusion criteria	Acute viral hepatitis, hepatorenal syndrome, significant GI bleeding, non-hepatic coma, need for fluid restriction
Age, gender and ethnicity	Age - Mean (SD): BCAA: 56 (3); neomycin: 55 (3). Gender (M:F): 75% male. Ethnicity: nr
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Extra comments	Nine patients had portocaval shunts. A neurologic examination was done daily. EEGs were planned on days 0, 2, 4, 6 and 10. Only data from the first 7 days of the study were reported so as to maintain statistically valid samples. No patients crossed over.
Indirectness of population	Serious indirectness: Approx. 50-60% patients had failed to improve encephalopathy over at least 48 hours.
Interventions	(n=12) Intervention 1: Branch chain amino acids - IV branch chain amino acids. F080 (BCAA-enriched solution, 36% equimolar (HeparAmine, 8% amino acid injection, American McGaw) low in aromatic acids and methionine in 25% dextrose) plus placebo tablets matching the appearance of neomycin. . Duration 4-14 days with a follow-up period of at least 7 days after the study or until death or discharge. To complete the study, a patient had to finish the first four days of therapy with complete data . Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or levodopa. Oral protein was restricted for the first six days of the study or until encephalopathy cleared. (n=10) Intervention 2: Oral non-absorbable antibiotics - neomycin. 4 grams per day given orally or by nasogastric tube in four divided doses daily. Duration 4-14 days with a follow-up period of at least 7 days after the study or until death or discharge. To complete the study, a patient had to finish the first four days of therapy with complete data . Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or levodopa. Oral protein was restricted for the first six days of the study or until encephalopathy cleared.
Funding	Funding not stated

Study	Cerra 1983[152]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus NEOMYCIN Protocol outcome 1: Survival at End of study - Actual outcome: Mortality at Study plus follow-up; Group 1: 2/12, Group 2: 4/10; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Patients whose encephalopathy improved to grade 0 at Study plus follow-up; Group 1: 5/9, Group 2: 2/8; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Patients whose encephalopathy improved to grade 0-1 at Study plus follow-up; Group 1: 8/9, Group 2: 6/8; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Cerra 1985[151]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in USA; Setting: Eight centres participated in the study. Three centres equally contributed 70% of the patients. The remaining patients were distributed among the remaining five centres.
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 14 days, with a follow-up period of at least 7 days post-study, or until death or discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 'For most patients that diagnosis was cirrhosis'. 65-75% of the patients in each group had this diagnosis made by biopsy, the rest by clinical criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Males and females between 18 and 85 years with chronic hepatic disease and at least acute grade 2 encephalopathy
Exclusion criteria	Acute viral hepatitis, acute fulminant hepatitis, hepatorenal syndrome, significant GI bleeding, non-hepatic coma,

Study	Cerra 1985[151]
	patients requiring severe fluid restriction
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): intervention: 53 (2), control: 53 (2). Gender (M:F): intervention: 80% male, control: 93% male. Ethnicity: nr
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Extra comments	The patients were screened by history and physical examination, electroencephalogram and by metabolic laboratory data. Encephalopathy was graded by a trained independent observer on a scale of 0-4.
Indirectness of population	Serious indirectness: Approx. 75% patients had failed to improve encephalopathy over at least 48 hours.
Interventions	(n=40) Intervention 1: Branch chain amino acids - IV branch chain amino acids. F080 - BCAA solution low in aromatic amino acids and methionine (Hepatamine, McGaw laboratories) in 25% dextrose, given via central vein catheter, plus placebo tablets matching the appearance of neomycin and given on the same dosing schedule. F080 contained 36% of the amino acids as the BCAA leucine, isoleucine and valine in essentially equimolar amounts; methionine, phenylalanine and glycine were decreased as compared to conventional solutions and arginine and alanine were somewhat increased. Day 1: 1.5 litres of solution; days 2-6: 2 litres of solution and up to a maximum of 3 litres per day thereafter. Duration up to 14 days. To complete the study, the patient had to finish the first four days of therapy with complete data. . Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or L-dopa. Oral intake was restricted until hepatic encephalopathy cleared, after which oral intake was allowed as tolerated. (n=35) Intervention 2: Oral non-absorbable antibiotics - neomycin. 4 grams of enteral neomycin daily along with 25% dextrose by central venous catheter in four divided doses. Duration up to 14 days. To complete the study, the patient had to finish the first four days of therapy with complete data. Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or L-dopa. Oral intake was restricted until hepatic encephalopathy cleared, after which oral intake was allowed as tolerated.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus NEOMYCIN

Protocol outcome 1: Survival at End of study
- Actual outcome: Death at During treatment; Group 1: 14/40, Group 2: 22/35; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Cerra 1985[151]
Protocol outcomes not reported by the study	Quality of life at End of study; No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Fiaccadori 1984[285]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=48)
Countries and setting	Conducted in Italy; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis based on clinical and laboratory data and confirmed in all cases but one by liver biopsy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Presence of liver cirrhosis. (2) Presence of hepatic encephalopathy. (3) No evidence of hepatorenal syndrome.
Exclusion criteria	Not given
Recruitment/selection of patients	Patients consecutively admitted to the study group's departments and selected according to the criteria
Age, gender and ethnicity	Age - Other: Mean = 50.8. Gender (M:F): 35/13. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Extra comments	23 out of 48 (47.9%) of the participants had had previous episodes of hepatic encephalopathy
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Non-absorbable disaccharides - lactulose enema. Administered via a nasogastric tube or enema, at 150 to 300mg per day. Duration 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35ml/min for 24 hours

Study	Fiaccadori 1984[285]
	(n=16) Intervention 2: Branch chain amino acids - IV branch chain amino acids. BS 666 infusion lasted for 12 hours with protein intake of around 0.8 to 1g/kg/bw/day. Duration 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35ml/min for 24 hours (n=16) Intervention 3: Branch chain amino acids - IV branch chain amino acids. BS 666 infusion lasted for 12 hours with protein intake of around 0.8 to 1g/kg/bw/day + lactulose administered via a nasogastric tube or enema, at 150 to 300mg per day. Duration 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35ml/min for 24 hours
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTULOSE ENEMA versus IV BRANCH CHAIN AMINO ACIDS Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: The number of participants that came out of coma at By the 7th day; Group 1: 5/8, Group 2: 15/16; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTULOSE ENEMA versus IV BRANCH CHAIN AMINO ACIDS + LACTULOSE Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: The number of participants that came out of coma at By the 7th day; Group 1: 5/8, Group 2: 16/16; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Survival at End of study; Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Gyr 1996[365]

Study	Gyr 1996[365]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=49)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised patients having chronic liver failure with mild to moderate degree of PSE (stage I - III or clinical PSE score 3 - 14)
Exclusion criteria	Acute fulminant liver failure; coma at any point of the study; metabolic coma other than due to liver failure; hepatitis superimposed on cirrhosis; liver tumours; severe cerebral atrophy as assessed by cranial computer aided tomography; and psychiatric disease except PSE; patients who reported to have taken psychotropic medication (including benzodiazepines)
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Intervention 55.5 (9.4) versus Control 53.6 (10.3). Gender (M:F): 34/15. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear (West Haven stage not reported). 2. Severity of the underlying liver disease : Child-Pugh B or C (Only 4% Child Pugh A).
Extra comments	Portal systemic encephalopathy (PSE) episodes resulting from common precipitating situations such as severe bleeding and infection were excluded, resulting in a selection of patients with apparently more spontaneous and stable PSE in chronic liver disease.
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: IV benzodiazepine antagonist - Flumazenil. [1] Three sequential bolus injections of flumazenil (0.4, 0.8, then 1mg) at one minute interval. [2] IV infusions of flumazenil at 1mg/hour for 3 hours. Duration 3 hours. Concurrent medication/care: Saline, gluicose, lactulose, potassium and vitamin K were allowed as additional treatments. (n=21) Intervention 2: Placebo. [1] Three sequential bolus injections of placebo (0.4, 0.8, then 1mg) at one minute interval. [2] IV infusions of placebo at 1mg/hour for 3 hours. Duration 3 hours. Concurrent medication/care: Saline, gluicose, lactulose, potassium and vitamin K were allowed as additional treatments.

Study	Gyr 1996[365]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUMAZENIL versus PLACEBO Protocol outcome 1: Survival at End of study - Actual outcome: death (from respiratory failure) during the observation period at 3hr treatment period + 5hr post-treatment observation period; Group 1: 0/28, Group 2: 1/21; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: death following the study (considered not related to study medication) at within 4 weeks following the study; Group 1: 4/28, Group 2: 5/21; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Number of patients with clinically relevant response (improvement of at least 2 points in PSE score from baseline, PSE score on a 0-16 scale, better indicated by lower values) at 3hr treatment period + 5hr post-treatment observation period; Group 1: 7/28, Group 2: 0/21; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Adverse events at 3hr treatment period + 5hr post-treatment observation period; Group 1: 4/28, Group 2: 0/21; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Hassanein 2007[375]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=70)
Countries and setting	Conducted in Multiple countries; Setting: Tertiary care centres
Line of therapy	1st line
Duration of study	Intervention + follow up: Maximum of 5 days of treatment (study period); patients followed up to 180 days after the

Study	Hassanein 2007[375]
	end of the study period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was determined by medical history, and confirmed clinically, biochemically and radiologically.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years of age or older, presenting with manifestations of cirrhosis and hepatic encephalopathy grade 3 or 4
Exclusion criteria	Active haemorrhage; haemodynamic instability; acute cardiopulmonary complications; pregnancy; active renal replacement therapy; presenting with drug intoxication / irreversible brain damage / non-hepatic causes of altered mental status; acute liver failure; hepatocellular carcinoma; liver transplant recipient
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Intervention 49 (20 - 67) versus Control 56 (32 - 76); p = 0.019. Gender (M:F): 39/31. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Grade 3-4 (III: 56%; IV: 44%). 2. Severity of the underlying liver disease : Child-Pugh B or C (All Child-Pugh C (range 10-15)).
Indirectness of population	Serious indirectness: Medium time to randomisation from first presentation with severe hepatic encephalopathy was 2 days. In the meantime, patients were managed with their respective local standards of care for hepatic encephalopathy.
Interventions	(n=39) Intervention 1: MARS. Extracorporeal albumin dialysis (ECAD) using molecular absorbent recirculating system (MARS; Teraklin AG, Germany) with standard medical therapy (SMT). Treatments done every day for 6 hours for 5 days or until a 2-grade improvement in hepatic encephalopathy (West Haven).SMT included treatment of the precipitating event of the acute episode of hepatic encephalopathy; oral lactulose titrated to achieve 2-3 daily bowel movements, oral neomycin or metronidazole and daily zinc sulfate. . Duration 5 days. Concurrent medication/care: Most patients received systemic antibiotics. (n=31) Intervention 2: No treatment. Standard medical therapy: included treatment of the precipitating event of the acute episode of hepatic encephalopathy; oral lactulose titrated to achieve 2-3 daily bowel movements, oral neomycin or metronidazole and daily zinc sulfate. . Duration 5 days. Concurrent medication/care: Most patients received systemic antibiotics
Funding	Study funded by industry (Grants from Teraklin AG; Rostock & Gambro Renal Products)

Study	Hassanein 2007[375]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MARS + SMT versus STANDARD MEDICAL Thepatic encephalopathyRAPY Protocol outcome 1: Survival at End of study - Actual outcome: death at 5 days; Group 1: 5/39, Group 2: 5/31; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Responder (people with an improvement of hepatic encephalopathy by 2 grades at any time during the 5 day study period). at 5 days; Group 1: 24/39, Group 2: 12/30; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: serious adverse events at 5 days; Group 1: 20/39, Group 2: 8/31; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[716]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=50)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: Until discharge from hospital or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was defined by clinical features, including a history consistent with chronic liver disease (CLD) as well as documented complication of CLD and/or imaging results consistent with cirrhosis and/or liver histologic findings consistent with cirrhosis.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Age 18 to 80 years; (2) Diagnosis of cirrhosis from any cause; (3) Presence of any grade of hepatic encephalopathy; (4) Availability of a legally authorised representative (LAR) for interview and consent.

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[716]
Exclusion criteria	(1) Acute liver failure, defined as coagulopathy with any degree of altered mental status in the absence of underlying CLD; (2) Altered mental status from a cause other than hepatic encephalopathy; (3) Treatment with rifaximin or neomycin within the previous 7 days; (4) Receipt of more than 1 dose of lactulose prior to consent; (5) Lack of an LAR to provide consent; (5) Refusal of consent by the LAR; (6) Previous participation in the present study; (7) Haemodynamic instability treated with vasopressors; (8) Pregnancy; (9) Being a prisoner.
Recruitment/selection of patients	As a person with cirrhosis and altered mental status with a suspected hepatic encephalopathy presented at the ED of the hospital (study site) between Jan 2011 and Jun 2012, their LAR was approached and interviewed to seek consent for study participation.
Age, gender and ethnicity	Age - Mean (SD): 56 (9). Gender (M:F): 31/19. Ethnicity: White Hispanic 70%; White non-Hispanic 20%; African American 8%; Asian 1%
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: Previous episodes of hepatic encephalopathy for the participants are unknown.
Interventions	(n=25) Intervention 1: Polyethylene gycol electrolyte solution, PEG 3350. 4 litres of PEG administered orally or via nasogastric tube in a single dose over 4 hours. After PEG administration, no lactulose (or other potential hepatic encephalopathy therapy) was allowed for 24 hours. After 24 hours, participants were allowed to receive lactulose per the standard care. Duration 4 hours. Concurrent medication/care: N/A (n=25) Intervention 2: Non-absorbable disaccharides - oral lactulose. 20 to 30g administered orally or by nasogastric tube (3 or more doses within 24 hours) or 200g by rectal tube if oral intake was not possible or inadequate. Duration 24 hours. Concurrent medication/care: N/A
Funding	Academic or government funding (National Institutes of Health (NIH) grant; NIH National Center for Advancing Translational Sciences grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYETHYLENE GLYCOL ELECTROLYTE SOLUTION, PEG 3350 versus ORAL LACTULOSE Protocol outcome 1: Survival at End of study - Actual outcome: death at 24 hours; Group 1: 1/25, Group 2: 2/25; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic	

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[716]
encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Improvement of 1 or more in hepatic encephalopathy grade at 24 hours (hepatic encephalopathy scoring algorithm hepatic encephalopathySA score) at 24 hours; Group 1: 21/25, Group 2: 13/25; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Time to hepatic encephalopathy resolution (defined as an improvement to grade 0, or two days at grade 1 after an initial improvement of at least 1 grade) at N/A; HR 1.76 (95%CI 0.97 to 3.18) Calculated – from curve + numbers at risk; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: No improvement of hepatic encephalopathySA grade at 24 hours at 24 hours; Group 1: 2/23, Group 2: 12/25; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Discharge from hospital at End of study - Actual outcome: Overall length of stay at N/A; Group 1: mean 4 Days (SD 3); n=25, Group 2: mean 8 Days (SD 12); n=25; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Number of adverse events (none considered definitely or probably related to the study interventions) at 24 hours; Group 1: 3/25, Group 2: 5/25; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study

Study	Laccetti 2000[495]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=54)
Countries and setting	Conducted in Italy; Setting: Hospital emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis of liver cirrhosis were made by pertinent clinical, laboratory and morphological procedures performed during previous hospitalisation.
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Laccetti 2000[495]
Inclusion criteria	People with a diagnosis of liver cirrhosis who presented with hepatic encephalopathy in the ED or developed hepatic encephalopathy during their hospital stay: of those, only individuals with chronic liver failure and more severe stages of hepatic encephalopathy (stages III-IV) were included.
Exclusion criteria	People with alcoholic liver cirrhosis
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Intervention 59.6 (6) versus Control 57.7 (5.4). Gender (M:F): 29/25. Ethnicity: Not stated
Further population details	1. Grade of acute hepatic encephalopathy : Grade 3-4 (Grade I and II excluded). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear (Only mean Child Pugh score reported).
Indirectness of population	No indirectness: Patients with alcoholic liver cirrhosis were excluded to avoid bias by neurological and psychiatric signs due to chronic or acute ethanol abuse.
Interventions	(n=28) Intervention 1: IV benzodiazepine antagonist - Flumazenil. 2mg in 50ml saline at 10ml/min. Duration 5 minutes. Concurrent medication/care: Conventional treatment similar for both groups (the following additional treatments were permitted: saline, glucose, lactulose enemas, BCAAs) (n=26) Intervention 2: Placebo. IV placebo 2mg in 50ml saline at 10ml/min. Duration 5 minutes. Concurrent medication/care: Conventional treatment similar for both groups (the following additional treatments were permitted: saline, glucose, lactulose enemas, BCAAs)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUMAZENIL versus PLACEBO

Protocol outcome 1: Survival at End of study
- Actual outcome: Mortality at 24 hours; Group 1: 6/28, Group 2: 5/26; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study
- Actual outcome: Improvement in neurological status (Increase in Glasgow coma score by 3 points) at 24 hours; Group 1: 22/28, Group 2: 14/26; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Laccetti 2000[495]
- Actual outcome: Side effects at 24 hours; Group 1: 0/28, Group 2: 0/26; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Loguercio 1987[533]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: Institute of General Medicine and clinical methodology, the faculty of medicine and surgery, University of Naples, Italy
Line of therapy	1st line
Duration of study	Intervention + follow up: 10 days treatment and a further 10 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Conn and Lieberthal method
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhotic patients
Exclusion criteria	nr
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Median (range): Enterococcus group: 58 (25-66), 57 (35-68). Gender (M:F): Enterococcus group: 13M/7F, lactulose group: 13M/F. Ethnicity: nr
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear (West Haven criteria not used). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Oral probiotics . Enterococcus strain SF68 (Bioflorin) is a lactic acid bacteria. Two capsules, three times per day after meals, each capsule containing at least 75 x 10^6 cells. Duration 10 days. Concurrent medication/care: none (n=20) Intervention 2: Non-absorbable disaccharides - oral lactulose. Lactulose (30ml, four times per day after meals). Duration 10 days. Concurrent medication/care: none

Study	Loguercio 1987[533]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL PROBIOTICS versus ORAL LACTULOSE Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Improvement in hepatic encephalopathy symptoms at Day 10; Group 1: 15/19, Group 2: 14/19; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Meteroism, abdominal pain, diarrhoea, hyperammonaemia, worsening of hepatic encephalopathy, constipation at 20 days; Group 1: 1/16, Group 2: 8/15; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Survival at End of study; Quality of life at End of study; Discharge from hospital at End of study

Study	Mas 2003[574]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=103)
Countries and setting	Conducted in Spain; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 5 to 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: After hospital admission, patients underwent detailed physical, neurological and psychometric assessment.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive cirrhotic patients with an acute hepatic encephalopathy episode, diagnosed in specified 13 hospitals in Spain from November 1995 to December 1997: with clinical, psychometric and electroencephalographic evidence of

Study	Mas 2003[574]
	grade I - III hepatic encephalopathy of < 2 days duration and PSE index > 0
Exclusion criteria	Major psychiatric illness; chronic renal and/or respiratory insufficiency; intercurrent infections; known hypersensitivity to rifamycin antibiotics and/or to disaccharides; patients having received treatment with sedatives or antibiotics within 7 days before inclusion; pregnant or lactating women; and patients who did not fulfill protocol requirements
Recruitment/selection of patients	Consecutive patients fulfilling criteria
Age, gender and ethnicity	Age - Mean (SD): Intervention 61.6 (9.7) versus Control 62.9 (0.6). Gender (M:F): 72/31. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear (West Haven Criteria not reported). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Oral non-absorbable antibiotics - rifaximin. Two 200mg rifaximin tablets taken orally or via nasogastric tube, every 8 hours. Duration Maximum of 10 days. Concurrent medication/care: 20g placebo sachet dissolved in 100ml of water, given orally or via nasogastric tube, every 8 hours (n=53) Intervention 2: Non-absorbable disaccharides - oral lactitol. One 20g lactitol sachet dissolved in 100ml of water given orally or via nasogastric tube, every 8 hours. Duration Maximum of 10 days. Concurrent medication/care: 2 tablets of placebo, externally indistinguishable from the rifaximin tablets, every 8 hours
Funding	Study funded by industry (The study was supported by a grant given by Zambon S.A. (Spain), and the interventional drugs were provided by Alfa Wassermann Pharmaceutical Company (Italy).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus LACTITOL

Protocol outcome 1: Survival at End of study
- Actual outcome: death considered unrelated to the study medication at within 28 days of the last dose; Group 1: 1/50, Group 2: 2/53; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study
- Actual outcome: Unchanged/failure (hepatic encephalopathy clinical syndrome not improved and blood ammonia levels not decreased / increase in blood ammonia, increase in PSE index and/or a shift to a higher stage of hepatic encephalopathy) - this is versus a resolution or improvement in hepatic encephalopathy clinical stage or blood ammonia at Post-treatment; Group 1: 9/50, Group 2: 10/53; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Mas 2003[574]
Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Adverse events at Post-treatment; Group 1: 3/50, Group 2: 2/53; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Paik 2005[662]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=54)
Countries and setting	Conducted in South Korea; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis based on clinical and laboratory findings
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospital inpatients with episodic hepatic encephalopathy affected by decompensated liver cirrhosis
Exclusion criteria	Age < 18 years; presence of a major neuropsychiatric illness; presence of intestinal obstruction or IBD; hypersensitivity to rifamycin/diasaccharides; a serum creatinine level > twice normal; received loop diuretics/antacids/cathartics within 12-hr period before study commencement; on antibiotics during preceding 7 days; previously treated with encephalopathy-causing agents
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Intervention 56.2 (7.1) versus Control 54.9 (6.6). Gender (M:F): 37/17. Ethnicity: Korean 100%
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear (West Haven criteria not reported). 2. Severity of the underlying liver disease : Child-Pugh B or C
Extra comments	The participants showed signs of the 1st to 3rd degree hepatic encephalopathy, according to Conn's modification of Parsons-Smith classification, and had serum ammonia levels > 75 µmol/L. Of the 64 participants, 26 (40.6%) had "acute hepatic encephalopathy" and 38 (59.4%) had "recurrent hepatic encephalopathy".
Indirectness of population	No indirectness

Study	Paik 2005[662]
Interventions	(n=32) Intervention 1: Oral non-absorbable antibiotics - rifaximin. 1200mg per day in 3 divided doses. Duration 7 days. Concurrent medication/care: Not reported (n=22) Intervention 2: Non-absorbable disaccharides - oral lactulose. Lactulose syrup, 90ml per day. Duration 7 days. Concurrent medication/care: Not reported
Funding	Equipment / drugs provided by industry (Ajou Pharmaceutical, Co. Ltd. Korea supplied rifaximin and lactulose.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus ORAL LACTULOSE Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Improvement in hepatic encephalopathy grade at 7 days; Group 1: 26/32, Group 2: 16/22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Improvement in hepatic encephalopathy index (taking into account hepatic encephalopathy grade, NCT, blood ammonia and severity of flapping tremor) at 7 days; Group 1: 27/32, Group 2: 21/22; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Adverse effects at 7 days; Group 1: 1/32, Group 2: 1/22; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Survival at End of study; Quality of life at End of study; Discharge from hospital at End of study

Study (subsidiary papers)	Rossi-fanelli 1982[743] (Rossi fanelli 1986[741], Rossi 1984[742])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=34)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Until 10 days after the start of therapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Study (subsidiary papers)	Rossi-fanelli 1982[743] (Rossi fanelli 1986[741], Rossi 1984[742])
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Presence of liver cirrhosis, diagnosed on clinical, biochemical and histological findings; (2) Presence of hepatic coma (grade 3 - 4 hepatic encephalopathy) assessed by two independent observers according to the classification of Adams & Foley as reported by Fischer et al.; (3) Absence of signs of hepatorenal syndrome assessed according to the criteria established at the symposium held in Sassari.
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients fulfilling the inclusion criteria between August 1979 and June 1980
Age, gender and ethnicity	Age - Other: Mean age only: Intervention = 57 versus Control = 60.8. Gender (M:F): 21/13. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Grade 3-4 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Branch chain amino acids - IV branch chain amino acids. BS 692 (leucine 1.1%, isoleucine 0.9%, valine 0,8% in 20% dextrose): 60ml/hour for the first 24 hours, and 80ml/hour thereafter until 48 hours after mental recovery. Duration Up to 48 hours (following this, patients who did not recover underwent a combination treatment). Concurrent medication/care: none (n=20) Intervention 2: Non-absorbable disaccharides - oral lactulose. Lactulose via (1) nasogastric tube: 30 - 40g every 4 hours until catharsis, thereafter, the dose adjusted to ensure 2 bowel movements/day. Or (2) via rectal route for patients who could not receive lactulose orally: 200 - 300g/day intermittent enemas. Duration Until 48 hours (following this, patients who did not recover underwent a combination treatment). Concurrent medication/care: Dextrose in isocaloric amounts and at the same rate as Group A
Funding	Academic or government funding (Ministry of Health, Rome, Italy)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus ORAL LACTULOSE

Protocol outcome 1: Survival at End of study
- Actual outcome: Number of deaths at Up to 10 days after mental recovery; Group 1: 4/17, Group 2: 5/17; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic

Study (subsidiary papers)	Rossi-fanelli 1982[743] (Rossi fanelli 1986[741], Rossi 1984[742])
encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Mean time of arousal at N/A; Group 1: mean 27.6 hours (SD 26.7); n=17, Group 2: mean 31.5 hours (SD 18.1); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Responsive: number of participants achieving complete mental recovery (consciousness regained and returned to grade 0 hepatic encephalopathy) at N/A; Group 1: 12/17, Group 2: 8/17; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Unresponsive: number of participants achieving complete mental recovery (consciousness regained and returned to grade 0 hepatic encephalopathy) at N/A; Group 1: 5/17, Group 2: 9/17; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Sharma 2013[795]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=120)
Countries and setting	Conducted in India; Setting: Tertiary care
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis was based on laboratory tests, endoscopic evidence, sonographic findings, and liver histology if available.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients at a tertiary care centre aged 18 to 80 years with liver cirrhosis and overt hepatic encephalopathy
Exclusion criteria	Serum creatinine >1.5mg/dL on admission; active alcohol intake < 4 weeks before present episode; other metabolic encephalopathies; hepatocellular carcinoma; degenerative central nervous system disease or major psychiatric illness; and significant comorbidity
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): 39.4 (9.6). Gender (M:F): 89:31. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Grade 3-4 (81.7% had grade 3 or 4 on admission, 18.3% grade 2.). 2.

Study	Sharma 2013[795]
	Severity of the underlying liver disease : Child-Pugh B or C
Extra comments	The mean age of the participants is relatively younger than that seen in other studies.
Indirectness of population	Serious indirectness: 18 patients were on regular lactulose for prophylaxis of hepatic encephalopathy
Interventions	(n=63) Intervention 1: Oral non-absorbable antibiotics - rifaximin. One 400mg capsule, 3 times a day. Duration Until complete recovery of hepatic encephalopathy or a maximum of 10 days if no recovery; discharge from hospital; or death. Concurrent medication/care: Lactulose 30 to 60ml, 3 times a day (n=57) Intervention 2: Non-absorbable disaccharides - oral lactulose. Lactulose via nasogastric tube, 30 to 60ml, 3 times a day. Duration Until complete recovery of hepatic encephalopathy or a maximum of 10 days if no recovery; discharge from hospital; or death. Concurrent medication/care: Placebo capsule resembling rifaximin, 3 times a day
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN + LACTULOSE versus ORAL LACTULOSE Protocol outcome 1: Survival at End of study - Actual outcome: Mortality at N/A; Group 1: 15/63, Group 2: 28/57; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Number of participants achieving complete reversal of hepatic encephalopathy (according to West Haven criteria) at within 10 days; Group 1: 48/63, Group 2: 29/57; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Discharge from hospital at End of study - Actual outcome: Length of hospital stay at N/A; Group 1: mean 5.8 days (SD 3.4); n=63, Group 2: mean 8.2 days (SD 4.6); n=57; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Side effects related to study medications at N/A; Group 1: 12/63, Group 2: 10/57; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study

Study	Strauss 1986[845]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in Brazil; Setting: Hospital Heliopolis and Hospital Municipal, Sao Paulo, Brazil
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 'mainly on a histological basis'
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed cirrhosis. hepatic encephalopathy characterised as a disturbance of consciousness assessed semiquantitatively as grades I to IV.
Exclusion criteria	If previous to randomisation, a specific treatment for the hepatic encephalopathy (i.e. neomycin, lactulose or L-dopa) had already been started.
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Range: 28-67. Gender (M:F): 26 men, 3 women. Ethnicity: nr
Further population details	1. Grade of acute hepatic encephalopathy : Grade 1-2 (22/32 were grade 1 or 2, the other 10 were grade 3). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Extra comments	Patients were treated equally for precipitating factors of the exogenous encephalopathy. Diuretics were always withdrawn and gastrointestinal bleeding due to oesophageal varices was treated with Sungstaken-Blakemore balloon and blood transfusion. Potassium was supplemented if necessary and laxatives were used only in obstipated patients. Infections were treated with antibiotics, mainly ampicillin (1-4g orally) or according to specific antibiograms.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Branch chain amino acids - IV branch chain amino acids. F080, which contains higher percentages of branched chain amino acids and reduced amounts of aromatic amino acids. Continuous intravenous administration of 60g of protein equivalent in 24 hours. A hypertonic glucose solution was given simultaneously, according to the needs of the patient. As the . Duration Until recovery. Concurrent medication/care: Grades I and II were allowed to eat, receiving initially a diet of 10g protein. Fluid and electrolyte supplementation were made according to each patient's needs. As the patient improved, dietary protein was increased (20 g every second day) while the parenteral solution was decreased until its total withdrawal after complete recovery of consciousness.

Study	Strauss 1986[845]
	(n=16) Intervention 2: Oral non-absorbable antibiotics - neomycin. 1 gram of neomycin sulphate orally every four hours. Intestinal cleansing was performed every 12 hours, with a litre of water and 2 grams of neomycin. As patients improved, dietary protein was increased (20 grams every second day) while the dosage of neomycin was decreased (2 grams every second day) until its total withdrawal after two days of complete recovery of consciousness. . Duration: Until recovery. Concurrent medication/care: Grades I and II were allowed to eat, receiving initially a diet of 10g protein. Fluid and electrolyte supplementation were made according to each patient's needs. As the patient improved, dietary protein was increased (20 g every second day) while the parenteral solution was decreased until its total withdrawal after complete recovery of consciousness.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus NEOMYCIN Protocol outcome 1: Survival at End of study - Actual outcome: Mortality at During treatment; Group 1: 2/16, Group 2: 2/16; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Time to recovery at During treatment; Group 1: mean 33.4 hours (SD 21.1); n=14, Group 2: mean 70.8 hours (SD 28.8); n=14; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Strauss 1992[846]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Brazil; Setting: Hospital
Line of therapy	1st line

Study	Strauss 1992[846]
Duration of study	Intervention + follow up: Patients followed up and analysed for mortality for 1 year after discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: histopathological and/or clinical-biochemical diagnosis of hepatic cirrhosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	January 1986 to December 1990
Age, gender and ethnicity	Age - Mean (SD): 49.23 (11.39). Gender (M:F): 34/5. Ethnicity:
Further population details	1. Grade of acute hepatic encephalopathy : Grade 1-2 (majority grade I or II (I: 41.0%; II: 23.1%; III: 35.9%; IV: 0%)). 2. Severity of the underlying liver disease : Child-Pugh B or C (12.8% CPB and 87.2% CPC).
Extra comments	8 of the 39 patients randomised had previous episodes of hepatic encephalopathy (but people with chronic hepatic encephalopathy or on specific treatment for hepatic encephalopathy at the time of randomisation or in the week before it were excluded)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Oral non-absorbable antibiotics - neomycin. Neomycin sulfate 1g every 4 hours (6g/day; oral for grades I and II, by nasogastric tube for grades II and IV) and 2g in 500ml of tepid water every 12 hours for intestinal cleansing. Patients in grades III and IV also received 60g/day of an enriched solution of BCAAs (Portamin) with IV hypertonic glucose. When improvement to grade 0 hepatic encephalopathy observed, neomycin decreased to 2g each second day (and if BCAAs given, decreased by 20g every other day). . Duration unclear. Concurrent medication/care: Grade I and II hepatic encephalopathy: oral diet continued but protein restricted to 10g/day; Grade III and IV hepatic encephalopathy: IV administration of necessary calories. When improvement to grade 0 hepatic encephalopathy observed, dietary protein increased to 20g/day (n=19) Intervention 2: Placebo. Placebo. Patients in grades III and IV also received 60g/day of an enriched solution of BCAAs (Portamin) with IV hypertonic glucose. When improvement to grade 0 hepatic encephalopathy observed, if BCAAs given, decreased by 20g every other day. Duration unclear. Concurrent medication/care: Grade I and II hepatic encephalopathy: oral diet continued but protein restricted to 10g/day; Grade III and IV hepatic encephalopathy: IV administration of necessary calories. When improvement to grade 0 hepatic encephalopathy observed, dietary protein increased to 20g/day

Study	Strauss 1992[846]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEOMYCIN versus PLACEBO Protocol outcome 1: Survival at End of study - Actual outcome: Therapeutic failure and death at 5th day of treatment; Group 1: 2/20, Group 2: 2/19; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Time until regression to grade 0 hepatic encephalopathy at N/A; Group 1: mean 36.11 hours (SD 23.04); n=20, Group 2: mean 49.47 hours (SD 21.92); n=19; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Sushma 1992[851]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=74)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Until recovery or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis was made by liver biopsy or clinical criteria when liver biopsy was not possible.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of cirrhosis or had had a surgical portal-systemic anastomosis; hepatic encephalopathy of < 7 days
Exclusion criteria	Treatment with lactulose for 24 hours or more before entry into the study or had active GI bleeding; History of neurological disease other than hepatic encephalopathy; Refusal to enter study by the responsible next of kin

Study	Sushma 1992[851]
Recruitment/selection of patients	Consecutive patients with cirrhosis and hepatic encephalopathy admitted to the gastroenterology ward of a hospital
Age, gender and ethnicity	Age - Mean (SD): Intervention 35.6 (18.4) versus Control 37.9 (12.8). Gender (M:F): 56/18. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Extra comments	Four out of the 74 patients had had portacaval shunt prior to entering the study. Out of these, 2 had cirrhosis and 2 had non-cirrhotic fibrosis.
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Sodium benzoate. Administered orally or via a nasogastric tube (if necessary), 5mg twice daily (each does dissolved in 30ml of tap water). Duration Until clinical recovery. Concurrent medication/care: Standard treatment for acute hepatic encephalopathy: twice daily bowel washes with tap water, maintenance of fluid and electrolyte levels, intake of at least 800 calories/day, restriction of oral intake of proteins to 20mg/day in whom oral intake was possible. (n=36) Intervention 2: Non-absorbable disaccharides - oral lactulose. Administered orally or via a nasogastric tube (if necessary), initially at 30ml every 8 hours, then adjusted to once in 24 hours to achieve 3 semi-formed stools/day. Duration Until clinical recovery. Concurrent medication/care: Standard treatment for acute hepatic encephalopathy: twice daily bowel washes with tap water, maintenance of fluid and electrolyte levels, intake of at least 800 calories/day, restriction of oral intake of proteins to 20mg/day in whom oral intake was possible.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SODIUM BENZOATE versus ORAL LACTULOSE

Protocol outcome 1: Survival at End of study
- Actual outcome: Mortality during treatment at N/A; Group 1: 8/38, Group 2: 7/36; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study
- Actual outcome: Mean duration of therapy before complete clinical recovery at N/A; Group 1: mean 11.6 Days (SD 6.4); n=38, Group 2: mean 12.8 Days (SD 9.1); n=36; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Number of participants with complete response (recovery to normal mental status with no evidence of asterixis) at N/A; Group 1: 30/38, Group 2:

Study	Sushma 1992[851]
29/36; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Number of participants who continued in grade 1+ mental status despite therapy for 21 days at 21 days; Group 1: 3/38, Group 2: 1/36; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Number of complications at During treatment; Group 1: 35/38, Group 2: 30/36; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Uribe 1981[895]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=18)
Countries and setting	Conducted in Mexico; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention time: Treatment continued until 48 hours after recovery then study was concluded
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: biopsy-proven cirrhosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis; developed within 24 hours an acute episode of hepatic encephalopathy (at least grade 2+ severity) plus 2 of the following abnormalities: arterial ammonia levels above 120ug% (normal <90ug%); abnormal slow waves in the EEG as blindly judged by a neurologist; time taken to perform a NCT at least double the normal range (>60s, normal is >30s) or patient unable to perform the test due to mental confusion or coma.
Exclusion criteria	Use of analgesics of sedatives; presented with acute renal failure; required or had ingested antibiotics; presented with active bleeding; presented with anorectal disease; had a history of previous neurological disease other than hepatic encephalopathy; no consent to participate from relatives.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Neomycin: 55 (9); Lactose: 51 (11). Gender (M:F): 6/12. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear (West Haven criteria not reported). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear

Study	Uribe 1981[895]
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Non-absorbable disaccharides - lactulose enema. 1 litre lactose (20%) enema . Duration: Until 48 hours after recovery. Concurrent medication/care: 2 placebo tablets which looked identical to neomycin tablets Comments: This is lactose and not lactulose. (n=10) Intervention 2: Oral non-absorbable antibiotics - neomycin. Two 0.5g neomycin tablets. Duration: Until 48 hours after recovery. Concurrent medication/care: 1 litre starch (10%) enema bottled in identical containers as lactose enema
Funding	Academic or government funding (Grants from Consejo Nacional de Ciencia y Tecnologia; Academia Nacional de Medicina, Chinoin Award)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTOSE ENEMA versus NEOMYCIN Protocol outcome 1: Survival at End of study - Actual outcome: Mortality at Within 1 month from the end of the study; Group 1: 1/8, Group 2: 1/10; Risk of bias: high; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Clinical-biochemical improvement (improvement of 1 grade in mental state (Conn's grading 0-4), a reduction of 30s in time taken to perform the number connection test (NCT) and ammonia reduction of 50ug% at N/A; Group 1: 7/8, Group 2: 7/10; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Treatment side effects at N/A; Group 1: 0/8, Group 2: 0/10; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Uribe 1987[896]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=15 (placebo arm discontinued, trial continued to recruit 45 people for lactitol versus lactose comparison))

Study	Uribe 1987[896]
Countries and setting	Conducted in Switzerland; Setting: not reported
Line of therapy	1st line
Duration of study	Intervention time: Response-dependent
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: cirrhosis diagnosis method unclear
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis; development within 24 hr of an acute episode of PSE, characterized by encephalopathy of at least Grade 2+ severity (3) plus two of the following abnormalities-(i) arterial ammonia levels above 120 µg% (n ≤ 90 µg%); (ii) abnormal slow waves in the electroencephalogram, and (iii) protracted performance of a number connection test (NCT) of at least double the normal time (n < 30 sec) or inability to perform the test due to mental confusion or coma. PSE could be precipitated by nitrogenous substances (dietary proteins, use of diuretics or idiopathic (endogenous) factors.
Exclusion criteria	(i) required or had received systemic or rectal antibiotics; (ii) presented with active gastrointestinal bleeding; (iii) presented with anorectal disease; (iv) had a history of previous neurological disease other than PSE, or (v) the relatives refused to sign a consent form.
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Other: not reported. Gender (M:F): not reported. Ethnicity: not reported
Further population details	1. Grade of acute HE : Not applicable / Not stated / Unclear (at least grade 2+). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Non-absorbable disaccharides - lactulose enema. 20% lactitol enema (Lactitol, Laboratories Zyma SA, Nyon, Switzerland). Duration variable and response-dependent. Concurrent medication/care: not reported (n=5) Intervention 2: Placebo. tap water enema at a dose of 1 litre t.i.d. Duration variable and response-dependent. Concurrent medication/care: not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTITOL ENEMA versus PLACEBO	

Study	Uribe 1987[896]
Protocol outcome 1: Survival at End of study - Actual outcome: Mortality at variable and response-dependent; Group 1: 0/10, Group 2: 3/5; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Therapeutic response (defined as (i) sustained improvement of one grade in mental state during ≤48 hours or (ii) improvement of more than two grades in mental state). at variable and response-dependent; Group 1: 10/10, Group 2: 1/5; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Vilstrup 1990[910]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=77)
Countries and setting	Conducted in Denmark; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: Until recovery or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis and hepatic encephalopathy Grade II/III/IV, according to the Fogarty classification
Exclusion criteria	Non-hepatic encephalopathy or psychosis including drug effects; lack of central venous access; oliguria that rendered the planned regimens impossible; malignancy with an expected life span of < 1 year
Recruitment/selection of patients	Consecutive patients fulfilling the inclusion criteria in 3 hospitals
Age, gender and ethnicity	Age - Mean (SD): Intervention 55 (9) versus Control 56 (12). Gender (M:F): 47/18. Ethnicity: Not reported
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear

Study	Vilstrup 1990[910]
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Branch chain amino acids - IV branch chain amino acids. IV BCAA (8%) via central venous lines by infusion pumps at 12.5ml/kg/day throughout day and night. Duration Up to recovery or death (max. of 16 days treatment). Concurrent medication/care: Glucose (50%) 12.5ml/kg/day + Laculose syrup 60ml/day + Cimetidine 200 to 400mg/day + Minerals + Vitamins + other medications according to needs (n=39) Intervention 2: Placebo. Glucose (8%) 12.5ml/kg/day in bottles that look identical to those for BCAA. Duration Up to recovery or death (max. of 16 days treatment). Concurrent medication/care: Glucose (50%) 12.5ml/kg/day + Laculose syrup 60ml/day + Cimetidine 200 to 400mg/day + Minerals + Vitamins + other medications according to needs
Funding	Academic or government funding (Grants from the Borgen Foundation, the Danish Medical Research Council, the Ebba Celinder's Foundation, and the Johann and Hanne Weimann, nee Seedorff's Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus GLUCOSE Protocol outcome 1: Survival at End of study - Actual outcome: Number of participants who died at 16 days; Group 1: 11/32, Group 2: 10/33; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Number of participants who woke up (to hepatic encephalopathy grade 0 or I by Fogarty classification) at 16 days; Group 1: 17/32, Group 2: 17/33; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Number of participants who had treatment failures other than death (hepatic encephalopathy deeper than grade I (Fogarty classification) after 16 days despite other improvements defined as failure) at 16 days; Group 1: 4/32, Group 2: 6/33; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Study	Wahren 1983[914]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in France, Sweden; Setting: Five medical centres.
Line of therapy	1st line
Duration of study	Intervention + follow up: A maximum of 5 days intervention. Last blood collected the morning after the end of the intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: EEG and neurological examinations
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical and laboratory evidence of cirrhosis verified histologically by liver biopsy, autopsy, angiography, laparoscopy, laparotomy
Exclusion criteria	Patients with severe respiratory failure, septic shock or uremia
Recruitment/selection of patients	17 from Paris, 12 from Marseille, 7 from Montpellier, 7 from Lille, 7 from Stockholm
Age, gender and ethnicity	Age - Mean (SD): BCAA: 59 (2), placebo: 52 (2). Gender (M:F): BCAA group: 13 male, 12 female. Placebo group: 15 male, 10 female. Ethnicity: nr
Further population details	1. Grade of acute hepatic encephalopathy : 2. Severity of the underlying liver disease :
Extra comments	Grade of hepatic encephalopathy at baseline. BCAA: grade II: 1, grade III: 10, grade IVa-IVc: 14. Placebo: grade II: 1, grade III: 8, grade IVa-IVc: 16 EEG grade IVa-IVdat baseline. 40% in BCAA group, 82% in placebo group.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Branch chain amino acids - IV branch chain amino acids. 20 g/litre in a solution containing 70% leucine, 20% valine, 10% isoleucine, in 5% glucose. 20 hours per day. Duration Given until 1 day after hepatic encephalopathy had improved to grade 0 or 1, for a maximum of five days. Concurrent medication/care: 5 patients in this group also received conventional therapy involving lactulose and/or neomycin. Four patients received antibiotics. (n=25) Intervention 2: Placebo. 5% glucose given 20 hours per day. Duration Given until 1 day after hepatic encephalopathy had improved to grade 0 or 1, for a maximum of five days. Concurrent medication/care: 3 patients in this group also received conventional therapy involving lactulose and/or neomycin. Seven patients received antibiotics.

Funding	Study funded by industry (Industry, medical research council and a charity)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus PLACEBO Protocol outcome 1: Survival at End of study - Actual outcome: Mortality during treatment at 5 days; Group 1: 10/25, Group 2: 5/25; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Positive response to treatment at 5 days; Group 1: 10/20, Group 2: 11/22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: No response to treatment at 5 days; Group 1: 7/20, Group 2: 7/22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Negative response to treatment at 5 days; Group 1: 3/20, Group 2: 4/22; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study; Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study

Appendix I: Economic evidence tables

I.1 Risk factors and risk assessment tools

None.

I.2 Diagnostic tests

Study	Canavan 2013[133]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov decision model **Approach to analysis:** • Simulated population monitored for cirrhosis and progressing to possible HCC or transplant • 3 month cycle length • 7 strategies compared, 3 of which are relevant to this question • States: fibrosis, compensated cirrhosis, decompensated cirrhosis, operable HCC, non-operable HCC, RFT/resection, recurrent HCC, transplant, palliative treatment **Perspective:** UK NHS **Time horizon:** Lifetime	**Population:** Chronic hepatitis C patients without fibrosis **Cohort settings:** Start age: 34 years Male: NR **Intervention 1:** No testing; Investigations only conducted after patients have become symptomatic **Intervention 2:** Annual biopsy, followed by HCC screening at 6-month intervals once cirrhosis is confirmed **Intervention 3:** Annual transient elastography followed by HCC screening at 6-month intervals once cirrhosis is	**Total costs (mean per patient):** Intervention 1: £4,500 Intervention 2: £16,250 Intervention 3: £8,000 Incremental (2−1): £11,750 (95% CI: NR; p=NR) Incremental (3−1): £3,500 (95% CI: NR; p=NR) Incremental (3−2): –£8,250 (95% CI: NR; p=NR) **Currency & cost year:** 2013 UK pounds **Cost components incorporated:** Liver biopsy, TE, AFP and ultrasound, CT scan, ablation, resection, transplant, compensated cirrhosis,	**QALYs (mean per patient):** Intervention 1: 18.20 Intervention 2: 17.20 Intervention 3: 18.75 Incremental (2−1): –1.00 (95% CI: NR; p=NR) Incremental (3−1): 0.55 (95% CI: NR; p=NR) Incremental (3−2): 1.55 (95% CI: NR; p=NR)	Annual liver biopsy is dominated by both alternatives (more expensive and less effective) **ICER (Intervention 3 versus Intervention 1):** £6557 per QALY gained (pa) 95% CI:NR **Analysis of uncertainty:** Univariate sensitivity analysis; ICER most sensitive to rate of developing cirrhosis from F3 fibrosis but TE still considered cost-effective using a £30,000 threshold. Changes in other parameters do not change the cost-effectiveness conclusions.

Discounting: Costs: 3.5%; Outcomes: 3.5%	confirmed	decompensated cirrhosis, HCC, annual palliative care costs		
Data sources				
Health outcomes: TE diagnostic accuracy obtained from a 2011 meta-analysis, liver biopsy diagnostic accuracy obtained from 2 studies (no meta-analyses). **Quality-of-life weights:** QALY values obtained from 8 sources that used the EQ-5D questionnaire. **Cost sources:** NHS reference costs, UK NHS hospital trust sources, NIHR HTA studies.				
Comments				
Source of funding: MRC Population Health Science Fellowship. **Limitations:** Quality of life estimates do not come from a meta-analysis but from single studies. Liver biopsy unit costs low compared to current UK NHS costs. The model did not include the polymerase inhibitor drug treatment as a parameter.				
Overall applicability[(a)]: directly applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; AFP: alpha-fetoprotein; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HCC: hepatocellular carcinoma; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; TE: transient elastography

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Steadman 2013[840]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: cost analysis (cost per additional correct diagnosis) **Study design:** decision tree **Approach to analysis:** Proportion of true and false outcomes of testing using the 2 strategies were calculated based on their diagnostic accuracy. **Perspective:** Canadian healthcare provider **Time horizon:** NA	**Population:** Meta-analysis of published diagnostic accuracy studies Five patient subgroups: HBV (8 studies), HCV (14), NAFLD (6) (also reported cholestatic liver disease, post-liver transplantation) **Intervention 1:** Transient elastography	**Total costs (mean per patient):** Intervention 1: £56 Intervention 2: £261 Incremental (2−1): £205 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Canadian dollars (presented here as 2010 UK pounds[(a)]) **Cost components**	**Correct diagnoses (per 1000 patient):** <u>Intervention 1:</u> Hep B: 820 Hep C: 898 NAFLD: 947 <u>Intervention 2:</u> Hep B: 1,000[(b)] Hep C: 1,000[(b)] NAFLD: 1,000[(b)] <u>Incremental (2−1):</u> Hep B: 180	**Cost per additional correct diagnosis (Intervention 2 versus Intervention 1):** Hep B: £1,136 (95% CI: £276–2,927) Hep C: £2,001 (95% CI: £284–7,317) NAFLD: £3,841 (95% CI: £288–NA) **Analysis of uncertainty:** Changes in sensitivity, specificity and prevalence have a significant effect on the resulting cost per correct diagnosis

Discounting: Costs: NA; Outcomes: NA	**Intervention 2:** Liver biopsy	**incorporated:** Only test costs considered	Hep C: 102 NAFLD: 53 (95% CI: NR; p=NR)	

Data sources
Health outcomes: Pooled diagnostic accuracy data was obtained from 57 studies (78% were considered of high quality by the authors). **Cost sources:** Liver biopsy costs were obtained from a single Canadian study, transient elastography costs were estimated through a micro costing process.
Comments
Source of funding: Alberta Health. **Limitations:** Differences in healthcare system may make results less applicable to UK, no health outcomes following diagnosis were considered in the model. TE diagnostic accuracy estimates were informed by observational data. **Other:** The study reported results in all 4 categories of the METAVIR classification scale. For the purpose of the report only F=4 is presented here.
Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; da: deterministic analysis; HBV: hepatitis; HCV: hepatitis C; NA: not applicable; NAFLD: non-alcoholic fatty liver disease
(a) Converted using 2010 purchasing power parities[654]
(b) The economic model assumed that the sensitivity and specificity of liver biopsy is equal to 1 (reference standard)
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Stevenson[842]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Discrete event simulation model **Approach to analysis:** Progression of liver disease/cirrhosis following cirrhosis diagnosis with regular monitoring for varices, ascites, hepatic encephalopathy and HCC	**Population:** Patients with suspected liver fibrosis related to alcohol consumption. **Cohort settings:** Start age: NR Male: NA **Intervention 1:** Percutaneous liver biopsy for all patients (assumed current practice) **Intervention 2:** Triage with TE (threshold: 11.5), biopsy all those in whom cirrhosis is indicated	**Total costs (mean per patient):** Details in Table 30, Chapter 6 **Currency & cost year:** 2012 UK pounds **Cost components incorporated:** Test costs, screening for varices,	**QALYs (mean per patient):** Details in Table 30, Chapter 6	**ICER (Intervention 2 versus Intervention 1):** Details in Table 30, Chapter 6. Biopsy only is the most effective strategy that is cost-effective at a threshold of £20,000. **Analysis of uncertainty:** There is high uncertainty in the results. This was explored with the identification of 36 scenarios for every strategy which were based on the combination of

Perspective: UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 3:** Triage with FibroTest (threshold: 0.70), biopsy all those in whom cirrhosis is indicated **Intervention 4:** Triage with ELF (threshold: 0.431), biopsy all those in whom cirrhosis is indicated **Intervention 5:** TE (threshold: 11.5) for all patients, diagnosis on basis on Fibroscan alone **Intervention 6:** ELF (threshold: 0.431) for all patients, diagnosis on basis of ELF alone	prophylaxis treatment, variceal bleeding treatment, electroencephalo-grams, lifestyle advice costs		changes in 4 key parameters: liver biopsy diagnostic accuracy, liver biopsy type (percutaneous or transjugular), NILT diagnostic accuracy, disutility level of liver biopsy.
Data sources				
Health outcomes: diagnostic accuracy data obtained from multiple published sources and were not pooled. **Quality-of-life weights:** published literature and clinical assumptions. **Cost sources:** published literature figures and clinical input.				
Comments				
Source of funding: UK National Institute for Health Research **Limitations:** Most of the quality of life values are taken from hepatitis C patients. For some health states, QALYs are based on assumptions. QoL and test accuracy estimates do not come from a meta-analysis but from single studies, there is inconsistency between the trial data used in the model, for some tests small patient numbers lead to high uncertainty over the test accuracy, ELF did not report sensitivity and specificity for detecting only cirrhosis results not subjected to probabilistic sensitivity analysis. **Other**: 10 strategies compared of which 6 are relevant and reported here.				
Overall applicability[(a)]: partially applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life year; NILT: non- invasive liver test

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

I.3 Severity risk tools

None.

I.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Study	Cucchetti 2012[205]

Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov decision model **Approach to analysis:** • Cycle length NR (assumed to be 6 months) • Model states: compensated cirrhosis, decompensated cirrhosis, surveillance, HCC diagnosis, HCC treatment, survival, death **Perspective:** Italian NHS **Time horizon:** 10 years **Discounting:** Costs: 3%; Outcomes: NR	**Population:** Data obtained from 918 patients from 11 medical institutions **Cohort settings:** Start age: 67 years Male: NR **Intervention 1:** Annual surveillance including liver function tests, AFP and ultrasound, CT scan performed to confirm positive diagnoses **Intervention 2:** Semi-annual surveillance including liver function tests, AFP and ultrasound, CT scan performed to confirm positive diagnoses **Treatment options for both groups:** Hepatic resection, liver transplant, percutaneous ablation, TACE	**Total costs (mean per patient):** Compensated cirrhosis: Intervention 1: £14,514 Intervention 2: £16,893 Incremental (2−1): £2,379 (95% CI: NR; p=NR) Decompensated cirrhosis: Intervention 1: £20,606 Intervention 2: £23,068 Incremental (2−1): £2,462 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Euros (presented here as 2010 UK pounds[(a)]) **Cost components incorporated:** Costs of surveillance and treatment of HCC	**QALYs (mean per patient):** Compensated cirrhosis: Intervention 1: 5.09 Intervention 2: 5.20 Incremental (2−1): 0.11 (95% CI: NR; p=NR) Decompensated cirrhosis: Intervention 1: unclear[(a)] Intervention 2: unclear[(b)] Incremental (2−1): 0.06 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Compensated cirrhosis: £21,230 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Decompensated cirrhosis: £40,540 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** In patients with compensated cirrhosis, a 7% and above annual HCC incidence (base case 5%) or a 1.6 and above risk ratio for survival gain (base case 1.4) make semi-annual surveillance a cost-effective option at a threshold of £20,000 per QALY gained. In patients with decompensated cirrhosis no plausible changes in the annual HCC incidence or the risk ratio for survival gain reduced the ICER to below £20,000 per QALY gained.
Data sources				
Health outcomes: Data on transition probabilities and ranges regarding treatment modality and survival were extracted from the ITA.LI.CA database. **Quality-of-life weights:** Utility values were taken from four sources: one systematic review and three single studies. **Cost sources:** Unit costs were extracted from data on payments from the Italian NHS.				
Comments				
Source of funding: NR. **Limitations:** Differences in healthcare system may make results less applicable to UK; the study claimed to use a societal perspective in terms of				

costs; no discounting applied to health effects. Unclear source of resource use for health states, only deterministic sensitivity analyses were conducted, no probabilistic analysis.

Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abreviations: AFP: alpha-foetoprotein; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years; TACE: trans-arterial chemoembolisation

(a) Converted using 2010 purchasing power parities[654]

(b) Directly applicable/partially applicable/not applicable

(c) Minor limitations/potentially serious limitations/very serious limitations

(d) Reported as 19.66 and 29.51 QALMs for interventions 1 and 2 respectively but at least 1 of these was misreported as the incremental difference between them should have been 0.73 QALMs (0.06 QALYs)

Study	**Thompson Coon 2008[871]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov model and decision tree **Approach to analysis:** • One-month cycle length • Four aetiologies reported (ALD, HBV, HCV, mixed aetiologies)[(a)] • Health states include: no HCC, occult HCC (S,M,L), known HCC (S,M,L), transplant and resection in 4 discrete model sections: surveillance programme, transplant waiting list, curative treatment, palliative treatment **Perspective:** UK NHS	**Population:** People with compensated cirrhosis aged 70 years or less **Cohort settings:** <u>ALD:</u> Start age: 53.3 Male: 70.1% <u>Hepatitis C:</u> Start age: 54 Male: 58.1% **Intervention 1:** No surveillance **Intervention 2:** Annual AFP **Intervention 3:** Annual	**Total costs (mean per patient)[(b)]:** <u>ALD</u> Intervention 1: £26,100 Intervention 2: £27,400 Intervention 5: £28,200 Intervention 7: £29,200 Incremental 2−1: £1,300 Incremental 5−2: £800 Incremental 7−5: £1,000 <u>Hepatitis C</u> Intervention 1: £27,600 Intervention 2: £29,500 Intervention 5: £30,600 Intervention 7: £31,600 Incremental 2−1: £1,900 Incremental 5−2: £1,100 Incremental 7−5: £1,000	**QALYs (mean per patient)[(b)]:** <u>ALD disease</u> Intervention 1: 9.359 Intervention 2: 9.410 Intervention 5: 9.433 Intervention 7: 9.445 Incremental 2−1: 0.051 Incremental 5−2: 0.023 Incremental 7−5: 0.012 <u>Hepatitis C</u> Intervention 1: 8.087 Intervention 2: 8.172 Intervention 5: 8.212 Intervention 7: 8.232 Incremental 2−1: 0.085 Incremental 5−2: 0.040 Incremental 7−5: 0.020	**ICER:** <u>ALD</u> Intervention 2 versus 1: £25,490 Intervention 5 versus 2: £34,783 Intervention 7 versus 5: £83,333 <u>Hepatitis C</u> Intervention 2 versus 1: £22,353 Intervention 5 versus 2: £27,500 Intervention 7 versus 5: £50,000 Interventions 3, 4 and 6 are extendedly dominated in both cases (that is, a combination of other interventions are both cheaper and more effective) More details in Section 8.4.1 of the full guideline document. **Analysis of uncertainty (probabilistic sensitivity analysis):**

Time horizon: Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	ultrasound **Intervention 4:** Annual AFP+ultrasound **Intervention 5:** Semi-annual AFP **Intervention 6:** Semi-annual ultrasound **Intervention 7:** Semi-annual AFP+ultrasound	**Currency & cost year:** 2004 UK pounds **Cost components incorporated:** HCC surveillance (AFP, CT scan, ultrasound, MRI, outpatient appointment), HCC treatment (PEI, RFA, TACE, transplant), management costs for patients (with compensated cirrhosis, decompensated cirrhosis, HCC state, liver transplant, post-transplant, resection, post resection, palliative care, false positive, incidental diagnosis)		ALD: At the £20,000 threshold, 'no surveillance' is likely to be the only cost-effective strategy (80% likelihood). At around £30,000 interventions 2, 5 and 7 are all equally likely to be the preferable option Hepatitis C: At the £20,000 threshold, 'no surveillance' is likely to be considered cost-effective (75% likelihood). At £30,000 semi-annual AFP is preferred to no surveillance.
Data sources				
Health outcomes: Obtained through literature searches, focusing on large, recent studies of UK patients diagnosed with cirrhosis. **Quality-of-life weights:** Majority of utilities extracted from 2 studies that used EQ-5D; 3 utility values were based on authors' assumptions. **Cost sources:** Resource use data based on published sources and authors' assumptions, unit costs based on UK sources and authors' assumptions.				
Comments				
Source of funding: UK NHS HTA programme. **Limitations:** Some quality of life values are based on authors' assumptions. Only HCC-related costs are considered; not including costs related to other cirrhosis complications (such as ascites, hepatic encephalopathy).				
Overall applicability[(c)]: directly applicable **Overall quality[(d)]:** minor limitations				

Abbreviations: AFP: alpha-foetoprotein; ALD: alcohol-related liver disease; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], ICER: incremental cost-effectiveness ratio; negative values mean worse than death); L: large; M: medium; MRI: magnetic resonance imaging NR: not reported; pa: probabilistic analysis; PEI: percutaneous ethanol injection; QALYs: quality-adjusted life years; RFA: radiofrequency ablation; S: small; TACE: transarterial chemoembolisation;

(a) Only ALD, HCV patient groups relevant to this review question and therefore presented here

(b) Interventions 3, 4, 6 were not reported as they were dominated in the incremental analysis

(c) Directly applicable/partially applicable/not applicable

(d) Minor limitations/potentially serious limitations/very serious limitations

I.5 Surveillance for the detection of varices

None.

I.6 Prophylaxis of variceal haemorrhage

Study	Norberto 2007[639]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA **Study design:** RCT **Approach to analysis:** Cost data including treatment medications, endoscopic treatment, follow-up endoscopies and visits, complications, readmissions for bleeding were collected during the trial **Perspective:** Italian acute hospital **Follow-up**: 14.6 months **Treatment effect duration:** 14.6 months **Discounting:** Costs: NR; Outcomes: NR	**Population:** 62 subjects were selected from the patients referred for liver transplantation **Cohort settings:** Mean age: 52.6 years Male: NR **Intervention 1:** Beta-blocker therapy – propranolol 20 mg twice a day, increasing by 20 mg/day until a 25% reduction of the baseline heart rate was obtained **Intervention 2:** Band ligation procedure – oesophagogastroduodenoscopy prior to the procedure, 1 day hospital stay, subsequent sessions every 2 weeks until varices eradicated	**Total costs (mean per patient):** Intervention 1: £920 Intervention 2: £2,770 Incremental (2−1): £1,850 (95% CI: NR; p=0.001) **Currency & cost year:** US dollars. Study did not mention cost year; 2007 was used for conversion (costs presented as 2007 British pounds)[(a)] **Cost components incorporated:** Initial treatment (including medications and endoscopy); follow-up (including appointments and endoscopy); hospitalisation due to complications, bleeding or re-bleeding	**Variceal bleeding:** Intervention 1: 9.7% patients Intervention 2: 6.5% patients Incremental (2−1): −3.2% patients (95% CI: NR; p=1) **Bleeding-related mortality:** Intervention 1: 6.5% Intervention 2: 3.2% Incremental (2−1): −3.2% (95% CI: NR; p=1)	**ICER (BB versus BL):** £57,812 per bleeding episode averted (or per death averted) **Analysis of uncertainty:** No sensitivity analysis conducted. Difference in costs was significant (p<0.001), but none of the 7 health outcomes had significant differences
Data sources				
Health outcomes: From RCT. **Quality-of-life weights:** NR. **Cost sources:** Resource use was captured through the trial records. Costs were taken from Italian Health Ministry cost assignments.				
Comments				
Source of funding: NR **Limitations:** It does not report QALYs, health outcomes and costs are not discounted. In addition, the study had a relatively short time horizon, no sensitivity analysis was performed.				
Overall applicability[(b)]: partially applicable **Overall quality[(c)]:** potentially serious limitations				

Abbreviations: RCT: randomised control trial; BB: beta-blocker therapy; BL: band ligation therapy; CCA: cost-consequences analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported

(a) Converted using 2007 purchasing power parities[654]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

I.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

None.

I.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large volume paracentesis (LVP) for ascites

Study	**Gines 2002[335]**			
Study details	**Population & interventions**	**Costs[(a)]**	**Health outcomes[(c)]**	**Cost-effectiveness**
Economic analysis: CCA **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Multicentre RCT (US and Spain), collecting total resource use (procedures) and applying Spanish unit costs **Perspective:** Spain acute hospital **Follow-up:** 2 years **Treatment effect duration:** 2 years **Discounting:** Costs: NR; Outcomes: NR	**Population:** Patients with refractory ascites (not responding to low sodium diet) **Patient characteristics:** n=70 Mean age: TIPS group: 59 (SE: ±2); LVP group: 56 (SE: ±2) Male: TIPS group: 68%; LVP group: 74% **Intervention 1:** LVP with albumin (repeated as necessary) **Intervention 2:** TIPS (with repeated TIPS and additional LVP if necessary)	**Total costs (mean per patient):** Intervention 1: £1820 Intervention 2: £3924 Incremental (2−1): £2104 (95% CI NR; p=NR) **Currency & cost year:** 2000 US dollars (presented here as 2000 UK pounds)[(b)] **Cost components incorporated:** Initial procedure (LVP, TIPS, additional stents); follow-up (TIPS correction or repeat, LVP, angioplasty)	**Death:** RR: 1.11 (95% CI: NR; p=0.6); ARD: 57 more per 1000 **Ascites re-accumulation:** Patients with ≥1 episode: RR: 0.59 (95% CI: 0.40, 0.85; p=0.003); ARD: 343 fewer per 1000 Total episodes: RR: 0.18 (95% CI: NR, p: NR); ARD: 8029 fewer episodes per 1000 people **Renal failure:** Patients with ≥1 episode: RR: 0.53 (95% CI: 0.27, 1.02); ARD: 229 fewer per 1000 **Spontaneous bacterial peritonitis:** Patients with ≥1 episode: RR: 0.5 (95% CI: 0.10, 2.56); ARD: 57 fewer per 1000	**ICERs:** Death: LVP dominates TIPS Ascites re-accumulation: £6,137 per patient with ascites averted; £262 per re-accumulation averted Renal failure: £9205 per patient SBP: £36,820 per patient Hepatic encephalopathy: LVP dominates TIPS **Analysis of uncertainty:** No sensitivity analysis was undertaken. Differences in the outcomes of ascites re-accumulation and renal failure were significant (at a level of p=0.05); differences in death, SBP and hepatic encephalopathy were not (though significantly more

Data sources				
Comments				
Study	**Gines 2002**[335]			
			Hepatic encephalopathy: Patients with ≥1 episode: RR: 1.17 (0.95% CI: 0.87, 1.58); ARD: 114 more episodes per 1000 patients	patients in the TIPS group had severe hepatic encephalopathy).
Data sources				
Health outcomes: Within-trial. **Cost sources:** Resource use (number of procedures) was captured through the trial records. Unit costs from the Spanish hospital were applied to the combined resource use.				
Comments				
Source of funding: Supported by grants from the Fondo de Investigacion Sanitaria (Spain), Veterans Administration (USA) and National Institutes of Health (USA) **Limitations:** Study was partially conducted in US – differences in healthcare system may make results less applicable to UK; discounting does not appear to have been used; no quality-of-life data collected. Clinical outcomes and resource usage based on a single RCT; unit costs derived from a single Spanish hospital; costs associated with some complications were not included, unclear whether costs of hospitals stays were included; no sensitivity analysis conducted. **Other:** Total costs were reported as TIPS: £5,797; LVP: £4,023, apparently due to miscalculation in the paper. Costs given above were recalculated using figures given in Table 6 of the study.				
Overall applicability[(d)]: partially applicable **Overall quality**[(e)]: potentially serious limitations				

Abbreviations: ARD: absolute risk difference; CCA: cost-consequences analysis; LVP: large-volume paracentesis; N/A: not applicable; NR: not reported; RCT: randomised control trial; RR: risk ratio; SBP: spontaneous bacterial peritonitis; SE: standard error; TIPS: transjugular intrahepatic portosystemic shunt

(a) The study presented Spanish and US costs; the Spanish costs are presented here as more applicable to the UK

(b) Converted using 2000 purchasing power parities[654]

(c) See also the clinical evidence table for Gines 2002 in Appendix H

(d) Directly applicable/partially applicable/not applicable

(e) Minor limitations/potentially serious limitations/very serious limitations

I.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

None.

I.10 Volume replacers in hepatorenal syndrome

None.

I.11 Management of an episode of acute hepatic encephalopathy

None.

Appendix J: GRADE tables

J.1 Risk factors and risk assessment tools

Table 19: Prognostic factor: alcohol consumption

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
MEN <1 drink/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HR[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	7.76 (3.35–18.0)	Low
WOMEN <1 drink/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HR[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported separately for men and women	Not reported	1.32 (0.51–3.42)	Very Low

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
WOMEN 1-7 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HR[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported separately for men and women	Not reported	1.19 (0.54–2.62)	Very Low
MEN 8–21 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	2.34 (1.18–4.64)	Low
WOMEN 8–21 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	5.33 (2.63–10.8)	Low
MEN 22–35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	10.4 (5.4–20.03)	Low
WOMEN 22–35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	10.8 (4.28–27.1)	Low
MEN >35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	20.4 (10.8–38.53)	Low
WOMEN >35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	None	14.1 (4.45–44.6)	Low
'Model 1' (alcohol abuse definition 1) versus non abusers for predicting death or hospitalisation with cirrhosis (adjusted ORs[c])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	Not reported	OR=0.71 (0.17–2.92)	Very low
'Model 2' (alcohol abuse definition 2) versus non abusers for predicting death or hospitalisation with cirrhosis (adjusted ORs[c])										
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	Not reported	OR=1.55 (0.36–6.78)	Very low
0.1–1.4 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	1/11,304 (0.009%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	0.21 (0.27–1.59)	Low
1.5–4.9 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	5/18,406 (0.03%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	0.69 (0.24–1.98)	Low

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
5.0–14.9 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	10/17,783 (0.06%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	1.27 (0.54–3.01)	Low
15.0–29.9 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	9/8,106 (0.11%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	1.86 (0.76–4.59)	Low
≥30 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	None[b]	None	15/4,521 (0.33%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	2.55 (1.06–6.11)	Moderate
Association of alcohol intake with death from cirrhosis[e]										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Blackwelder 1980	Cohort study	Very serious	No inconsistency	No indirectness	CIs not reported	None	Total n=8008 Events per alcohol intake level (ml/day): 0: 6 events 1–10:1 event 11–30:2 events 31+: 7 events	Not reported	Standardised coefficient from multivariate analysis = 0.341 (t=3.11, estimated coefficient divided by its standard error, p<0.01)	Low
MEN current abstainers versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	7/350 (2.00%) versus 27/9165 (0.29%)		10.00 (4.32–23.15)	Low
WOMEN current abstainers versus 2–4 drinking days/week in women (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	2/370 (0.54%) versus 15/9481 (0.16%)		4.03 (0.91–17.85)	Very Low
MEN <1 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	14/2946 (0.48%) versus 27/9165 (0.29)		1.34 (0.67–2.68)	Very Low
WOMEN <1 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	16/7682 (0.21%) versus 15/9481 (0.16%)		1.45 (0.71–2.96)	Very Low
MEN 1 drinking day/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	8/2401 (0.33%) versus 27/9165 (0.29%)		1.30 (0.59–2.86)	Very Low
WOMEN 1 drinking day/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	5/4345 (0.12%) versus 15/9481 (0.16%)		0.81 (0.29–2.26)	Very Low

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
MEN 5–6 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	30/4495 (0.67%) versus 27/9165 (0.29%)		1.43 (0.84–2.43)	Very Low
WOMEN 5–6 drinking days/week versus 2–4 drinking days/week in women (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	17/3147 (0.54%) versus 15/9481 (0.16%)		2.30 (1.14–4.64)	Low
MEN 7 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	171/7276 (2.35%) versus 27/9165 (0.29%)		3.65 (2.39–5.57)	Low
WOMEN 7 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcoholic cirrhosis (adjusted HRs[f])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	30/3931 (0.76%) versus 15/9481 (0.16%)		1.73 (0.85–3.52)	Very Low

[a] *Methods multivariable analysis, key covariates included: age, smoking habits, number of years in school education, percentage wine of total alcohol intake*
[b] *If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded.*
[c] *Methods multivariable analysis, key covariates included: BMI, triglycerides, 2 definitions of alcohol abuse*
[d] *Methods multivariable analysis, key covariates included: age, smoking status, BMI, regular aspirin use, regular vigorous exercise, high plasma cholesterol level*
[e] *Methods multivariable analysis, key covariates included: age, cigarettes smoked per day, systolic blood pressure, serum cholesterol, relative weight*
[f] *Methods multivariable analysis, key covariates included: age, smoking, education, and waist circumference.*

Table 20: Prognostic factor: BMI

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
BMI <20 versus 20–24 for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	2.2(1.3–3.9)	Low
BMI >30 versus 20–24 for predicting death or discharge with alcoholic induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	2.2 (1.5–3.4)	Low
BMI overweight 25- <30 versus normal <25 (adjusted HRs[c])										
Ioannou 2003	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	35/3774 versus 34/5752	HR= 1.08 (0.6–1.9)	Low
BMI obese ≥30 versus normal <25 (adjusted HRs[c])										

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Ioannou 2003	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	20/1939 versus 34/5752	HR= 1.65 (0.9–3.1)	Low
'Model 1' (alcohol abuse definition 1) elevated BMI[f] versus non-obese for predicting death or hospitalisation with cirrhosis (adjusted ORs[d])										
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	OR=1.27 (1.09–1.48)	Low
'Model 2' (alcohol abuse definition 1) elevated BMI[f] versus non-obese for predicting death or hospitalisation with cirrhosis (adjusted ORs[d])										
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	OR=1.26 (1.08–1.47)	Low
BMI <22.5 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs[e])										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	414/237,619 (0.17%) versus 402/331,480 (0.12%)	(0.12%)	1.36 (1.23–1.50)	Low

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
BMI 25 to <27.5 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	343/266,795 (0.13%) versus 402/331,480 (0.12%)	(0.12%)	1.05 (0.94–1.17)	Very Low
BMI 27.5 to <30 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	236/173,498 (0.14%) versus 402/331,480 (0.12%)	(0.12%)	1.11 (0.97–1.26)	Very low
BMI 30 to <35 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	283/156,733 (0.18%) versus 402/331,480 (0.12%)	(0.12%)	1.49 (1.33–1.68)	Low
BMI ≥35 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	133/64,537 (0.21%) versus 402/331,480 (0.12%)	(0.12%)	1.77 (1.49–2.10)	Low

[a] *Methods multivariable analysis, key covariates included: age, smoking habits, number of years in school education, percentage wine of total alcohol intake*
[b] *If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded.*
[c] *Methods multivariable analysis, key covariates included: BMI, triglycerides, 2 definitions of alcohol abuse*
[d] *Methods multivariable analysis, key covariates included: age, alcohol consumption, sex, race, education, household income, geographic location in the United States. Adjusted HR reported in this review also adjusted for presence of diabetes.*
[e] *Methods multivariable analysis, key covariates included: age, region, socioeconomic status, alcohol consumption, smoking, physical activity*
[f] *Elevated BMI presumed to be >30 but unclear as reported in paper*

Table 21: Prognostic factor: diabetes

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
Diabetes versus no diabetes (in people with BMI 22.5 to <25) for predicting death or hospitalisation with cirrhosis (adjusted HRs[a])										

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
Liu 2010	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	4.29 (2.74 to 6.73)	LOW

[a] *Adjusted for age, region, socioeconomic status, physical activity, and alcohol consumption and smoking as appropriate*
[b] *If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded.*

J.2 Diagnostic tests

None

J.3 Severity risk tools

None

J.4 Surveillance for the detection of hepatocellular carcinoma (HCC)

Table 22: Clinical evidence profile: Surveillance versus no surveillance

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surveillance	No surveillance	Relative (95% CI)	Absolute		
Survival (follow-up median 9 months reported by one study, follow-up in other study not reported; assessed with: adjusted hazard ratio [HR >1 indicates an advantage to the surveillance group][1])												
2	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	–	–	Not pooled	Not pooled	VERY LOW	CRITICAL
Survival (follow-up 5-7 years from recruitment estimated; assessed with: adjusted odds ratio [OR >1 indicates an advantage to the surveillance group][4])												
1	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	–	–	OR 1.13 (0.64 to 2.01)	[5]	VERY LOW	CRITICAL
Detection of HCC at a very early stage (single nodule ≤2 cm) (assessed with: adjusted odds ratio [OR >1 indicates an advantage to the surveillance group][6])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 5.4 (2.35 to 12.4)	[5]	LOW	IMPORTANT
Detection of HCC at a non-advanced stage (single nodule ≤5 cm or 3 nodules each ≤3 cm without vascular and lymphonodal invasion and metastases) (assessed with: adjusted odds ratio [OR >1 indicates an advantage to the surveillance group][6])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 3.1 (1.85 to 5.2)	[5]	LOW	IMPORTANT
Detection of HCC at an advanced stage (according to Milano criteria) - surveillance versus incidental diagnosis (assessed with: adjusted odds ratio [OR <1 indicates an advantage to the surveillance group][7])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 0.29 (0.17 to 0.49)	[5]	LOW	IMPORTANT
Detection of HCC at an advanced stage (according to Milano criteria) - surveillance versus symptom diagnosis (assessed with: adjusted odds ratio [OR <1 indicates an advantage to the surveillance group][7])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 0.18 (0.09 to 0.37)	[5]	LOW	IMPORTANT

1 Study 1 adjusted for the following confounders: gender, Child-Pugh score, number of tumoral nodules (1/>1), AFP value, AFP (normal/increased), type of treatment (treated/not treated) and modality of diagnosis (follow-up/incidental). Study 2 adjusted for the following confounders: Child-Pugh status, tumour characteristics, treatment applied for HCC
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias (main reasons for risk of bias include no adjustment for lead time bias or no adjustment for all the key confounders)
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 Adjusted for factors found to be statistically significant in the univariate analysis: degree of liver function, screening, tumour size, and (curative versus palliative). In this analysis, screening was not statistically significant (not an independent predictor of survival)
5 Control group risk not reported for calculation of absolute effect
6 Adjustment for the confounding factors (age, gender, surveillance, aetiologies, AFP levels, cirrhosis)
7 Adjusted for centre of enrolment, age, sex, aetiology of cirrhosis, Child-Pugh class, AFP level and type of diagnosis

Table 23: Clinical evidence profile: Yearly versus 6-monthly surveillance

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yearly surveillance	6 monthly surveillance	Relative (95% CI)	Absolute		
Survival (assessed with: adjusted hazard ratio [HR >1 indicates an advantage to the 6-monthly surveillance group][1])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	–	–	HR 1.39 (1.06 to 1.82)	[3]	VERY LOW	CRITICAL
Detection of HCC beyond a very early stage (solitary nodule >2 cm or multinodular tumour with/without vascular invasion and/or metastases) (assessed with: adjusted odds ratio [OR >1 indicates an advantage to the 6-monthly surveillance group][4])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 5.99 (2.57 to 13.98)	[3]	LOW	IMPORTANT

1 Adjusted variables: age, platelet count, AFP, Child-Pugh class and oesophageal varices
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Control group risk not reported for calculation of absolute effect
4 Adjusted variables included those associated with a tumour beyond the very early stage: surveillance interval aetiology, ALT, AFP, and Child-Pugh class

Table 24: Clinical evidence profile: 3-monthly versus 6-monthly surveillance

Quality assessment	Number of patients	Effect	Quality	Importan

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 monthly surveillance**	**6 monthly surveillance**	**Relative (95% CI)**	**Absolute**		**ce**
Survival (follow-up median 47 months; assessed with: Hazard ratio [HR <1 indicates an advantage to the 3-monthly surveillance group])												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	–	14.2%2	HR 0.87 (0.64 to 1.19)	17 fewer per 1000 (from 49 fewer to 25 more)3	MODERATE	CRITICAL
HCC occurrence (follow-up median 47 months)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	53/640 (8.3%)	11%	RR 0.75 (0.54 to 1.06)	27 fewer per 1000 (from 51 fewer to 7 more)	MODERATE	IMPORTANT
Diameter of the largest HCC nodule ≤30 mm (follow-up median 47 months; assessed with: positive outcome, RR<1 indicates an advantage to the 6-monthly group)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	42/640 (6.6%)	7.7%	RR 0.85 (0.57 to 1.27)	12 fewer per 1000 (from 33 fewer to 21 more)	LOW	
Diameter of the largest HCC nodule >30 mm (follow-up median 47 months; assessed with: negative outcome, RR<1 indicates an advantage to the 3-monthly group)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	11/640 (1.7%)	3.3%	RR 0.52 (0.25 to 1.07)	16 fewer per 1000 (from 25 fewer to 2 more)	MODERATE	IMPORTANT
Number of lesions - Uninodular (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious4	No serious inconsistency	No serious indirectness	Serious[1]	None	31/640 (4.8%)	6.4%	RR 0.75 (0.48 to 1.19)	16 fewer per 1000 (from 33 fewer to 12 more)	LOW	IMPORTANT
Number of lesions - 2 or 3 nodules (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious4	No serious inconsistency	No serious indirectness	Very serious[4]	None	15/640 (2.3%)	1.9%	RR 1.25 (0.59 to 2.64)	5 more per 1000 (from 8 fewer to 31 more)	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 monthly surveillance	6 monthly surveillance	Relative (95% CI)	Absolute	Quality	Importance
Survival (follow-up median 47 months; assessed with: Hazard ratio [HR <1 indicates an advantage to the 3-monthly surveillance group])												
Number of lesions - >3 nodules (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious4	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/640 (0.63%)	1.1%	RR 0.57 (0.17 to 1.94)	5 fewer per 1000 (from 9 fewer to 10 more)	VERY LOW	IMPORTANT
Number of lesions - Infiltrative (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious4	No serious inconsistency	No serious indirectness	Serious[1]	None	3/640 (0.47%)	1.6%	RR 0.3 (0.08 to 1.08)	11 fewer per 1000 (from 15 fewer to 1 more)	LOW	IMPORTANT
HCC stage (within Milan criteria: one nodule ≤50mm or 2 or 3 nodules ≤30 mm) (follow-up median 47 months; assessed with: positive outcome, RR<1 indicates an advantage to the 6-monthly group)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	42/640 (6.6%)	7.8%	RR 0.84 (0.56 to 1.24)	12 fewer per 1000 (from 34 fewer to 19 more)	MODERATE	IMPORTANT
HCC stage (beyond Milan criteria: one nodule ≤50mm or 2 or 3 nodules ≤30 mm) (follow-up median 47 months; assessed with: negative outcome, RR<1 indicates an advantage to the 3-monthly group)												
1	Randomised trials	Serious4	No serious inconsistency	No serious indirectness	Serious[1]	None	11/640 (1.7%)	3.1%	RR 0.55 (0.26 to 1.13)	14 fewer per 1000 (from 23 fewer to 4 more)	LOW	IMPORTANT
Liver transplant (follow-up median 47 months)												
1	Randomised trials	Serious4	No serious inconsistency	No serious indirectness	Very serious[4]	None	17/640 (2.7%)	2%	RR 1.3 (0.64 to 2.66)	6 more per 1000 (from 7 fewer to 33 more)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Survival at 60 months in the control group was 85.8%

3 Based on survival rate of control group at 60 months
4 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

J.5 Surveillance for the detection of varices

None

J.6 Prophylaxis of variceal haemorrhage

Table 25: Clinical evidence profile: non-selective beta-blockers versus placebo or no intervention: medium or large varices

Quality assessment							Number of patients		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Large non-selective beta-blockers versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
2	Randomised trials	No serious risk of bias	Serious1	No serious indirectness	Serious[2]	None	-	33.8 %3	HR 1.2 (0.78 to 1.84)	52 more per 1000 (from 63 fewer to 194 more)	LOW	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Variceal bleeding (follow-up median 24 months4)												
3	Randomised trials	No serious	Serious5	Serious6	Very serious[2]	None	15/136 (11%)	36.4 %	RR 0.28 (0.06 to	262 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Large non-selective beta-blockers versus placebo	Control	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias							1.3)	342 fewer to 109 more)		
Upper gastrointestinal bleeding (follow-up median 24 months[4])												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	40/227 (17.6%)	35.2 %	RR 0.55 (0.39 to 0.78)	158 fewer per 1000 (from 77 fewer to 215 fewer)	MODERATE	IMPORTANT
Bleeding-related mortality (follow-up median 21 months[4])												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	20/199 (10.1%)	14.9 %	RR 0.67 (0.39 to 1.13)	49 fewer per 1000 (from 91 fewer to 19 more)	MODERATE	IMPORTANT

[1] I squared value 36%. Heterogeneity by visual inspection of the forest plots (different directions of effect). Cannot perform predefined subgroups. Random effects model used.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Calculated from the median control group rate at the end of study
[4] Median of the mean follow-up times of the individual studies where reported
[5] Statistical heterogeneity. Cannot investigate predefined subgroups. Random effects model used.
[6] Reported as a dichotomous outcome not time-to-event

Table 26: Clinical evidence profile: non-selective beta-blockers versus placebo or no intervention: small varices

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Small non-selective beta-blockers versus placebo	Control	Relative (95% CI)	Absolute	Quality	Importance
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Small non-selective beta-blockers versus placebo	Control	Relative (95% CI)	Absolute		
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Mortality (follow-up mean 25 months)												
1	Randomised trials	Serious [1]	No serious inconsistency	Serious [2]	Very serious [3]	None	3/77 (3.9%)	2.7%	RR 1.42 (0.24 to 8.27)	11 more per 1000 (from 21 fewer to 196 more)	VERY LOW	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Variceal bleeding (follow-up median 24 months [4])												
3	Randomised trials	Serious [1]	Serious [5]	Serious [2]	Very serious [3]	None	6/118 (5.1%)	6.9%	RR 1.24 (0.31 to 5)	17 more per 1000 (from 48 fewer to 276 more)	VERY LOW	CRITICAL
Upper gastrointestinal bleeding (follow-up median 24.5 months [4])												
2	Randomised trials	Serious [1]	Serious [6]	No serious indirectness	Very serious [3]	none	4/92 (4.3%)	9.5%	RR 0.9 (0.04 to 20.15)	10 fewer per 1000 (from 91 fewer to 1000 more)	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Reported as a dichotomous outcome not time-to-event
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[4] Median of the mean follow-up times of the individual studies where reported
[5] I squared value 13%. Heterogeneity by visual inspection of the forest plots (different directions of effect). Cannot perform predefined subgroups. Random effects model used.
[6] Statistical heterogeneity. Cannot investigate predefined subgroups. Random effects model used.

Table 27: Clinical evidence profile: band ligation versus no intervention: medium or large varices

Quality assessment							Number of patients		Effect		Quality	Importan

													ce
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Large varices: banding ligation versus no intervention**	**Control**	**Relative (95% CI)**	**Absolute**			
Quality of life													
0	No evidence available	-	-	-	-	None	-	-	-	-	-		CRITICAL
Survival													
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	47.2%2	HR 0.5 (0.33 to 0.75)	199 fewer per 1000 (from 91 fewer to 282 fewer)	MODERATE		CRITICAL
Mortality (follow-up 14-25 months)													
2	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	Serious[4]	None	16/87 (18.4%)	31.1%	RR 0.57 (0.33 to 0.97)	134 fewer per 1000 (from 9 fewer to 208 fewer)	VERY LOW		CRITICAL
Free from variceal bleeding													
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	40.8%2	HR 0.39 (0.25 to 0.63)	223 fewer per 1000 (from 127 fewer to 285 fewer)	MODERATE		CRITICAL
Variceal bleeding (follow-up 14-25 months)													
2	Randomised trials	Serious[1]	Serious[5]	Serious[3]	Serious[4]	None	18/87 (20.7%)	46.7%	RR 0.4 (0.17 to 0.93)	280 fewer per 1000 (from 33 fewer to 388 fewer)	VERY LOW		CRITICAL
Upper gastrointestinal bleeding (follow-up median 20.6 months6)													
5	Randomise	Serious	Serious[5]	No serious	Serious[4]	None	48/224	39.4	RR 0.49	201 fewer	VERY		IMPORTA

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Large varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute		
	d trials	[1]		indirectness			(21.4%)	%	(0.31 to 0.76)	per 1000 (from 95 fewer to 272 fewer)	LOW	NT
Bleeding-related mortality (follow-up 25 months6)												
3	Randomised trials	Very serious [1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	10/151 (6.6%)	15.2 %	RR 0.36 (0.18 to 0.71)	97 fewer per 1000 (from 44 fewer to 125 fewer)	LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Calculated from the median control group rate at the end of study
[3] Reported as a dichotomous outcome not time-to-event
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[5] Statistical heterogeneity. Cannot investigate predefined subgroups. Random effects model used.
[6] Median of the mean follow-up times of the individual studies where reported

Table 28: Clinical evidence profile: band ligation versus no intervention: small varices

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Small varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Small varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute		
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Upper gastrointestinal bleeding (follow-up mean 20.6 months)												
1	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/14 (7.1%)	0%	See comment	70 more per 1000 (from 100 fewer to 240 more)[3]	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Manual calculation of absolute risk difference due to zero events in the control arm

Table 29: Clinical evidence profile: band ligation versus non-selective beta-blockers: medium or large varices

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Large varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Large varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute	Quality	Importance
7	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	-	33.3 %2	HR 1.03 (0.8 to 1.34)	8 more per 1000 (from 56 fewer to 86 more)	MODERATE	CRITICAL
Mortality (follow-up median 14.5 months[3])												
12	Randomised trials	Serious[4]	No serious inconsistency	Serious5	Serious[1]	None	56/381 (14.7%)	14%	RR 0.83 (0.61 to 1.13)	24 fewer per 1000 (from 55 fewer to 18 more)	VERY LOW	CRITICAL
Free from variceal bleeding												
7	Randomised trials	No serious risk of bias	Serious6	No serious indirectness	Very serious[1]	None	-	27.3 %2	HR 0.68 (0.35 to 1.31)	78 fewer per 1000 (from 167 fewer to 68 more)	VERY LOW	CRITICAL
Variceal bleeding (follow-up median 16.5 months3)												
10	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[5]	No serious imprecision	None	21/276 (7.6%)	14.5 %	RR 0.44 (0.27 to 0.71)	81 fewer per 1000 (from 42 fewer to 106 fewer)	MODERATE	CRITICAL
Upper gastrointestinal bleeding (follow-up median 19 months3)												
20	Randomised trials	No serious risk of bias	Serious7	No serious indirectness	Serious[1]	None	102/785 (13%)	15.9 %	RR 0.71 (0.54 to 0.92)	46 fewer per 1000 (from 13 fewer to 73 fewer)	LOW	IMPORTANT
Bleeding-related mortality (follow-up median 19 months[3])												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Large varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute		
15	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	26/621 (4.2%)	6.5%	RR 0.67 (0.42 to 1.08)	21 fewer per 1000 (from 38 fewer to 5 more)	MODERATE	IMPORTANT
Hospitalisation (follow-up 0.5-18 months)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious1	None	5/45 (11.1%)	27.3 %	RR 0.41 (0.16 to 1.06)	161 fewer per 1000 (from 229 fewer to 16 more)	LOW	IMPORTANT
Adverse events – lethargy												
2	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/86 (0%)	28.8 %	OR 0.09 (0.04 to 0.22)	253 fewer per 1000 (from 206 fewer to 272 fewer)	MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[2] Calculated from the median control group rate at the end of study
[3] Median of the mean follow-up times of the individual studies where reported
[4] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[5] Reported as a dichotomous outcome not time-to-event
[6] Statistical heterogeneity and heterogeneity from visual inspection of forest plot. Cannot investigate predefined subgroups. Random effects model used.
[7] I squared value 13%. Heterogeneity by visual inspection of the forest plots (CIs do not overlap).Predefined subgroup analyses performed but no statistical difference between subgroups. Random effects model used.

Table 30: Clinical evidence profile: band ligation versus non-selective beta-blockers: small varices

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Small varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

J.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Table 31: Clinical evidence profile: IV ceftriaxone 2 g versus oral ciprofloxacin 500 mg twice daily

Quality assessment							No of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ceftriaxone 2 g	Oral ciprofloxacin 500 mg twice daily	Relative (95% CI)	Absolute	Quality	Importance
Bacterial infections (follow-up mean 7 days)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2/66 (3%)	20.6%	RR 0.13 (0.03 to 0.56)	179 fewer per 1000 (from 91 fewer to 200 fewer)	MODERATE	CRITICAL
Health-related quality of life												

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ceftriaxone 2 g	Oral ciprofloxacin 500 mg twice daily	Relative (95% CI)	Absolute		
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

Table 32: Clinical evidence profile: IV ceftriaxone 1 g versus oral norfloxacin 400 mg twice daily

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ceftriaxone 1 g	Oral norfloxacin 400 mg twice daily	Relative (95% CI)	Absolute		
Bacterial infections (follow-up mean 10 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	6/54 (11.1%)	26.3%	RR 0.42 (0.18 to 1.01)	153 fewer per 1000 (from 216 fewer to 3 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality (follow-up mean 10 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	8/54 (14.8%)	10.5%	RR 1.41 (0.52 to 3.79)	43 more per 1000 (from 50 fewer to 293 more)	VERY LOW	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1/2 increments because the majority of the evidence had indirect outcomes*
[3] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 33: Clinical evidence profile: oral norfloxacin 800 mg versus oral ofloxacin 400 mg

Quality assessment							No of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral norfloxacin 800 mg	Oral ofloxacin 400 mg	Relative (95% CI)	Absolute	Quality	Importance
Bacterial infections (follow-up mean 10 days)												
1	Randomised trials	Very serious [1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	26/183 (14.2%)	14.8%	RR 0.96 (0.58 to 1.58)	6 fewer per 1000 (from 62 fewer to 86 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 34: Clinical evidence profile: oral norfloxacin 800 mg + IV ceftriaxone (combination) versus oral norfloxacin 800 mg (monotherapy)

Quality assessment							No of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral norfloxacin 800 mg + IV ceftriaxone	Oral norfloxacin 800 mg	Relative (95% CI)	Absolute	Quality	Importance
Bacterial infections (follow-up mean 3 weeks)												

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral norfloxacin 800 mg + IV ceftriaxone	Oral norfloxacin 800 mg	Relative (95% CI)	Absolute		
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	3/24 (12.5%)	18.2%	RR 0.69 (0.17 to 2.73)	56 fewer per 1000 (from 151 fewer to 315 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality (follow-up mean 3 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	1/24 (4.2%)	9.1%	RR 0.46 (0.04 to 4.71)	49 fewer per 1000 (from 87 fewer to 338 more)	VERY LOW	CRITICAL
Length of hospital stay (days, follow-up mean 3 weeks; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	24	22	-	MD 0 higher (4.07 lower to 4.07 higher)	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1/2 increment(s) because the majority of the evidence had indirect outcomes
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

J.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 35: Clinical evidence profile: TIPS versus LVP

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TIPS versus LVP – ascites re-accumulation	Control	Relative (95% CI)	Absolute		
Ascites re-accumulation (follow-up 12 months)												
4	Randomised trials	No serious risk of bias	Serious[4]	No serious indirectness	Serious[2]	None	75/150 (50%)	88.4 %	RR 0.57 (0.40 to 0.82)	382 fewer per 1000 (from 160 fewer to 533 fewer)	LOW	CRITICAL
Quality of life – physical score (follow-up 12 months; measured with: SF-36 score; scale not reported, better indicated by lower values)												
1	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[2]	None	52	57	-	MD 3.36 lower (7.53 lower to 0.81 higher)	LOW	CRITICAL
Quality of life – mental score (follow-up 12 months; measured with: SF-36 score; scale not reported, better indicated by lower values)												
1	Randomised trials	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[2]	None	52	57	-	MD 2.13 lower (5.45 lower to 1.19 higher)	VERY LOW	CRITICAL
Transplant-free survival												
5	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	Serious[2]	None	-	65.3 %3	HR 0.58 (0.35 to 0.96)	194 fewer per 1000 (from 15 fewer to 343 fewer)	LOW	CRITICAL
Spontaneous bacterial peritonitis												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/87 (6.9%)	7.5%	RR 1.05 (0.35 to 3.1)	4 more per 1000 (from 49 fewer to 157 more)	LOW	IMPORTANT
Acute renal failure												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	12/87 (13.8%)	26%	RR 0.64 (0.35 to 1.18)	94 fewer per 1000 (from 169 fewer to 47 more)	MODERATE	IMPORTANT
Hepatic encephalopathy												
5	Randomised trials	No serious risk of	Serious6	No serious indirectness	Serious[2]	None	104/179 (58.1%)	34.9 %	RR 1.64 (1.14 to 2.36)	227 more per 1000 (from 50 more to 483	LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TIPS versus LVP – ascites re-accumulation	Control	Relative (95% CI)	Absolute	Quality	Importance
		bias								more)		

[1] Downgraded by 1 increment because of heterogeneity, I^2=74%, p=0.002, unexplained by subgroup analysis
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Calculated from the median control group rate at the end of study
[4] Downgraded by 1 increment because heterogeneity, I^2=79%, p=0.003, unexplained by subgroup analysis.
[5] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[6] Downgraded by 1 increment because of heterogeneity, I^2=58%, p=0.05, unexplained by subgroup analysis

J.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 36: Clinical evidence profile: antibiotic prophylaxis versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis versus placebo or no treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
Spontaneous bacterial peritonitis (follow-up median 6 months)												
6	Randomised trials	Serious1	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/242 (2.9%)	18.7%	RR 0.22 (0.11 to 0.46)	146 fewer per 1000 (from 101 fewer to 166 fewer)	MODERATE	CRITICAL
All-cause mortality (time-to-event) (follow-up 6 to 12 months)												
3	Randomis	No serious	No serious inconsistenc	No serious indirectnes	No serious	None	-	28%	HR 0.40 (0.22 to		HIGH	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis versus placebo or no treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
	ed trials	risk of bias	y	s	imprecision				0.73)	157 fewer per 1000 (from 67 fewer to 210 fewer)		
All-cause mortality (dichotomous) - mortality at ~1 month follow-up (follow-up mean 25.5 days)												
1	Randomised trials	Serious[1]	No serious inconsistency	Very serious[4,5]	Very serious[2]	None	2/29 (6.9%)	16.7%	RR 0.39 (0.08 to 1.85)	102 fewer per 1000 (from 154 fewer to 142 more)	VERY LOW	CRITICAL
All-cause mortality (dichotomous) - mortality at ~4 months' follow-up (follow-up mean 132 days)												
1	Randomised trials	Very serious 1	No serious inconsistency	Serious[4]	Very serious[2]	None	8/53 (15.1%)	18.5%	RR 0.82 (0.35 to 1.91)	33 fewer per 1000 (from 120 fewer to 168 more)	VERY LOW	CRITICAL
All-cause mortality (dichotomous) - mortality at 6 months' follow-up (follow-up mean 6 months)												
1	Randomised trials	Very serious [1]	No serious inconsistency	Very serious[4,5]	Very serious[2]	None	4/26 (15.4%)	22.2%	RR 0.76 (0.24 to 2.43)	53 fewer per 1000 (from 169 fewer to 317 more)	VERY LOW	CRITICAL
Adverse event: renal failure (follow-up mean 12 months)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	14/85 (16.5%)	33.2%	RR 0.54 (0.31 to 0.96)	153 fewer per 1000 (from 13	LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis versus placebo or no treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 229 fewer)		
Adverse event: liver failure (follow-up mean 8.5 months)												
4	Randomised trials	Very serious [1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	12/164 (7.3%)	3.5%	RR 1.43 (0.54 to 3.79)	15 more per 1000 (from 16 fewer to 98 more)	VERY LOW	IMPORTANT
Length of hospital stay (follow-up mean 3.4 months; better indicated by lower values)												
2	Randomised trials	Serious[1]	Serious6	No serious indirectness	Serious[2]	None	60	63	-	MD 3.12 lower (14.15 lower to 7.92 higher)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[3] *Calculated from median control group rate at 6 to 12 months*
[4] *The majority of the evidence had indirect outcomes*
[5] *The majority of the evidence had an indirect population*

[6] Downgraded by 1/2 increments because the confidence intervals across studies show minimal or no overlap and heterogeneity, I^2=50%, p=0.04, unexplained by subgroup analysis.

J.10 Volume replacers in hepatorenal syndrome

None

J.11 Management of an episode of acute hepatic encephalopathy

J.11.1 Non-absorbable disaccharides versus single therapy

Table 37: Clinical evidence summary: non-absorbable disaccharides versus neomycin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-absorb disaccharides	Neomycin	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/8 (12.5%)	10%	RR 1.25 (0.09 to 17.02)	25 more per 1000 (from 91 fewer to 1000 more)	VERY LOW	CRITICAL
Clinical-biochemical improvement (improvement of 1 grade in mental state (Conn's grading 0-4), a reduction of 30s in time taken to perform the NCT and ammonia reduction of 50ug%)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/8 (87.5%)	70%	RR 1.25 (0.77 to 2.03)	175 more per 1000 (from 161 fewer to 721 more)	LOW	CRITICAL
Side effects												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/8 (0%)	0%	not pooled	not pooled	MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 38: Clinical evidence summary: non-absorbable disaccharides versus Rifaximin

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-absorbable disaccharides	Rifaximin	Relative (95% CI)	Absolute		
Mortality (considered unrelated to medication; at 28 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/53 (3.8%)	2%	RR 1.89 (0.18 to 20.17)	18 more per 1000 (from 16 fewer to 383 more)	LOW	CRITICAL
Unchanged/failure (hepatic encephalopathy clinical syndrome not improved and blood ammonia levels not decreased / increase in blood ammonia, increase in PSE index and/or a shift to a higher stage of hepatic encephalopathy)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/53 (18.9%)	18%	RR 1.05 (0.46 to 2.36)	9 more per 1000 (from 97 fewer to 245 more)	LOW	CRITICAL
Improvement in hepatic encephalopathy grade (at 7 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	16/22 (72.7%)	81.3%	RR 0.9 (0.66 to 1.21)	81 fewer per 1000 (from 276 fewer to 171 more)	LOW	CRITICAL
Improvement in hepatic encephalopathy index (taking into account hepatic encephalopathy grade, NCT, blood ammonia and severity of flapping tremor; at 7 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	21/22 (95.5%)	84.4%	RR 1.13 (0.95 to 1.35)	110 more per 1000 (from 42 fewer to 295 more)	LOW	CRITICAL
Adverse events												
2	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1]	none	3/75 (4%)	4.6%	RR 0.8 (0.19 to 3.39)	9 fewer per 1000 (from 37 fewer to 110 more)	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] The point estimate varies widely across studies, unexplained by subgroup analysis.

Table 39: Clinical evidence summary: non-absorbable disaccharides versus BCAA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-absorb disaccharides	BCAA	Relative (95% CI)	Absolute		
Mortality (up to 10 days after mental recovery)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/17 (29.4%)	23.5%	RR 1.25 (0.4 to 3.87)	59 more per 1000 (from 141 fewer to 674 more)	LOW	CRITICAL
Time of arousal (hours, Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17	17	-	MD 3.9 higher (11.43 lower to 19.23 higher)	MODERATE	IMPORTANT
Complete mental recovery (study 1 defines as consciousness regained and returned to grade 0 hepatic encephalopathy; study 2 defines as come out of coma by day 7)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/33 (54.5%)	82.2%	RR 0.67 (0.47 to 0.94)	271 fewer per 1000 (from 49 fewer to 436 fewer)	MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 40: Clinical evidence summary: non-absorbable disaccharides versus PEG

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-absorb disaccharides	PEG 3350	Relative (95% CI)	Absolute		
Mortality (at 24 hours)												
1	randomise	no	no serious	no serious	very	none	2/25	4%	RR 2 (0.19	40 more per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-absorb disaccharides	PEG 3350	Relative (95% CI)	Absolute		
	d trials	serious risk of bias	inconsistency	indirectness	serious[1]		(8%)		to 20.67)	(from 32 fewer to 787 more)		
hepatic encephalopathy resolution (defined as an improvement to grade 0, or two days at grade 1 after an initial improvement of at least 1 grade)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	-	0%	HR 0.57 (0.31 to 1.05)	-3	LOW	CRITICAL
Improvement of 1 or more in hepatic encephalopathy grade (hepatic encephalopathySA score; at 24 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	13/25 (52%)	91.3 %	RR 0.57 (0.38 to 0.85)	393 fewer per 1000 (from 137 fewer to 566 fewer)	LOW	CRITICAL
Length of hospital stay (days) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25	25	-	MD 4 higher (0.85 lower to 8.85 higher)	LOW	IMPORTANT
Adverse Events (at 24 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/25 (20%)	12%	RR 1.67 (0.45 to 6.24)	80 more per 1000 (from 66 fewer to 629 more)	LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] [c] Not possible to calculate control risk.

Table 41: Clinical evidence summary: non-absorbable disaccharides versus probiotics

Quality assessment	No of patients	Effect	Qualit	Importan

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Non-absorb disaccharides**	**Pro-biotics**	**Relative (95% CI)**	**Absolute**	**y**	**ce**
Improvement in hepatic encephalopathy symptoms (at day 10)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/19 (73.7%)	79%	RR 0.93 (0.65 to 1.33)	55 fewer per 1000 (from 277 fewer to 261 more)	VERY LOW	CRITICAL
Adverse events (at 20 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/15 (53.3%)	6.3%	RR 8.53 (1.21 to 60.33)	474 more per 1000 (from 13 more to 1000 more)	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 42: Clinical evidence summary: non-absorbable disaccharides versus sodium benzoate

Quality assessment							**No of patients**		**Effect**			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Non-absorb disaccharides**	**Sodium benzoate**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/36 (19.4%)	21.1%	RR 0.92 (0.37 to 2.29)	17 fewer per 1000 (from 133 fewer to 272 more)	LOW	CRITICAL
Complete response (recovery to normal mental status with no evidence of asterixis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	29/36 (80.6%)	79%	RR 1.02 (0.81 to 1.28)	16 more per 1000 (from 150 fewer to 221 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Non-absorb disaccharides**	**Sodium benzoate**	**Relative (95% CI)**	**Absolute**		
Continued in grade 1+ mental status despite therapy for 21 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/36 (2.8%)	7.9%	RR 0.35 (0.04 to 3.23)	51 fewer per 1000 (from 76 fewer to 176 more)	LOW	CRITICAL
Complications during treatment												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/36 (83.3%)	92.1%	RR 0.9 (0.76 to 1.08)	92 fewer per 1000 (from 221 fewer to 74 more)	HIGH	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

J.11.2 Combination therapy (1 intervention + non-absorbable disaccharides) versus non-absorbable disaccharides

Table 43: Clinical evidence summary: Rifaximin + non-absorbable disaccharides versus non-absorbable disaccharides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rifaximin+non-absorb disaccharides**	**Non-absorb disaccharides**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15/63 (23.8%)	49.1%	RR 0.48 (0.29 to 0.81)	255 fewer per 1000 (from 93 fewer to 349 fewer)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rifaximin+non-absorb disaccharides	Non-absorb disaccharides	Relative (95% CI)	Absolute		
Complete reversal of hepatic encephalopathy (according to West Haven criteria; at 10 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48/63 (76.2%)	50.9%	RR 1.5 (1.12 to 2)	255 more per 1000 (from 61 more to 509 more)	MODERATE	CRITICAL
Length of Hospital Stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63	57	-	MD 2.4 lower (3.86 to 0.94 lower)	MODERATE	IMPORTANT
Side effects related to study medications												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/63 (19%)	17.5%	RR 1.09 (0.51 to 2.32)	16 more per 1000 (from 86 fewer to 231 more)	LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 44: Clinical evidence summary: BCAA + non-absorbable disaccharides versus non-absorbable disaccharides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCAA+non absorb disaccharides	Non absorb disaccharides	Relative (95% CI)	Absolute		
Mortality (at 16 days)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[1]	none	11/32 (34.4%)	30.3%	RR 1.13 (0.56 to	39 more per 1000 (from 133	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCAA+non absorb disaccharides	Non absorb disaccharides	Relative (95% CI)	Absolute		
		risk of bias							2.3)	fewer to 394 more)		
Wake up (study 1 defines as woke up to hepatic encephalopathy grade 0 or I by Fogarty classification at 16 days; study 2 defines as came out of coma by day 7))												
2	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[1]	none	33/48 (68.8%)	57%	RR 1.24 (0.91 to 1.69)	137 more per 1000 (from 51 fewer to 393 more)	VERY LOW	CRITICAL
Treatment failures other than death (hepatic encephalopathy deeper than grade I (Fogarty classification) despite other improvements; at 16 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/32 (12.5%)	18.2%	RR 0.69 (0.21 to 2.21)	56 fewer per 1000 (from 144 fewer to 220 more)	LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis.

Table 45: Clinical evidence summary: Flumazenil + non-absorbable disaccharides versus non-absorbable disaccharides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flumazenil	Placebo (concurrent lactulose)	Relative (95% CI)	Absolute		
Mortality (during the observation period, 3hr treatment + 5hr observation)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	4.8%	OR 0.1 (0 to 5.09)	43 fewer per 1000 (from 48 fewer to 156	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flumazenil	Placebo (concurrent lactulose)	Relative (95% CI)	Absolute		
										more)		
Clinically relevant response (improvement of at least 2 points in PSE score, PSE score on a 0-16 scale, at 8 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/28 (25%)	0%	Peto OR 7.39 (1.49 to 36.61)	250 more per 1000 (from 80 more to 420 more)	LOW	CRITICAL
Adverse events (at 8 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/28 (14.3%)	0%	Peto OR 6.47 (0.84 to 49.99)	140 more per 1000 (from 0 to 290 more)	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

J.11.3 Combination therapy (2 interventions + non-absorbable disaccharides) versus combination therapy (1 intervention + non-absorbable disaccharides)

Table 46: Clinical evidence summary: Flumazenil + BCAA + non-absorbable disaccharides versus BCAA + non-absorbable disaccharides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flumazenil	Placebo (concurrent lactulose and BCAA)	Relative (95% CI)	Absolute		
Mortality (at 24 hours)												
1	randomis	very	no serious	no serious	very	none	6/28	19.2%	RR 1.11	21 more per	VERY	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flumazenil	Placebo (concurrent lactulose and BCAA)	Relative (95% CI)	Absolute		
	ed trials	serious[1]	inconsistency	indirectness	serious[2]		(21.4%)		(0.39 to 3.22)	1000 (from 117 fewer to 426 more)	LOW	
Improvement in neurological status (Increase in Glasgow coma score by 3 points; at 24 hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/28 (78.6%)	53.9%	RR 1.46 (0.97 to 2.19)	248 more per 1000 (from 16 fewer to 641 more)	VERY LOW	CRITICAL
Side Effects (at 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	0%	not pooled	not pooled	LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 47: Clinical evidence summary: LOLA + metronidazole + non-absorbable disaccharides versus metronidazole + non-absorbable disaccharides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LOLA (lactulose+metronidazole)	Placebo (lactulose+metronidazole)	Relative (95% CI)	Absolute		
Mortality (inpatient stay)												
2	randomised trials	no serious	no serious inconsistenc	serious[1]	very serious[2]	none	6/100 (6%)	10.8%	RR 0.55	49 fewer per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LOLA (lactulose+metronidazole)**	**Placebo (lactulose+metronidazole)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
		s risk of bias	y						(0.21 to 1.42)	(from 85 fewer to 45 more)		
Complete improvement defined as improvement of 2 grades from baseline (day 3)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	45/54 (83.3%)	46.3%	RR 1.8 (1.32 to 2.46)	370 more per 1000 (from 148 more to 676 more)	HIGH	CRITICAL
Achieved hepatic encephalopathy grade 0 (at 5 days)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	37/40 (92.5%)	77.5%	RR 1.19 (0.99 to 1.44)	147 more per 1000 (from 8 fewer to 341 more)	VERY LOW	CRITICAL
Adverse events												
2	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/100 (1%)	0%	Peto OR 7.39 (0.15 to 372.38)	10 more per 1000 (from 20 fewer to 40 more)	VERY LOW	IMPORTANT

[1] The majority of the evidence had indirect outcomes
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

J.11.4 Single therapy versus placebo

Table 48: Clinical evidence summary: non-absorbable disaccharides versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-absorbable disaccharides	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/10 (0%)	60%	OR 0.03 (0 to 0.4)	557 fewer per 1000 (from 225 fewer to 600 fewer)	LOW	CRITICAL
Therapeutic response (assessed with: defined as (i) sustained improvement of one grade in mental state during ≤48 hours or (ii) improvement of more than two grades in mental state)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/10 (100%)	20%	RR 3.82 (0.95 to 15.36)	564 more per 1000 (from 10 fewer to 1000 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 49: Clinical evidence summary: BCAA versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCAA	Placebo	Relative (95% CI)	Absolute	Quality	Importance

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCAA	Placebo	Relative (95% CI)	Absolute		
Mortality (at 5 days)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/25 (40%)	20%	RR 2 (0.8 to 5.02)	200 more per 1000 (from 40 fewer to 804 more)	LOW	CRITICAL
Positive response to treatment (at 5 days)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/20 (50%)	50%	RR 1 (0.55 to 1.83)	0 fewer per 1000 (from 225 fewer to 415 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 50: Clinical evidence summary: Neomycin (+BCAA in grades III and IV) versus placebo (+BCAA in grades III and IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neomycin	Placebo (concurrent BCAA in grade III/IV)	Relative (95% CI)	Absolute		
Mortality (at day 5)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/20 (10%)	10.5%	RR 0.95 (0.15 to 6.08)	5 fewer per 1000 (from 89 fewer to 533 more)	VERY LOW	CRITICAL
Time until regression to grade 0 hepatic encephalopathy (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	19	-	MD 13.36 lower (27.47 lower to 0.75 higher)	LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

J.11.5 Single therapy versus single therapy

Table 51: Clinical evidence summary: BCAA versus neomycin

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BCAA**	**Neomycin**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Mortality												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	18/68 (26.5%)	40%	RR 0.57 (0.36 to 0.89)	172 fewer per 1000 (from 44 fewer to 256 fewer)	VERY LOW	CRITICAL
Full improvement to grade 0 hepatic encephalopathy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/9 (55.6%)	25%	RR 2.22 (0.58 to 8.44)	305 more per 1000 (from 105 fewer to 1000 more)	VERY LOW	CRITICAL
Improvement to grade 0 or 1 hepatic encephalopathy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	8/9 (88.9%)	75%	RR 1.19 (0.75 to 1.88)	143 more per 1000 (from 188 fewer to 660 more)	LOW	CRITICAL
Time to recovery (hours) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	14	-	MD 37.4 lower (56.1 to 18.7 lower)	MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

J.11.6 Combination therapy (1 intervention + non-absorbable disaccharides) versus single therapy

Table 52: Clinical evidence summary: BCAA+non-absorbable disaccharides versus BCAA

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCAA+non-absorbable disaccharides	BCAA	Relative (95% CI)	Absolute	Quality	Importance
Came out of coma (at 7 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/16 (100%)	93.8%	RR 1.06 (0.9 to 1.26)	56 more per 1000 (from 94 fewer to 244 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

J.11.7 MARS versus Standard Medical Therapy

Table 53: Clinical evidence summary: MARS versus Standard Medical Therapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MARS	Standard Medical Therapy	Relative (95% CI)	Absolute	Quality	Importance
Mortality (at 5 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/39 (12.8%)	16.1%	RR 0.79 (0.25 to 2.5)	34 fewer per 1000 (from 121 fewer to 241 more)	LOW	CRITICAL
Responder (improvement of hepatic encephalopathy by 2 grades at any time; at 5 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	24/39 (61.5	40%	RR 1.54 (0.93 to 2.55)	216 more per 1000 (from 28 fewer to 620 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MARS	Standard Medical Therapy	Relative (95% CI)	Absolute	Quality	Importance
							%)					
Serious Adverse Events (at 5 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/39 (51.3 %)	25.8%	RR 1.99 (1.02 to 3.89)	255 more per 1000 (from 5 more to 746 more)	MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Appendix K: Forest plots

K.1 Risk factors and risk assessment tools

K.1.1 Risk factors

Prognostic Factor: Alcohol

Figure 13: Prognostic factor: alcohol consumption (Askgaard 2015)

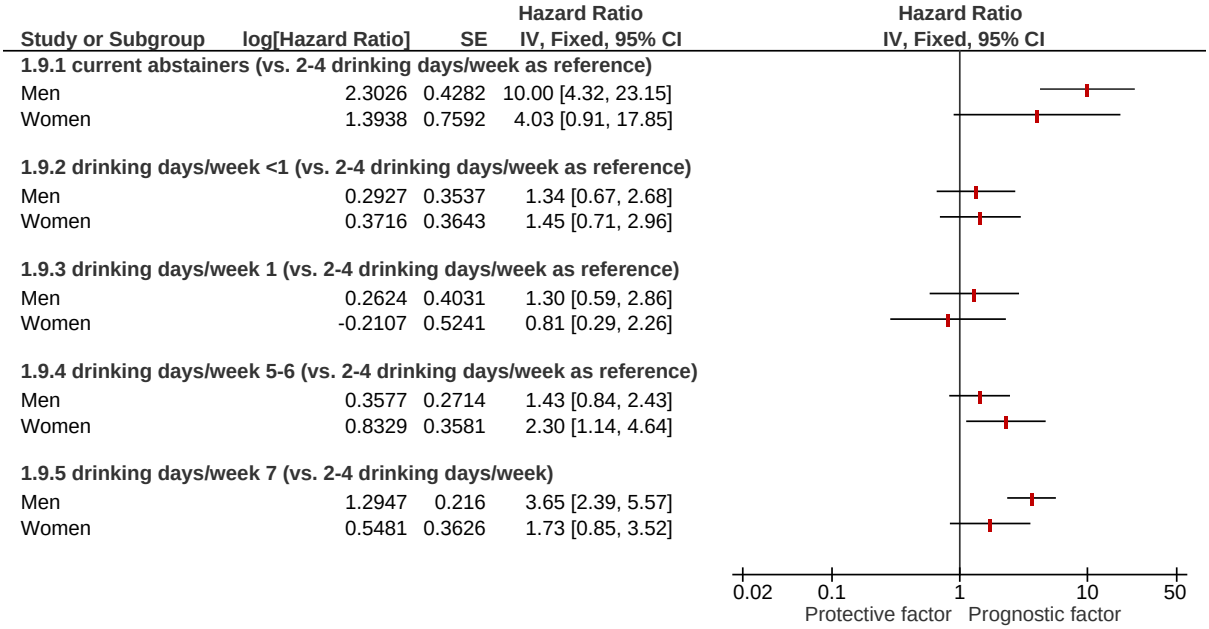


Figure 14: Prognostic factor: alcohol consumption (Becker 2002)

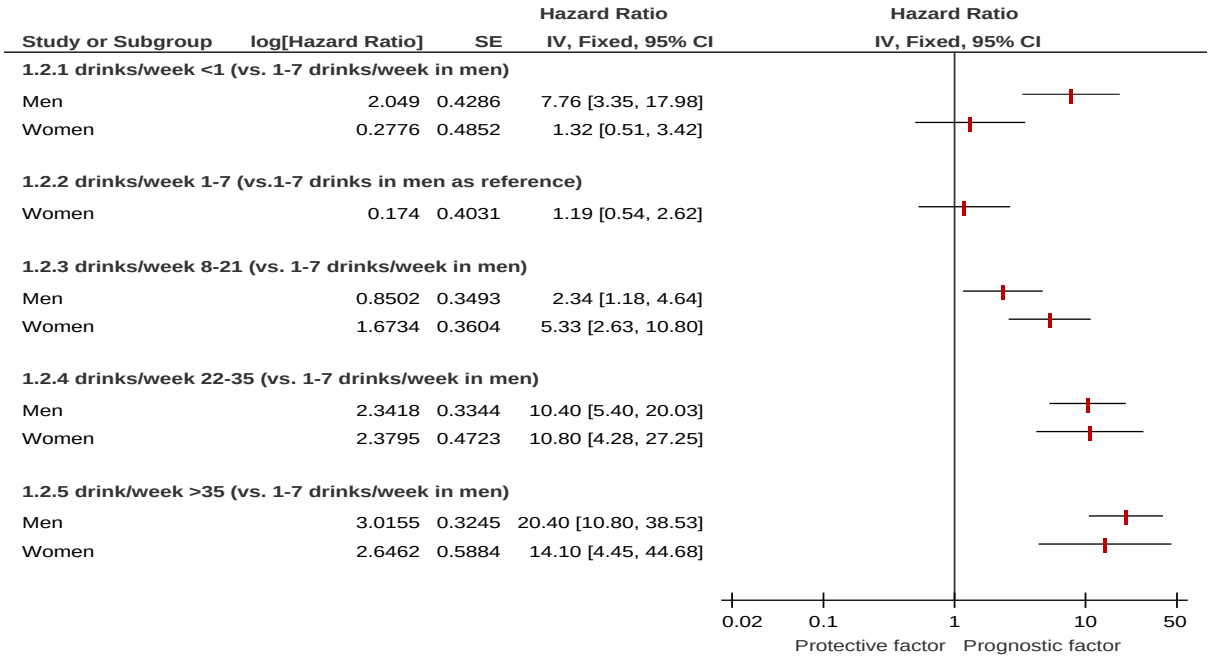


Figure 15: Prognostic factor: alcohol consumption (Fuchs 1995)

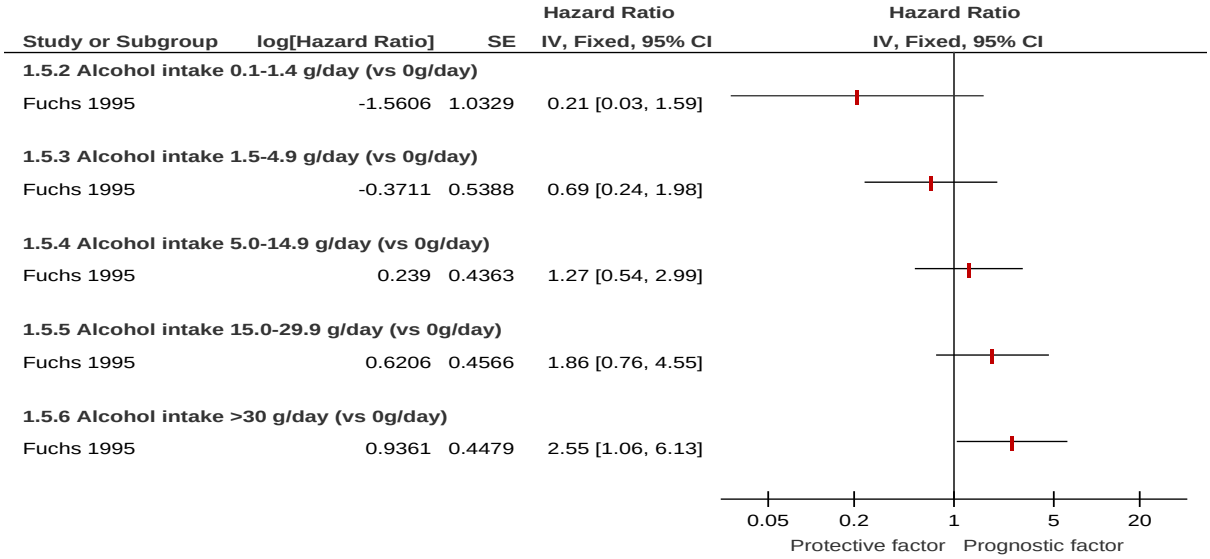
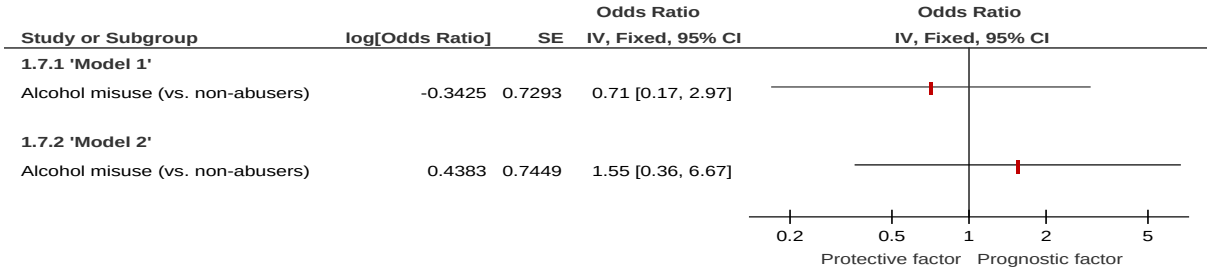
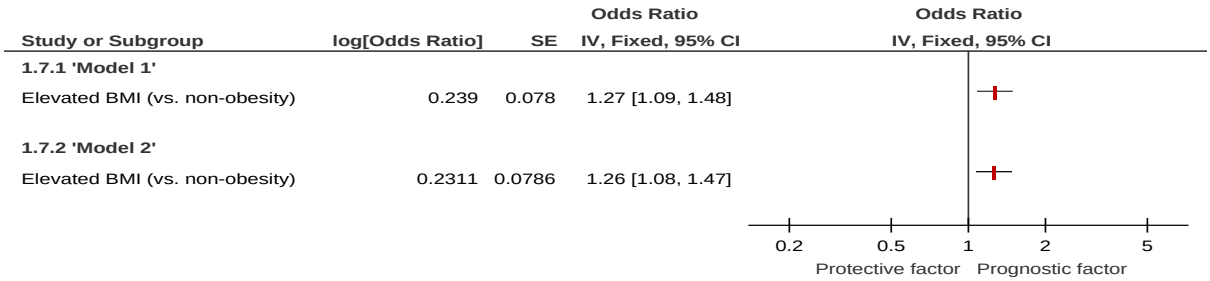


Figure 16: Prognostic factor: alcohol consumption (Schult 2011)



Prognostic Factor: BMI

Figure 17: Prognostic factor: BMI (Schult 2011)



Note: elevated BMI presumed to be >30 but unclear as reported in paper

Figure 18: Prognostic factor: BMI (Becker 2002)

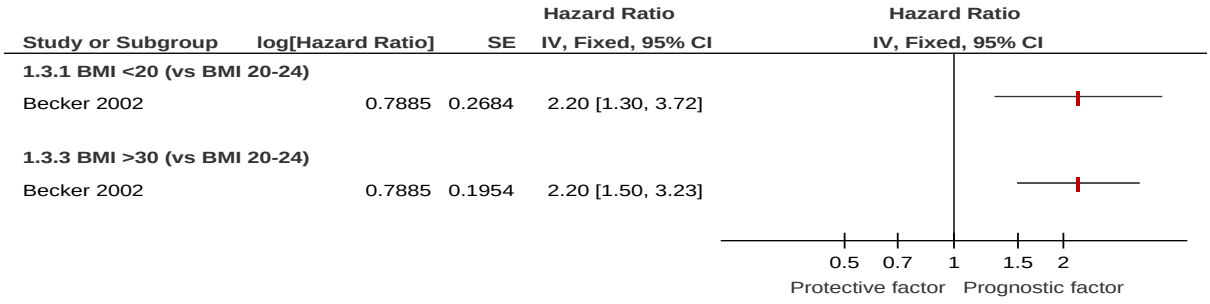


Figure 19: Prognostic factor: BMI (Liu 2010A)

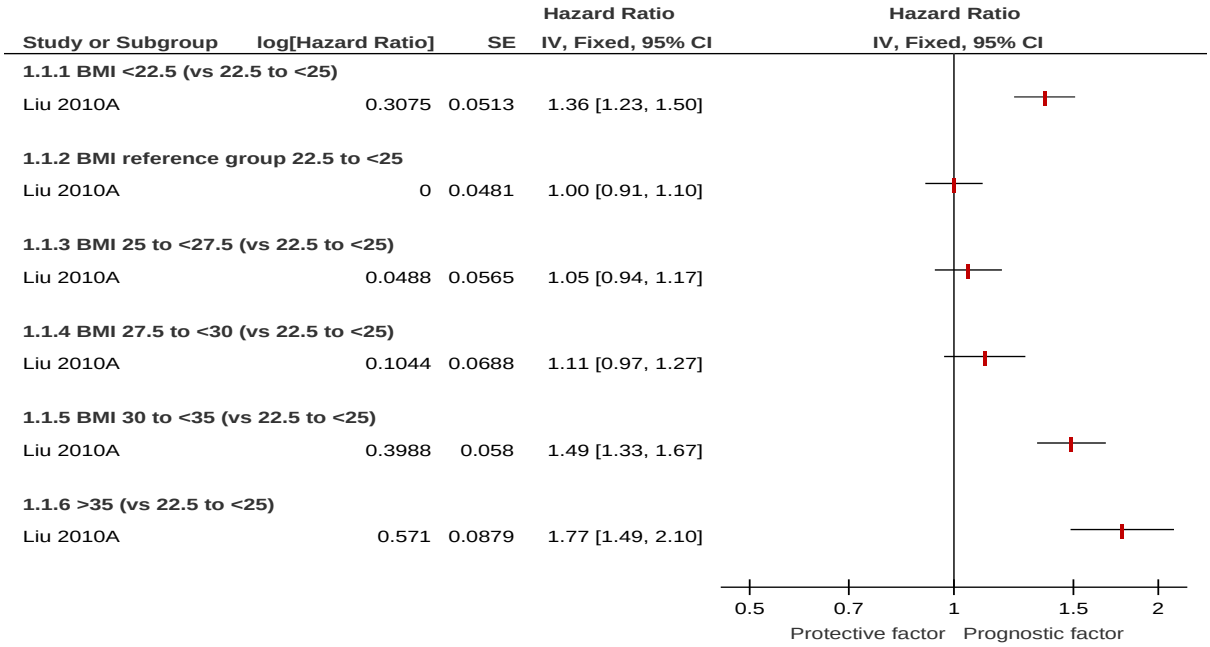
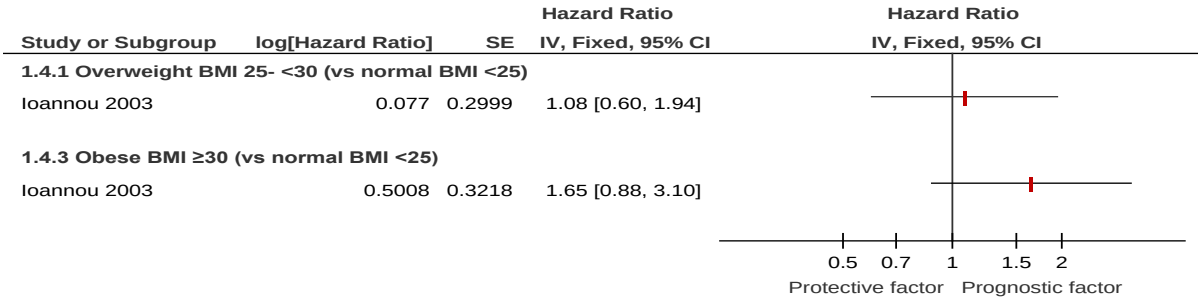
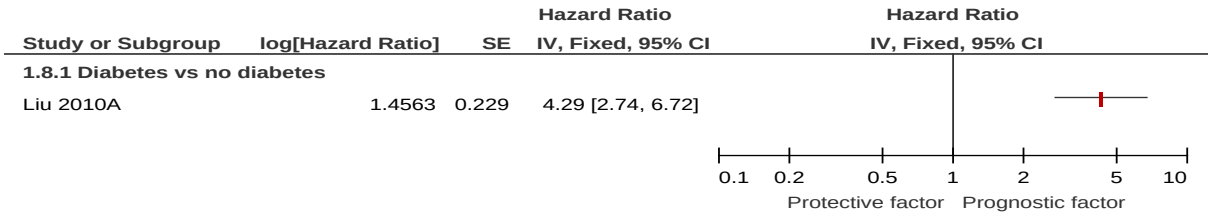


Figure 20: Prognostic factor: BMI (Ioannou 2003)



Prognostic Factor: diabetes

Figure 21: Prognostic factor: diabetes (Liu 2010)



K.1.2 Risk tools

No relevant clinical studies were identified.

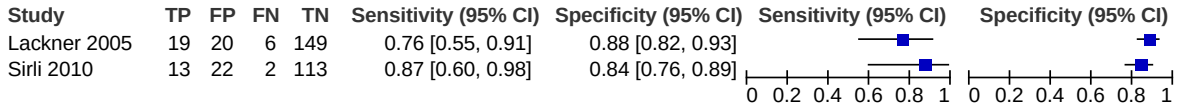
K.2 Diagnostic tests

K.2.1 Hepatitis C

K.2.1.1 Individual blood tests

Coupled sensitivity/specificity forest plots

Figure 22: Platelets



AUC plots

Figure 23: Platelets

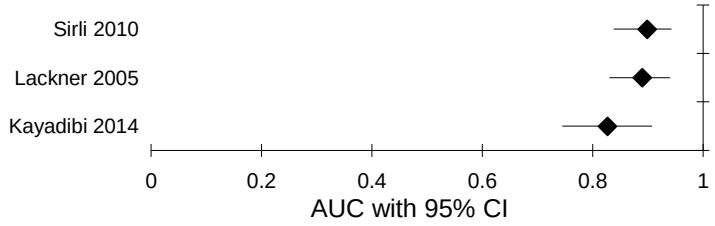


Figure 24: AST

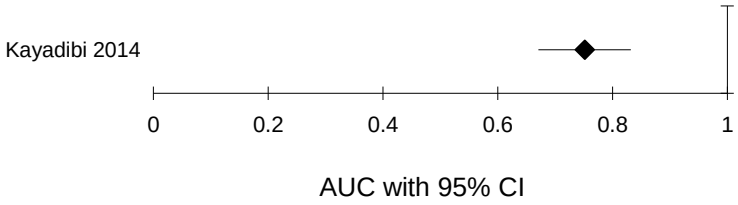
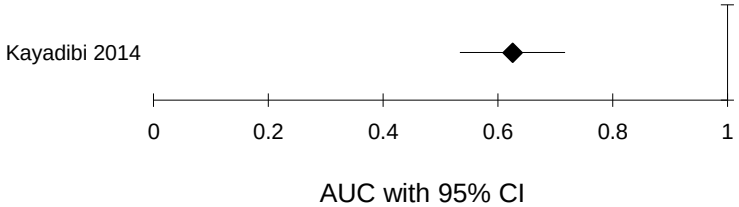


Figure 25: ALT



K.2.1.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

Figure 26: AST/ALT ratio

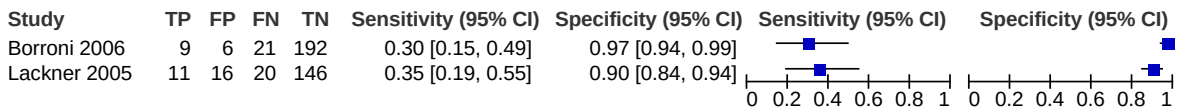
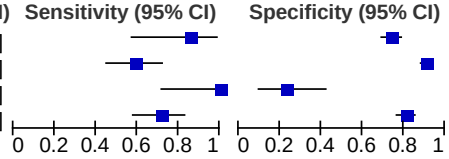


Figure 27: FibroTest

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Halfon 2007	12	89	2	253	0.86 [0.57, 0.98]	0.74 [0.69, 0.79]
Leroy 2013	33	41	23	413	0.59 [0.45, 0.72]	0.91 [0.88, 0.93]
Stibbe 2011	11	23	0	7	1.00 [0.72, 1.00]	0.23 [0.10, 0.42]
Zarski 2012	40	62	16	264	0.71 [0.58, 0.83]	0.81 [0.76, 0.85]



FibroTest data that could not be combined in the analysis:

Friedrich-rust 2010[305]: cut-off 0.73, sensitivity: 67%, specificity: 81%;

Leroy 2014[518]: cut-off 0.74, sensitivity: 59%, specificity: 91%.

Figure 28: FibroTest sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region.

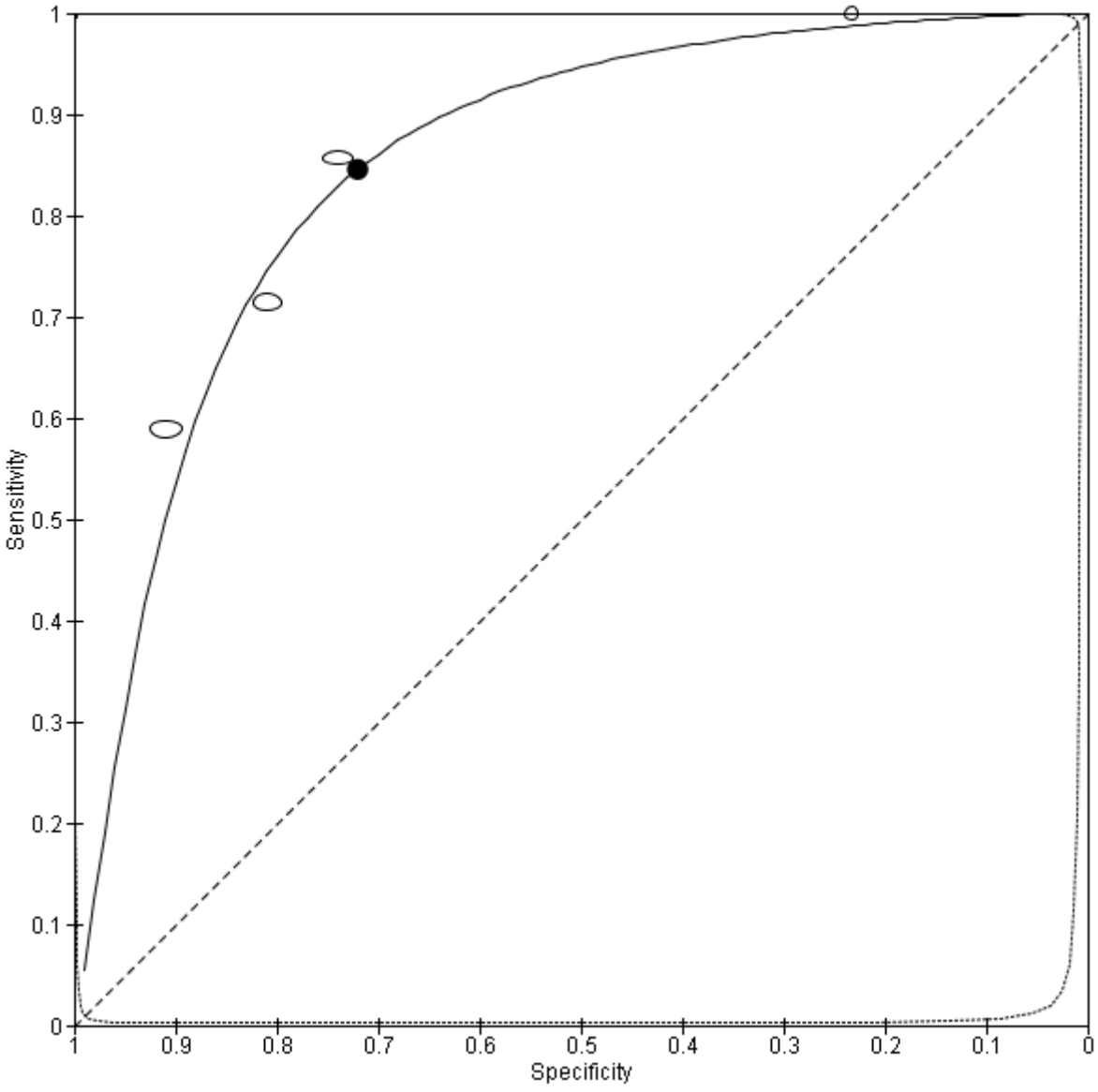


Figure 29: ELF

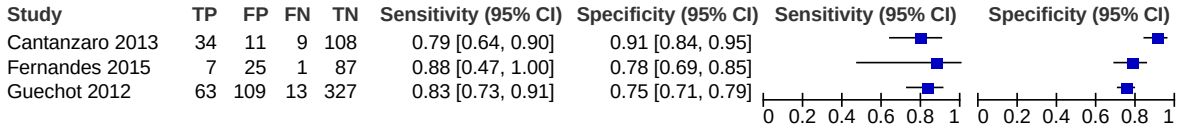
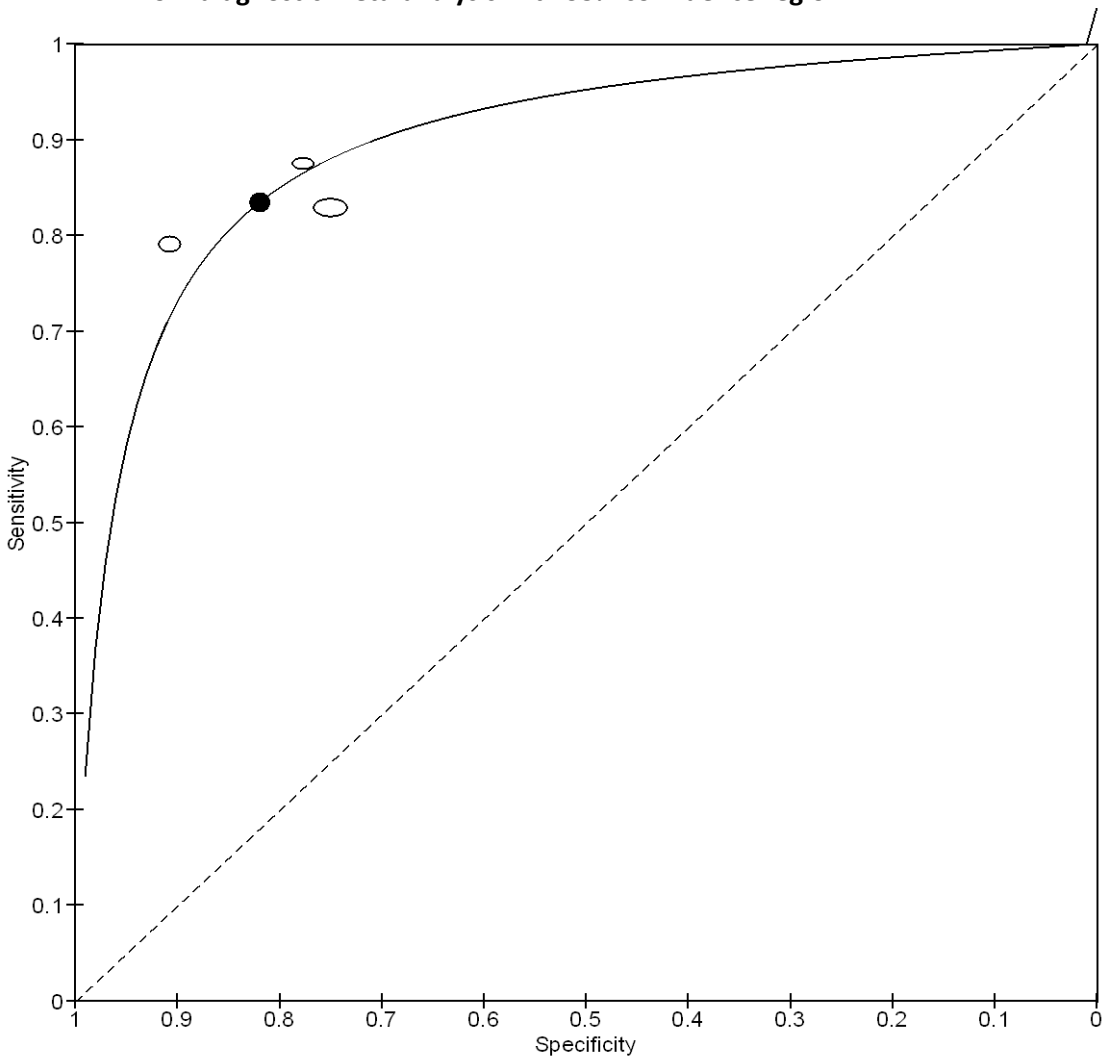


Figure 30: ELF sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region



ELF data that could not be combined in the analysis:

Friedrich-rust 2010[305]: cut-off 10.31, sensitivity: 89%, specificity: 63%.

Figure 31: APRI (low threshold)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bota 2011a	24	47	6	135	0.80 [0.61, 0.92]	0.74 [0.67, 0.80]
Cantanzaro 2013	32	15	11	104	0.74 [0.59, 0.86]	0.87 [0.80, 0.93]
Chrysanthos 2006	35	64	23	162	0.60 [0.47, 0.73]	0.72 [0.65, 0.77]
Halfon 2007	14	58	0	284	1.00 [0.77, 1.00]	0.83 [0.79, 0.87]
Lackner 2005	30	49	2	114	0.94 [0.79, 0.99]	0.70 [0.62, 0.77]
Martinez 2011	102	57	22	159	0.82 [0.74, 0.89]	0.74 [0.67, 0.79]
Sirli 2010	14	23	1	112	0.93 [0.68, 1.00]	0.83 [0.76, 0.89]

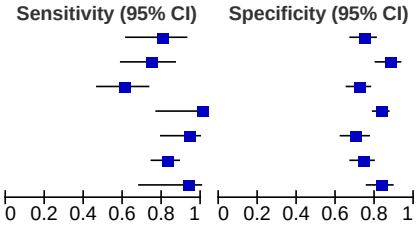
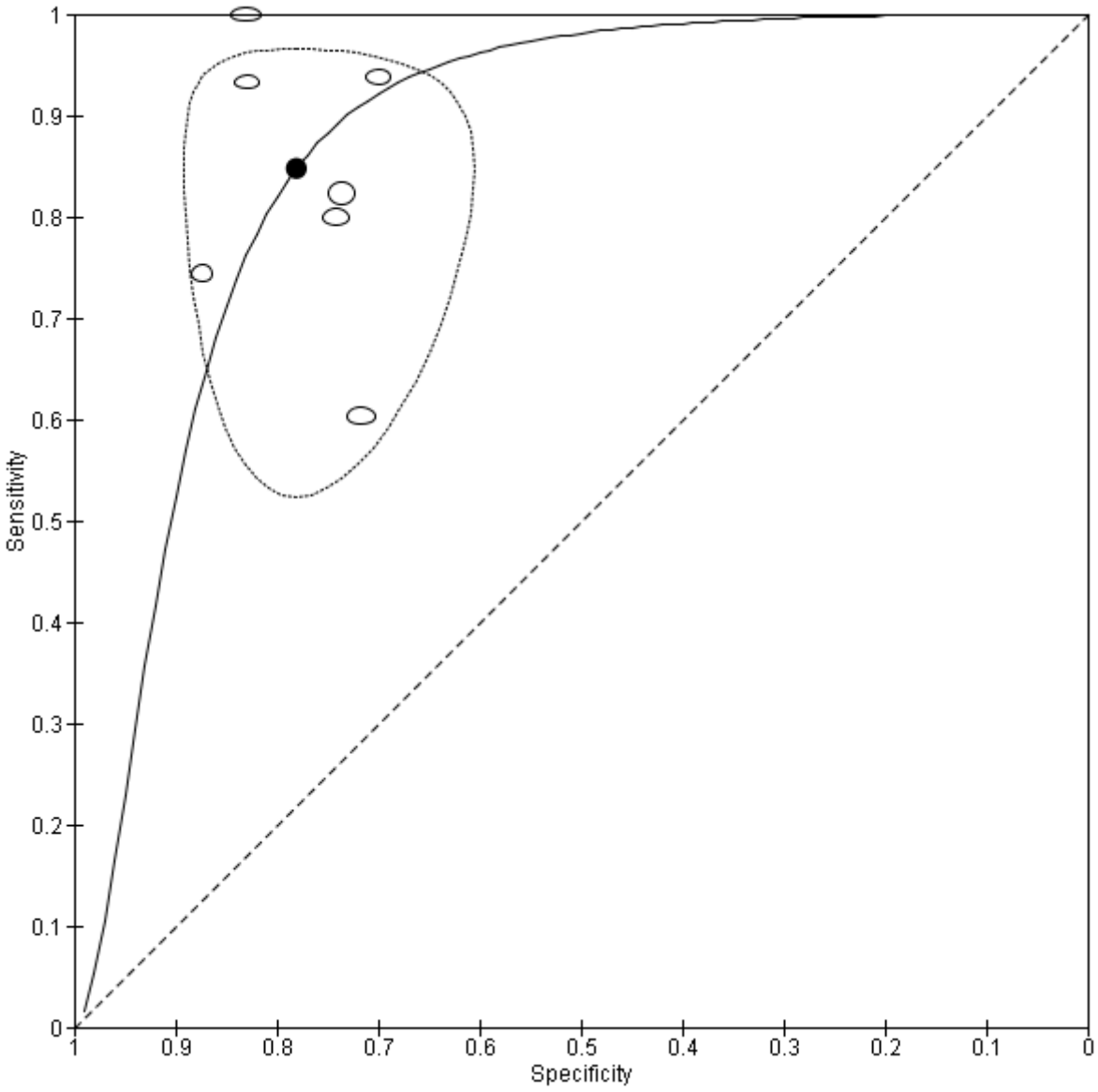


Figure 32: APRI (low threshold) sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region



APRI (low threshold) data that could not be combined in the analysis:

Shehab 2014[798]: cut-off 0.5, sensitivity: 100%, specificity: 12.8%.

Figure 33: APRI (high threshold)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Borroni 2006	13	12	17	186	0.43 [0.25, 0.63]	0.94 [0.90, 0.97]
Chrysanthos 2006	22	20	36	206	0.38 [0.26, 0.52]	0.91 [0.87, 0.95]
Martinez 2011	61	20	63	196	0.49 [0.40, 0.58]	0.91 [0.86, 0.94]
Silva Junior 2014	6	3	3	39	0.67 [0.30, 0.93]	0.93 [0.81, 0.99]
Zarski 2012	4	1	52	325	0.07 [0.02, 0.17]	1.00 [0.98, 1.00]

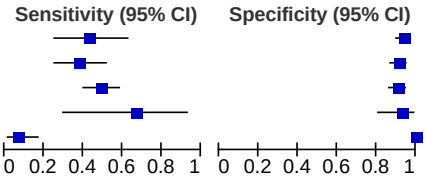
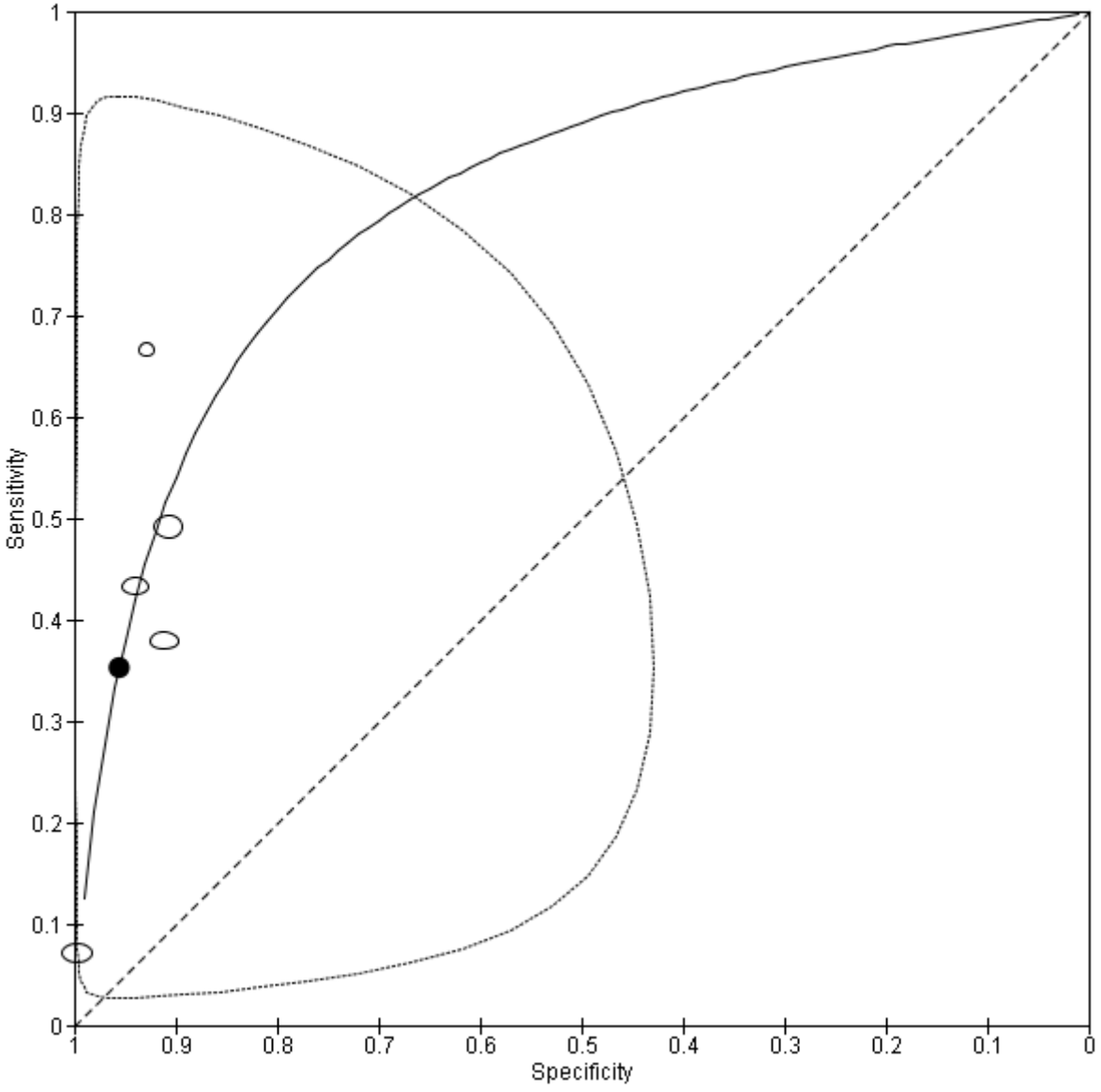


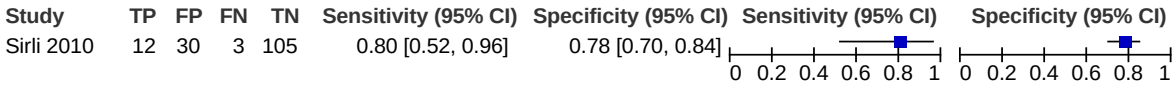
Figure 34: APRI (high threshold) sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region



APRI (high threshold) data that could not be combined in the analysis:

Shehab 2014[798]: cut-off 2.0, sensitivity: 15.4%, specificity: 96%.

Figure 35: FIB4



FIB4 data that could not be combined in the analysis:

Shehab 2014[798]: cut-off 3.25, sensitivity: 28.2%, specificity: 93.5%.

AUC plots

Figure 36: AST/ALT ratio

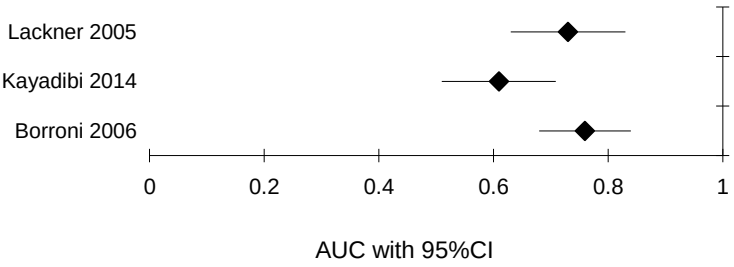


Figure 37: FibroTest

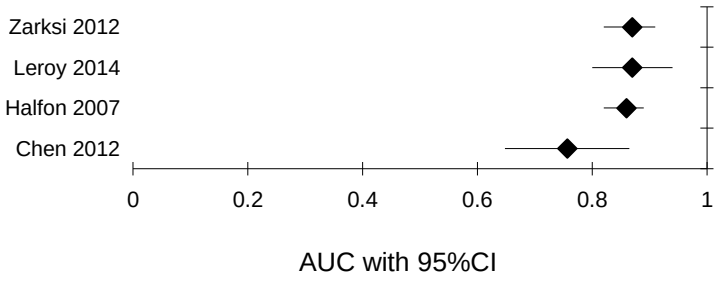


Figure 38: ELF

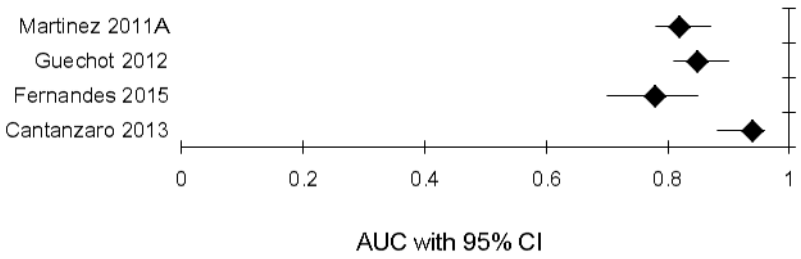


Figure 39: APRI

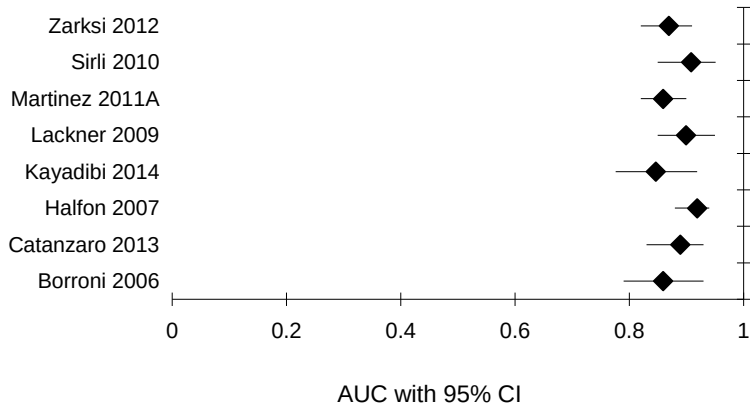
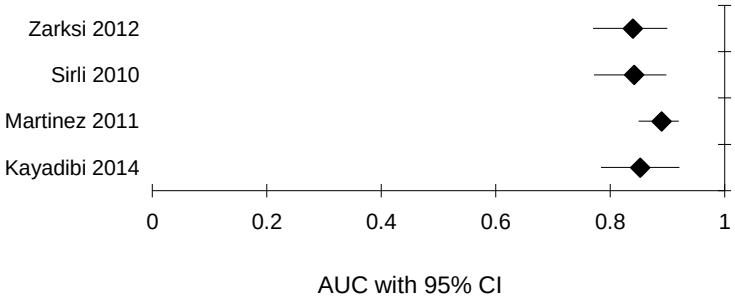


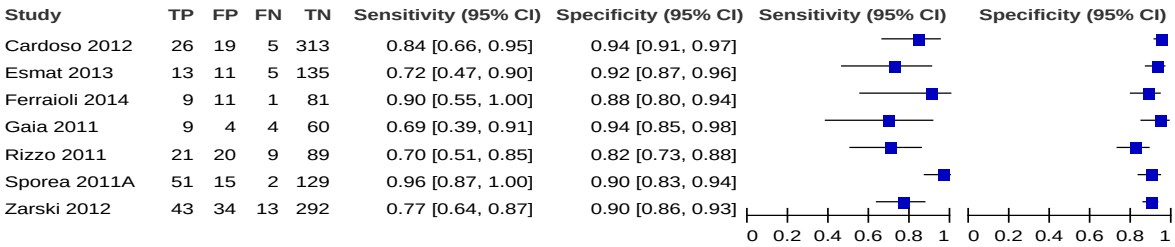
Figure 40: FIB4



K.2.1.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 41: Transient elastography (low threshold)



TE (low threshold) data that could not be combined in the analysis:

Friedrich-rust 2010: cut-off 12.5kPa, sensitivity: 78%, specificity: 84%.

Figure 42: Transient elastography (low threshold) sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region.

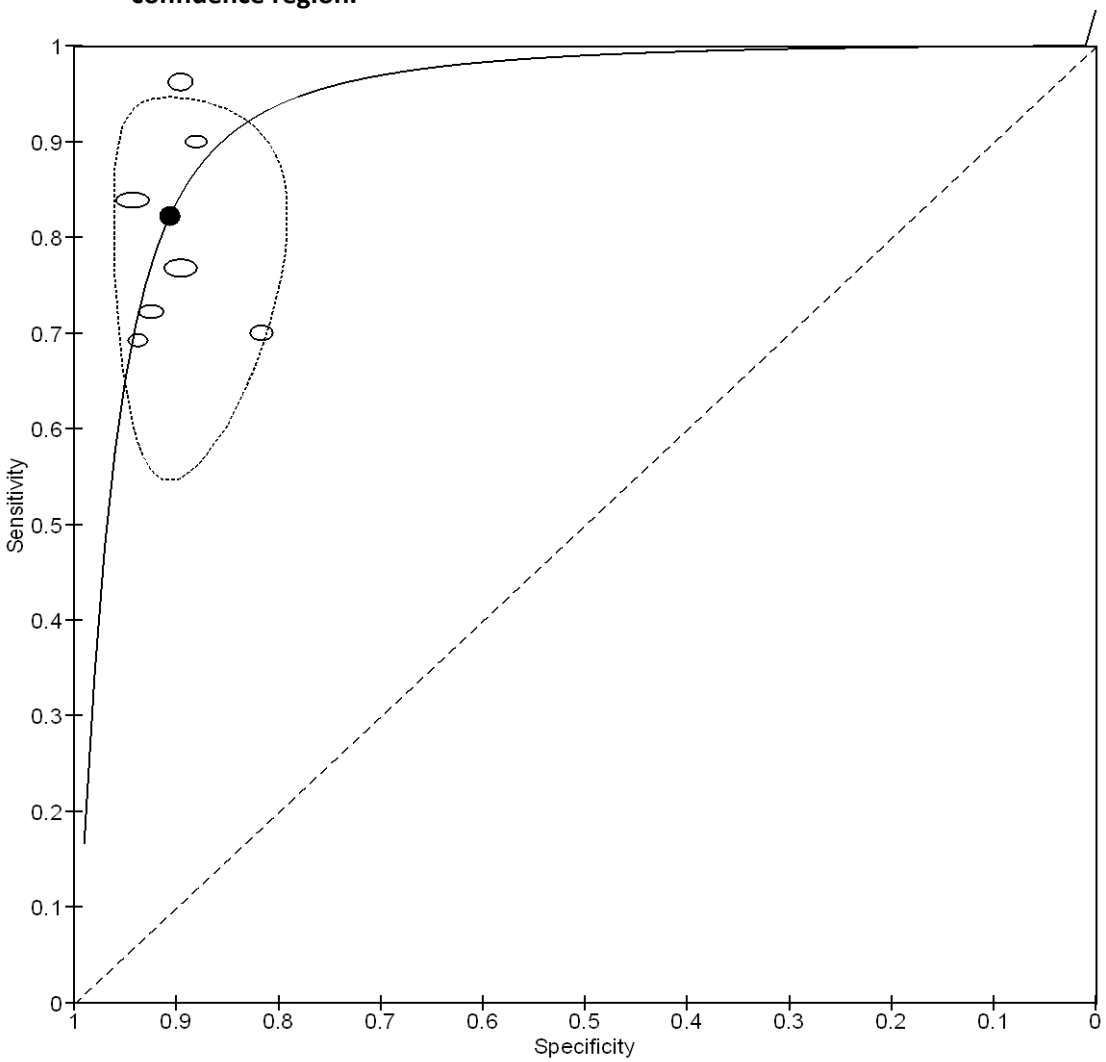


Figure 43: Transient elastography (medium threshold)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Arena 2008	27	10	2	111	0.93 [0.77, 0.99]	0.92 [0.85, 0.96]
Bota 2011a	28	5	2	177	0.93 [0.78, 0.99]	0.97 [0.94, 0.99]
Caviglia 2013	16	1	2	38	0.89 [0.65, 0.99]	0.97 [0.87, 1.00]
Lupsor Platon 2013	350	55	23	773	0.94 [0.91, 0.96]	0.93 [0.91, 0.95]
Sirli 2010	14	5	1	130	0.93 [0.68, 1.00]	0.96 [0.92, 0.99]
Sporea 2012A	40	8	2	62	0.95 [0.84, 0.99]	0.89 [0.79, 0.95]
Stibbe 2011	10	8	1	22	0.91 [0.59, 1.00]	0.73 [0.54, 0.88]

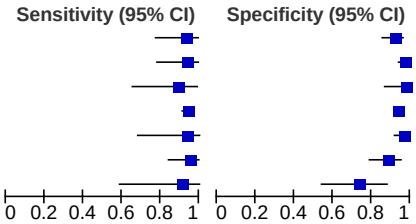


Figure 44: Transient elastography (medium threshold) sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region.

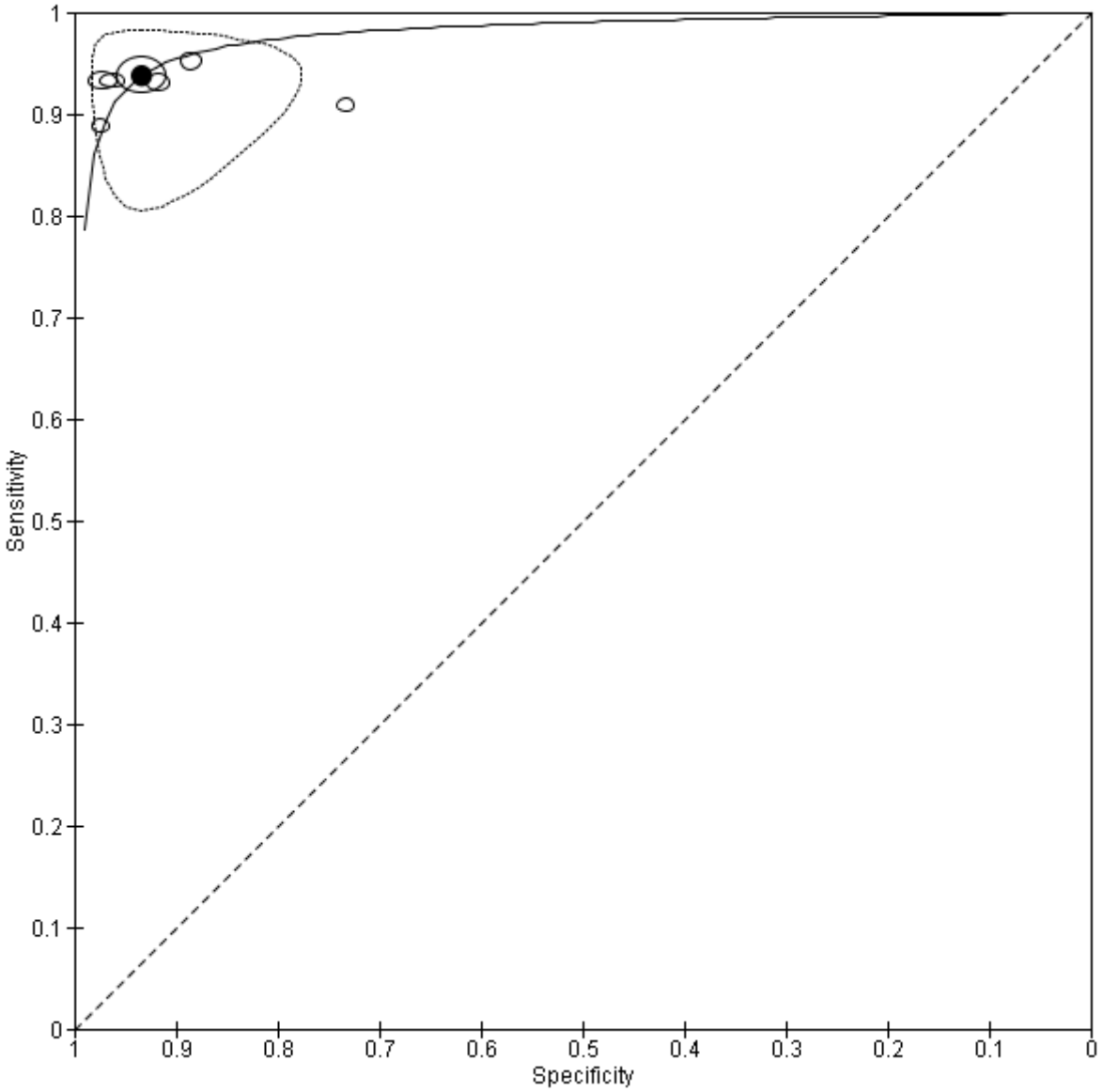


Figure 45: Transient elastography (high threshold)

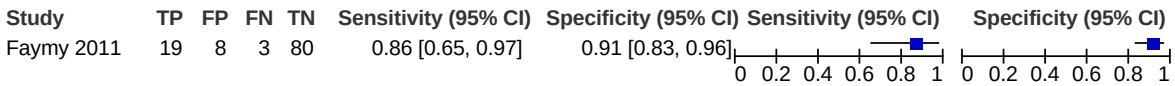


Figure 46: ARFI

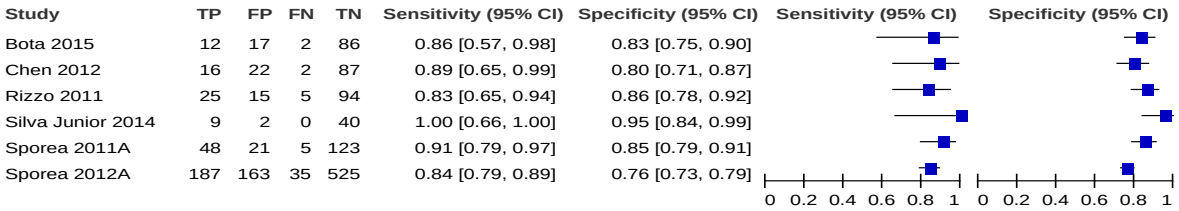


Figure 47: ARFI sROC with studies results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region.

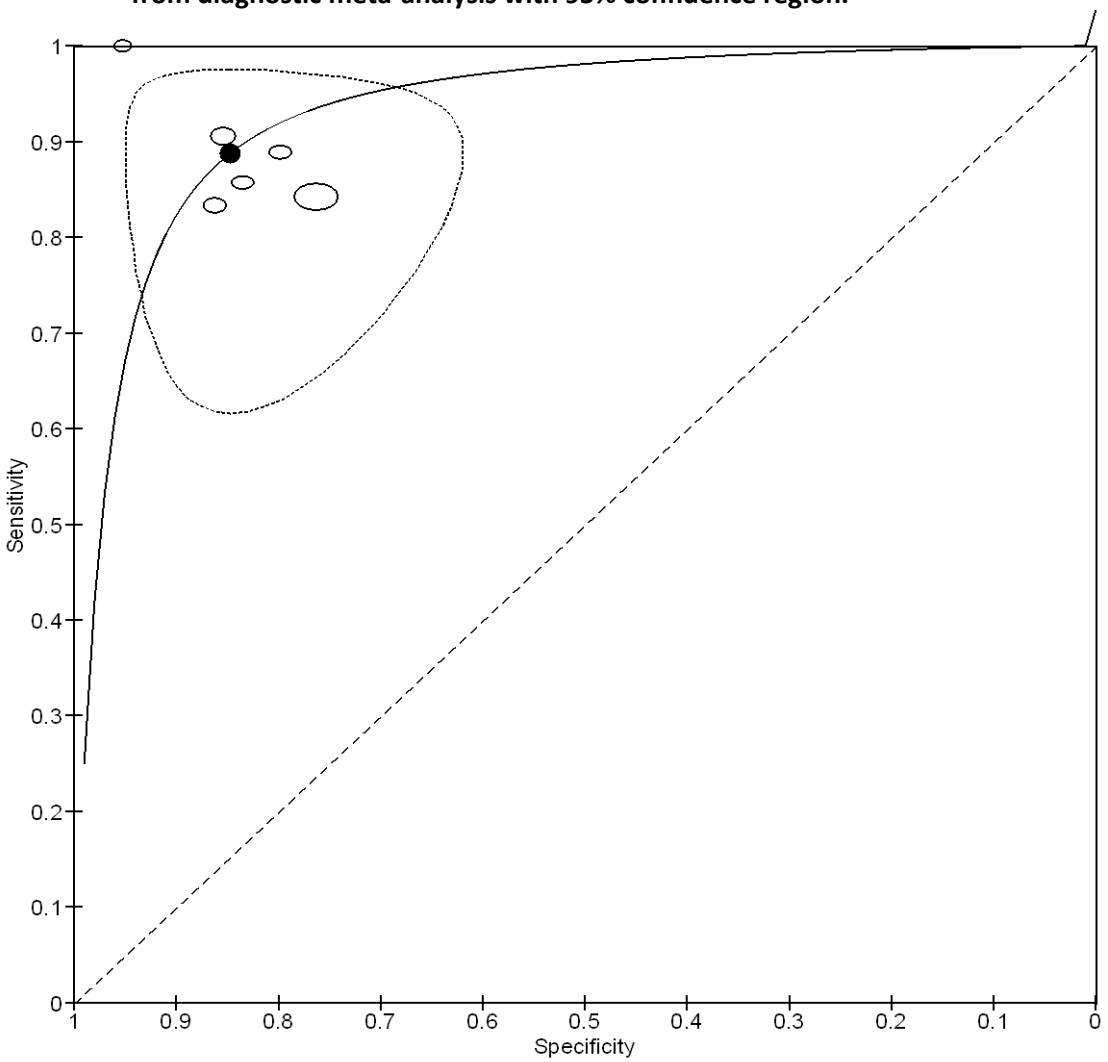
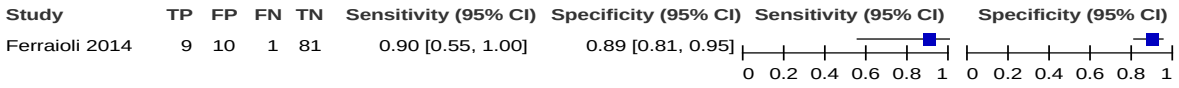


Figure 48: pSWE



AUC plots

Figure 49: Transient elastography

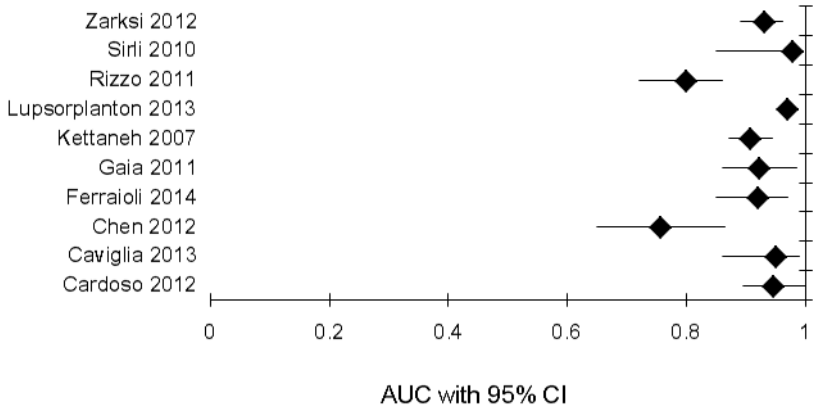


Figure 50: ARFI

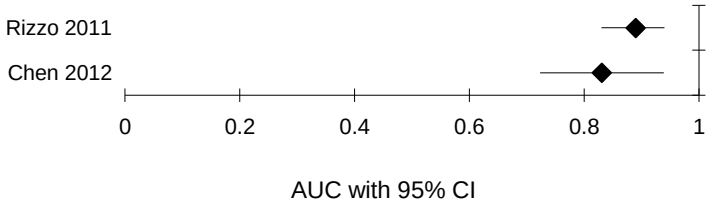
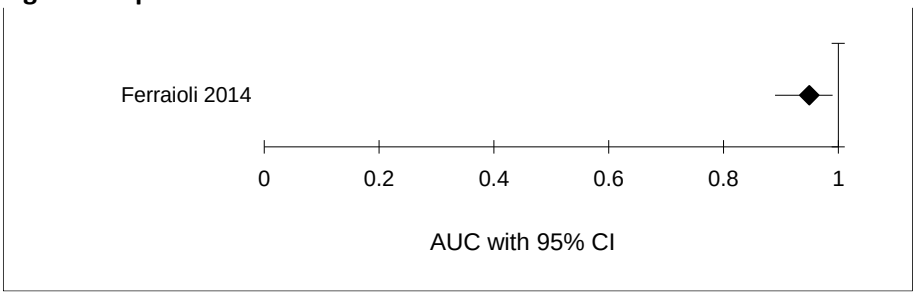


Figure 51: pSWE



K.2.1.4 Combinations of tests

Coupled sensitivity / specificity forest plots

Figure 52: Transient elastography and ARFI

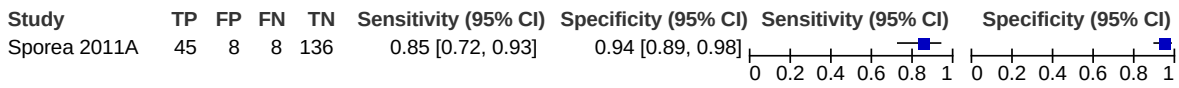


Figure 53: Transient elastography or ARFI

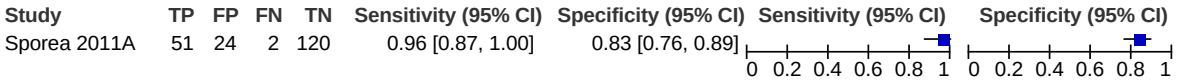


Figure 54: SAFE algorithm

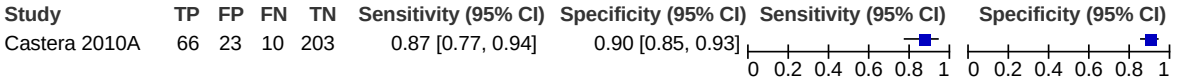
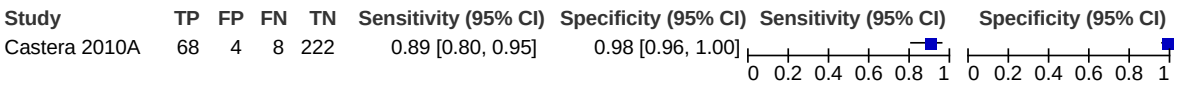


Figure 55: Castera algorithm



AUC plots

Figure 56: SAFE algorithm

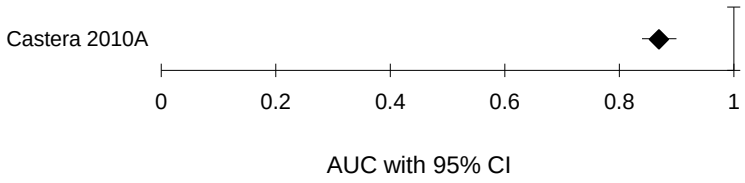
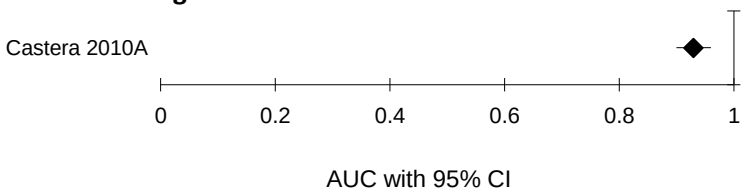


Figure 57: Castera algorithm



K.2.2 NAFLD

K.2.2.1 Individual blood tests

None reported

K.2.2.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

None reported

AUC plots

Figure 58: AST/ALT ratio

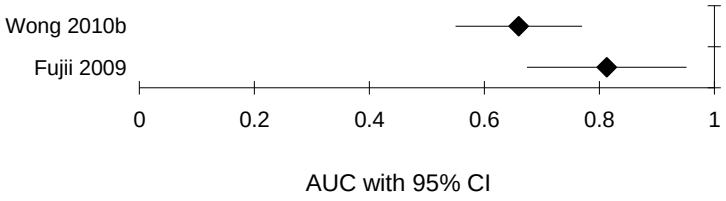


Figure 59: APRI

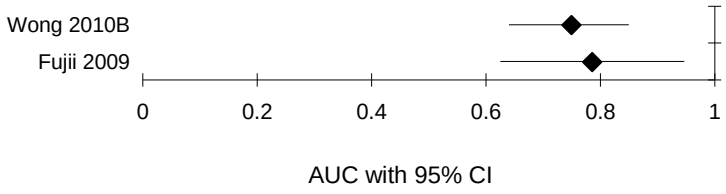
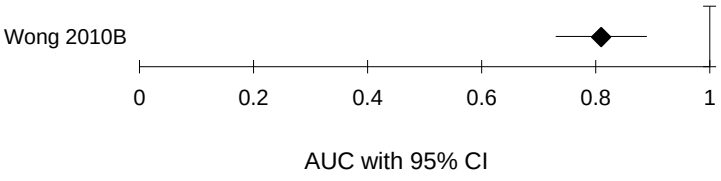


Figure 60: FIB4



K.2.2.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 61: Transient elastography (low threshold)

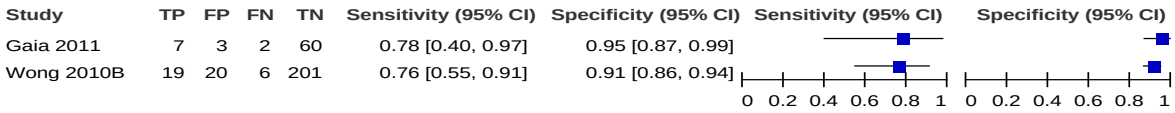


Figure 62: Transient elastography (high threshold)

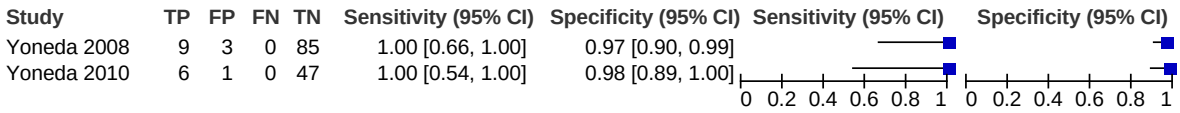
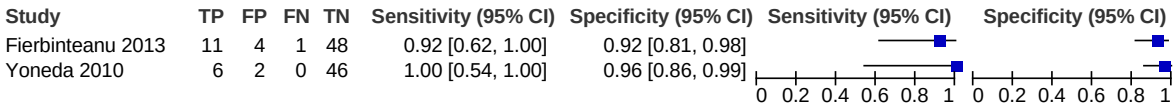


Figure 63: ARFI



AUC plots

Figure 64: Transient elastography

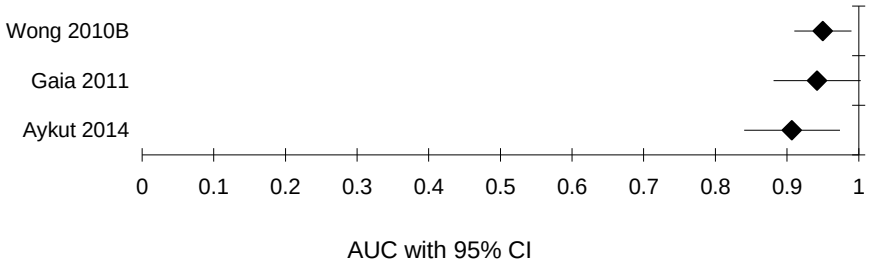
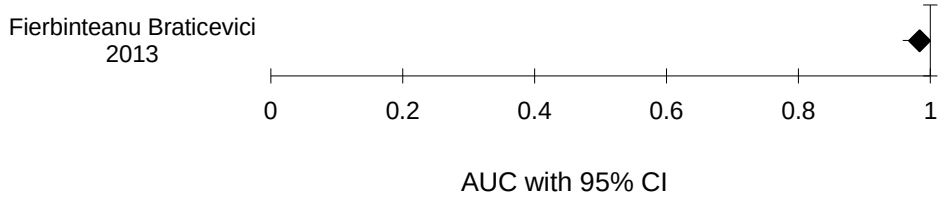


Figure 65: ARFI



K.2.2.4 Combinations of tests

None reported

K.2.3 ALD

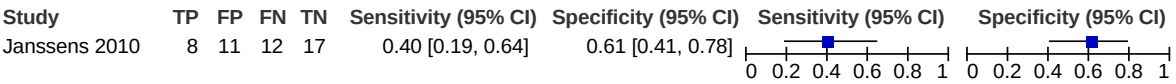
K.2.3.1 Individual blood tests

None reported

K.2.3.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

Figure 66: APRI (high threshold)



AUC plots

None reported

K.2.3.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 67: Transient elastography (low threshold)

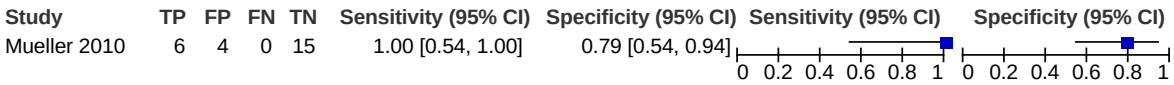
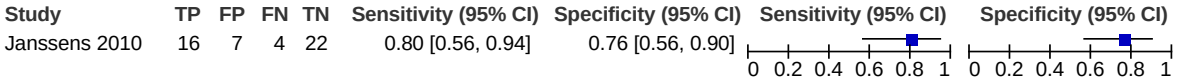
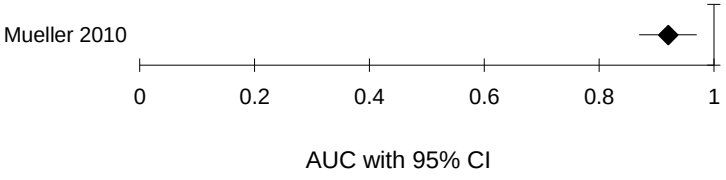


Figure 68: Transient elastography (high threshold)



AUC plots

Figure 69: Transient elastography



K.2.3.4 Combinations of tests

None reported

K.2.4 Primary biliary cirrhosis

K.2.4.1 Individual blood tests

None reported

K.2.4.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

None reported

AUC plots

Figure 70: AST/ALT ratio

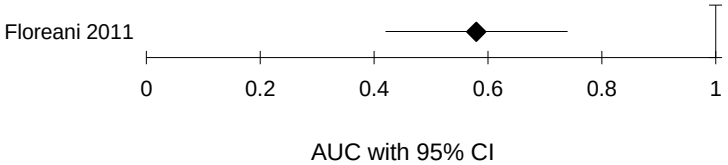


Figure 71: APRI

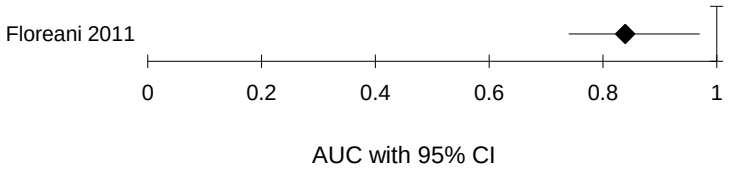
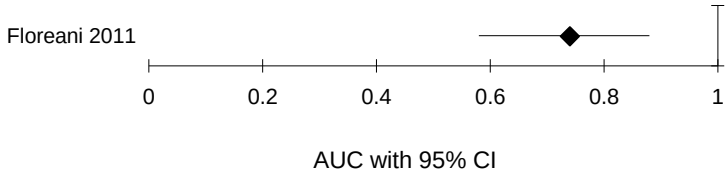


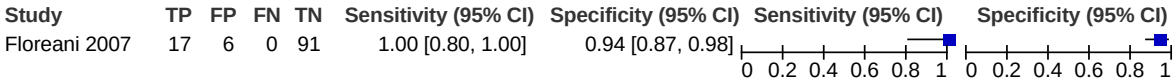
Figure 72: FIB4



K.2.4.3 Imaging tests

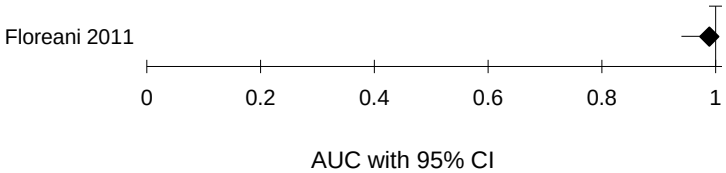
Coupled sensitivity/specificity forest plots

Figure 73: Transient elastography



AUC plots

Figure 74: Transient elastography



K.2.4.4 Combinations of tests

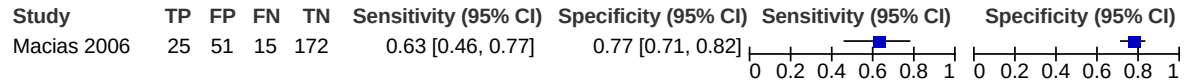
None reported

K.2.5 HIV/HCV

K.2.5.1 Individual blood tests

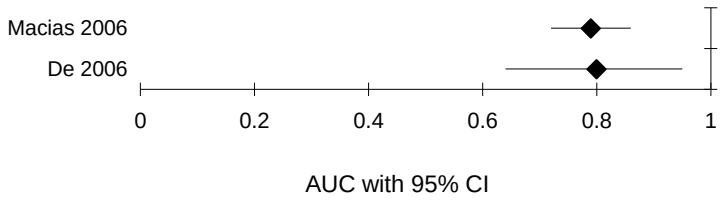
Coupled sensitivity/specificity forest plots

Figure 75: Platelets



AUC plots

Figure 76: Platelets



K.2.5.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

Figure 77: AST/ALT ratio

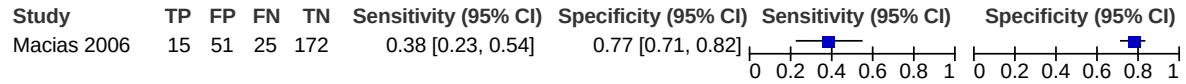


Figure 78: APRI (low threshold)

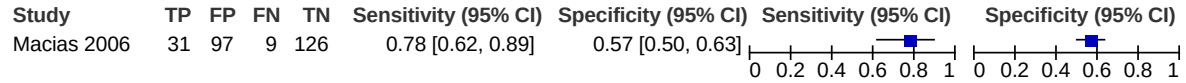
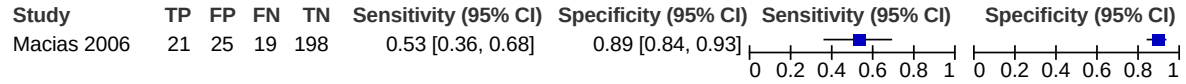


Figure 79: APRI (high threshold)



AUC plots

Figure 80: AST/ALT ratio

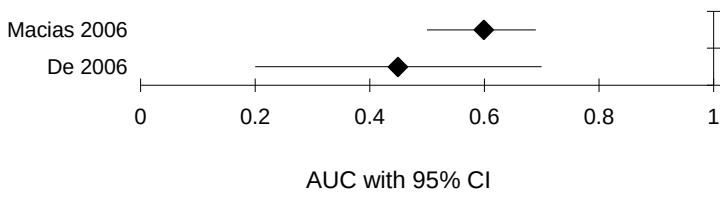


Figure 81: APRI

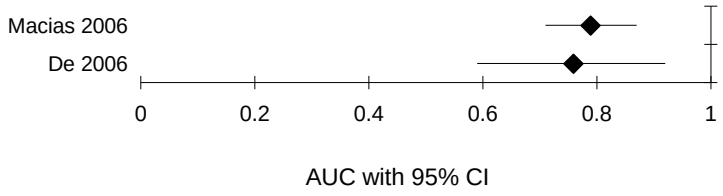
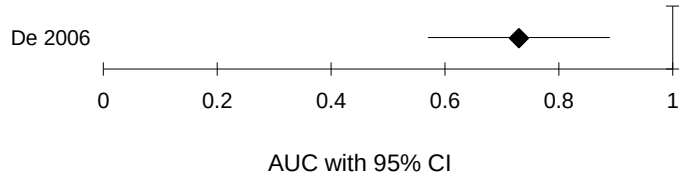


Figure 82: FIB4



K.2.5.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 83: Transient elastography (low threshold)

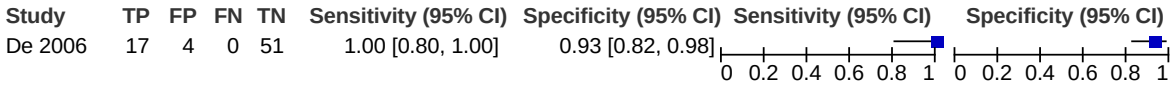
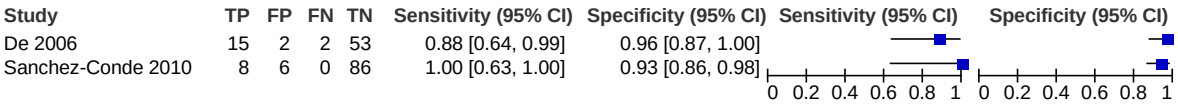
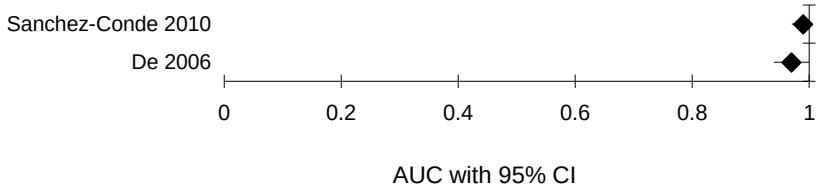


Figure 84: Transient elastography (medium threshold)



AUC plots

Figure 85: Transient elastography



K.2.5.4 Combinations of tests

None reported

K.3 Severity risk tools

K.3.1 Coupled sensitivity/specificity forest plots

Figure 86: Sensitivity and specificity of MELD for predicting 90-day mortality

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Finkenstedt 2012	69	59	12	288	16.0	0.85 [0.76, 0.92]	0.83 [0.79, 0.87]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Figure 87: Sensitivity and specificity of transient elastography for predicting death and decompensation

Transient elastography - composite of death and other clinical events (8.0 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	40	113	0	7	8.0	1.00 [0.91, 1.00]	0.06 [0.02, 0.12]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (10.5 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	39	108	1	12	10.5	0.97 [0.87, 1.00]	0.10 [0.05, 0.17]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (12.5 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	37	101	3	19	12.5	0.93 [0.80, 0.98]	0.16 [0.10, 0.24]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - clinical disease progression

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wang 2014	28	55	21	116	14.0	0.57 [0.42, 0.71]	0.68 [0.60, 0.75]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (15 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	34	88	6	32	15.0	0.85 [0.70, 0.94]	0.27 [0.19, 0.36]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (20 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	32	73	8	47	20.0	0.80 [0.64, 0.91]	0.39 [0.30, 0.48]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (30 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	12	56	28	64	30.0	0.30 [0.17, 0.47]	0.53 [0.44, 0.62]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (50 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	2	8	38	112	50.0	0.05 [0.01, 0.17]	0.93 [0.87, 0.97]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Transient elastography - composite of death and other clinical events (70 kPa)

Study	TP	FP	FN	TN	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klibanksy 2012	1	2	39	118	70.0	0.03 [0.00, 0.13]	0.98 [0.94, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Figure 88: Sensitivity and specificity of transient elastography for predicting decompensation

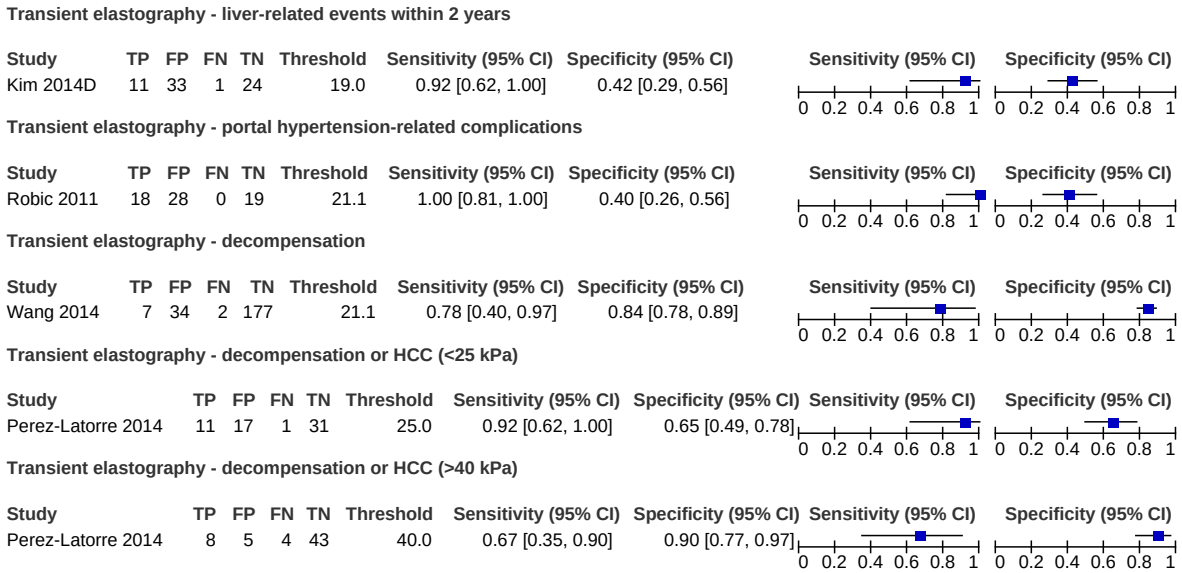


Figure 89: Sensitivity and specificity of transient elastography for predicting HCC

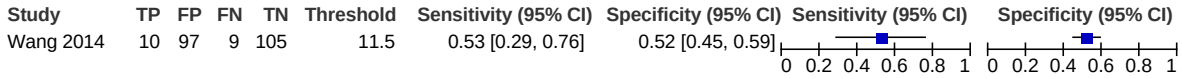


Figure 90: Sensitivity and specificity of transient elastography for predicting portal hypertension progression (hepatic decompensation, varices development and varices growth)

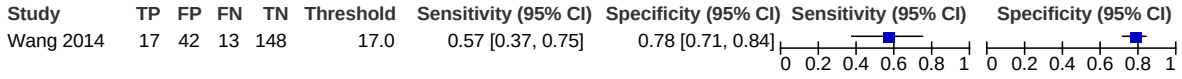
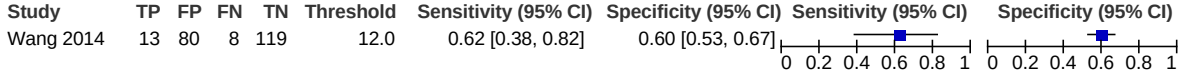


Figure 91: Sensitivity and specificity of transient elastography for predicting varices progression



K.3.2 AUC plots

Figure 92: Accuracy of Child Pugh in predicting 1-year mortality

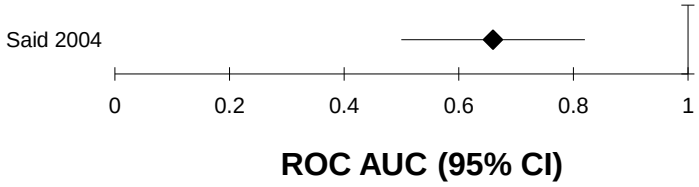


Figure 93: Accuracy of MELD in predicting 1-year mortality

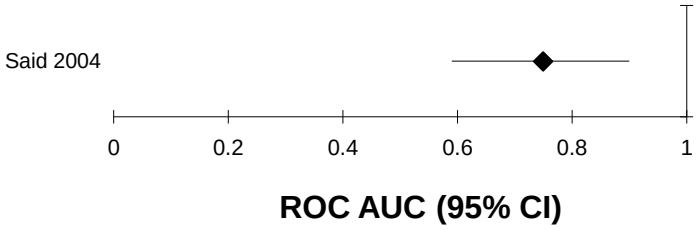


Figure 94: Accuracy of MELD in predicting 90-day mortality

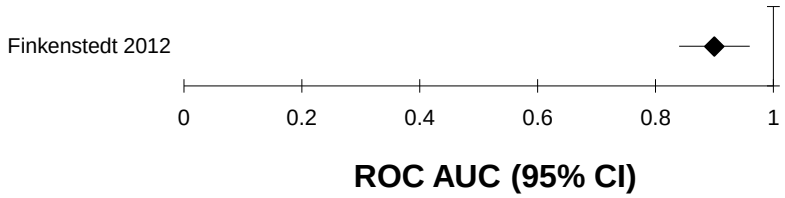


Figure 95: Accuracy of MELD in predicting death and decompensation

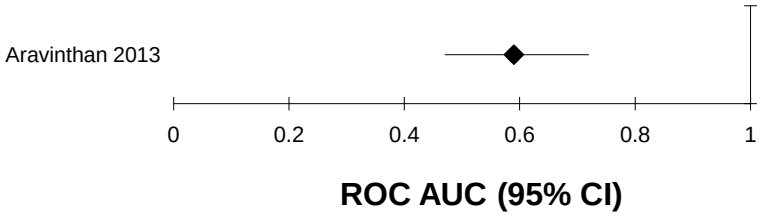


Figure 96: Accuracy of transient elastography in predicting death and decompensation

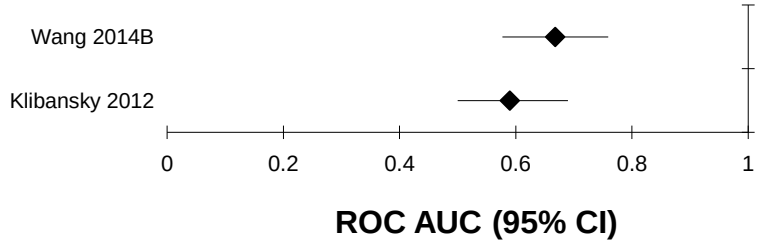
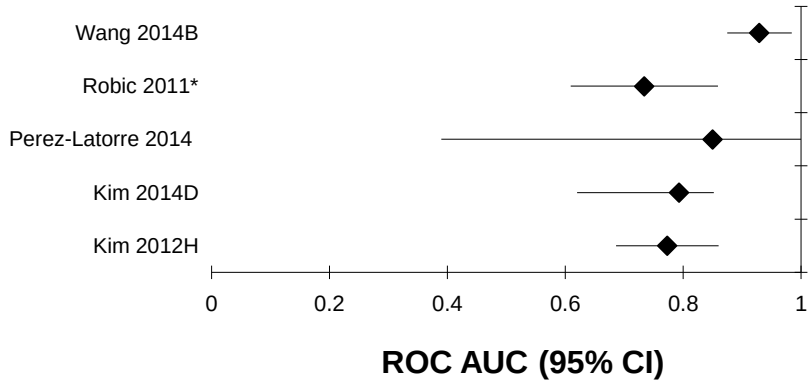


Figure 97: Accuracy of transient elastography in predicting decompensation



**variceal bleeding and/or ascites*

Figure 98: Accuracy of transient elastography in predicting decompensation or HCC

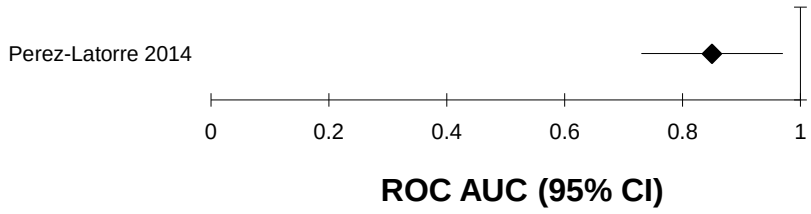


Figure 99: Accuracy of transient elastography in predicting HCC

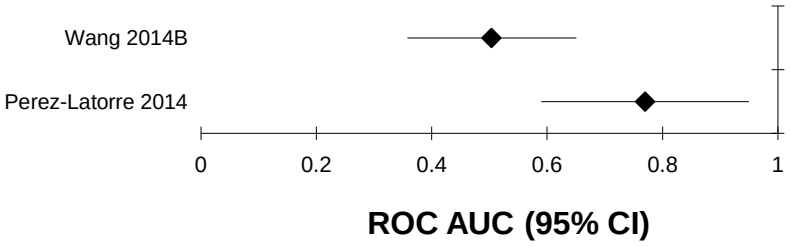


Figure 100: Accuracy of transient elastography in predicting decompensation and varices development

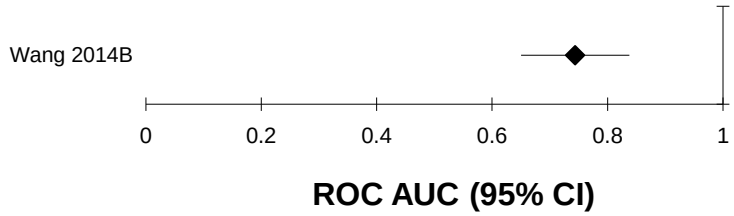
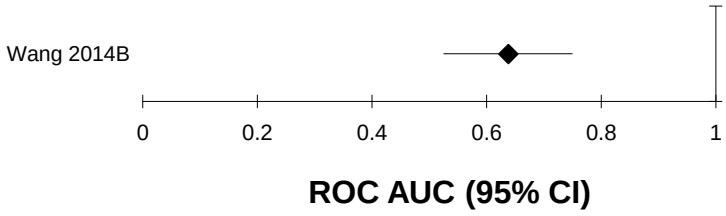


Figure 101: Accuracy of transient elastography in predicting varices progression



K.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

K.4.1 Surveillance versus no surveillance

Figure 102: Survival (adjusted HR >1 indicates an advantage to the surveillance group)

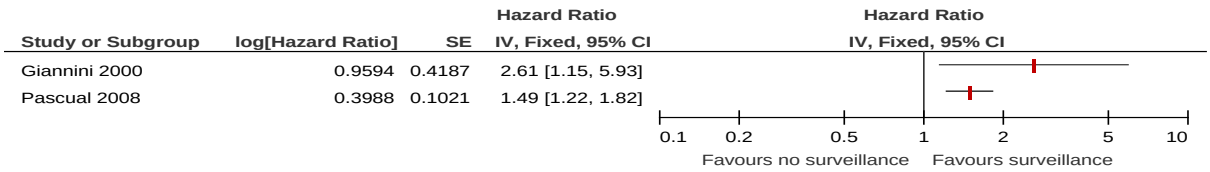


Figure 103: Survival (adjusted OR >1 indicates an advantage to the surveillance group)

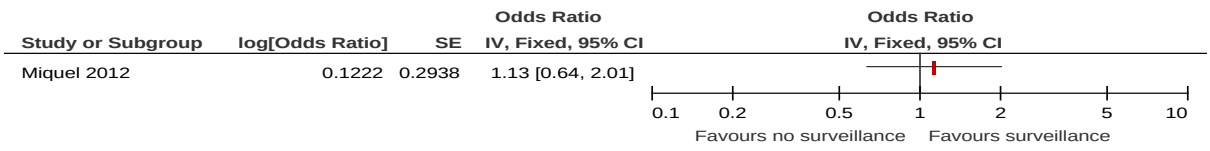


Figure 104: Detection of HCC at a very early stage (single nodule ≤2 cm; OR >1 indicates an advantage to the surveillance group)

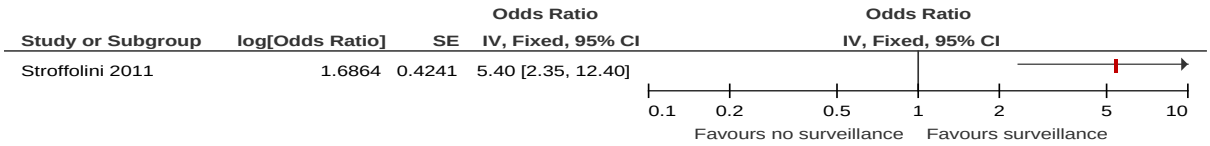


Figure 105: Detection of HCC at a non-advanced stage (single nodule ≤5 cm or 3 nodules each ≤3 cm without vascular and lymphonodal invasion and metastases; OR >1 indicates an advantage to the surveillance group)

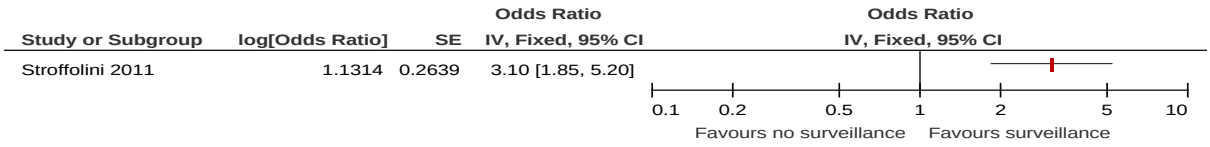
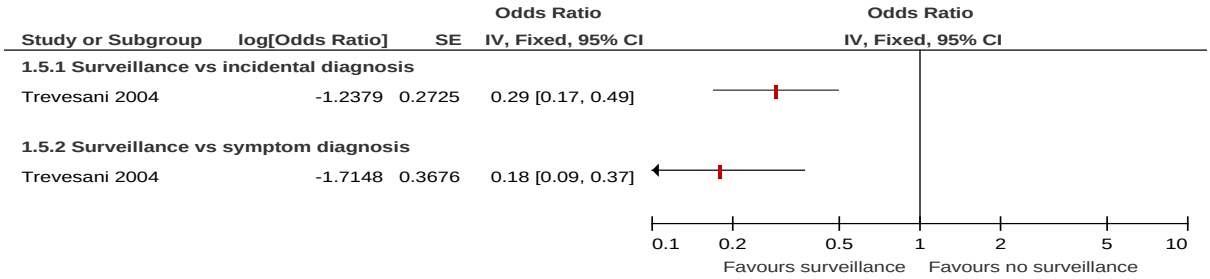


Figure 106: Detection of HCC at an advanced stage (according to Milano criteria; OR <1 indicates an advantage to the surveillance group)



K.4.2 Yearly surveillance versus 6-monthly surveillance

Figure 107: Survival (HR >1 indicates an advantage to the 6-monthly surveillance group)

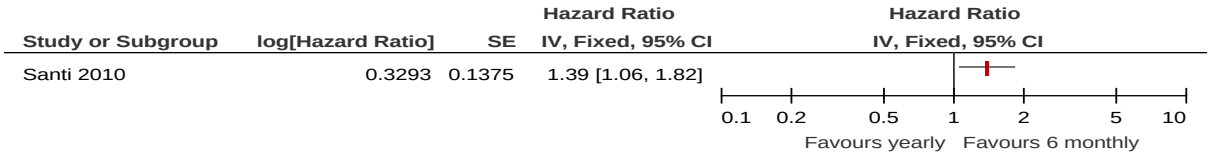
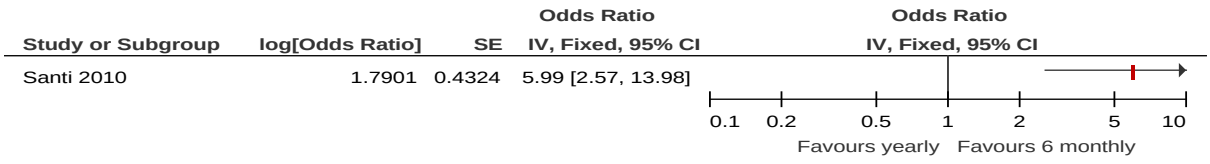


Figure 108: Detection of HCC beyond a very early stage (solitary nodule >2 cm or multinodular tumour with/without vascular invasion and/or metastases; OR >1 indicates an advantage to the 6-monthly surveillance group)



K.4.3 3-monthly surveillance versus 6-monthly surveillance

Figure 109: Survival (HR <1 indicates an advantage to the 3-monthly surveillance group)

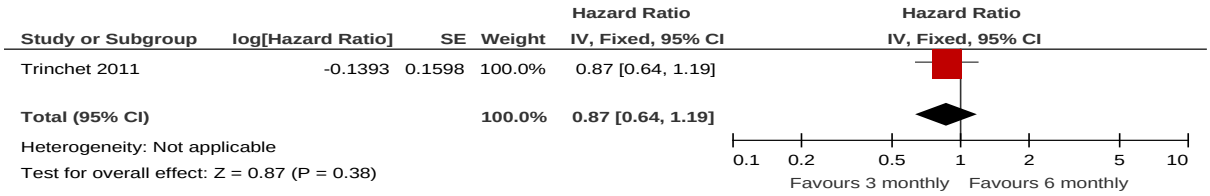


Figure 110: HCC occurrence

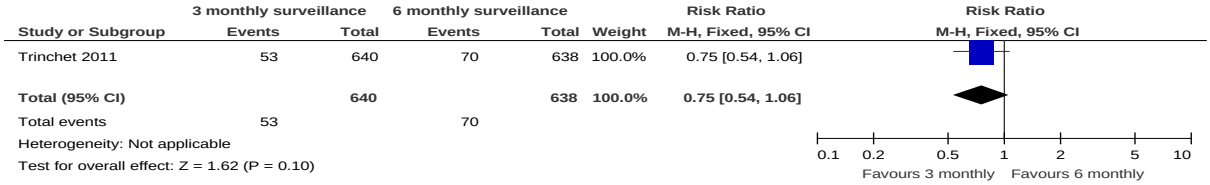


Figure 111: Diameter of the largest HCC nodule ≤30 mm (positive outcome, RR<1 indicates an advantage to the 6-monthly group)

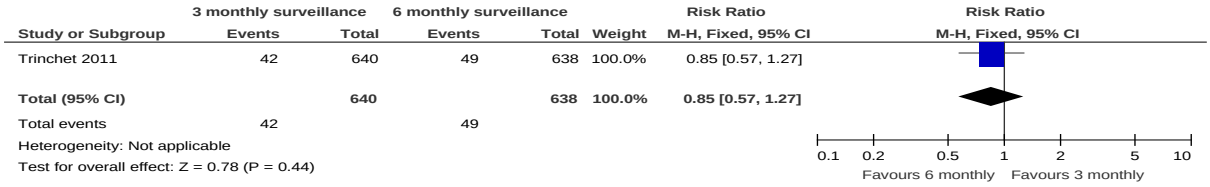


Figure 112: Diameter of the largest HCC nodule >30 mm (negative outcome, RR<1 indicates an advantage to the 3-monthly group)

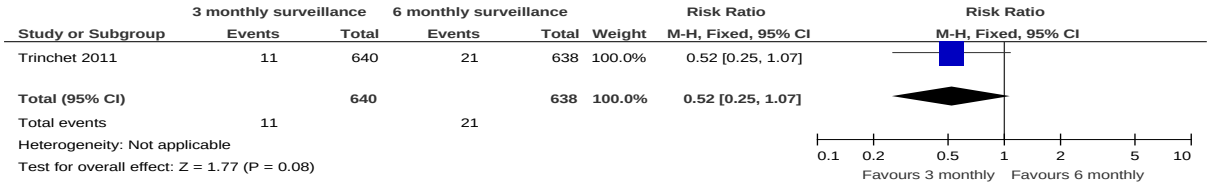


Figure 113: Number of lesions (RR<1 indicates fewer events in the 3-monthly group)

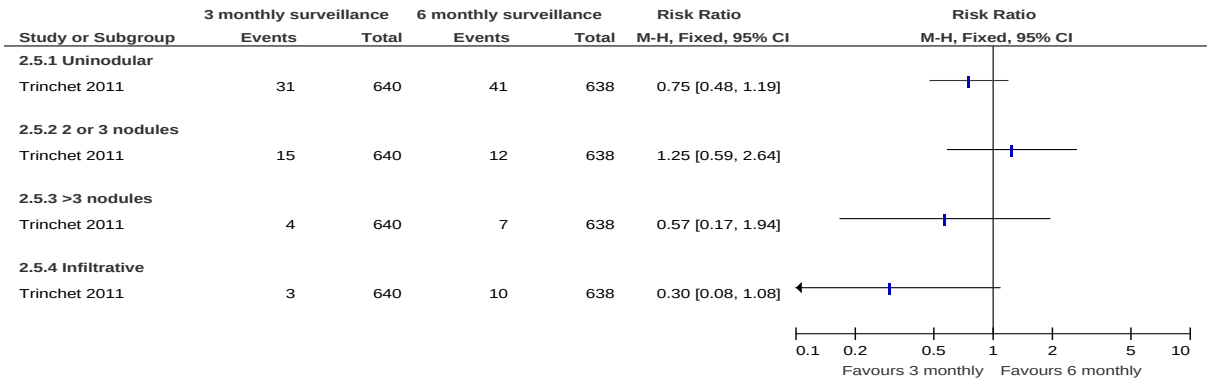


Figure 114: HCC stage (within Milan criteria: one nodule ≤50 mm or 2 or 3 nodules ≤30 mm; positive outcome, RR<1 indicates an advantage to the 6-monthly group)

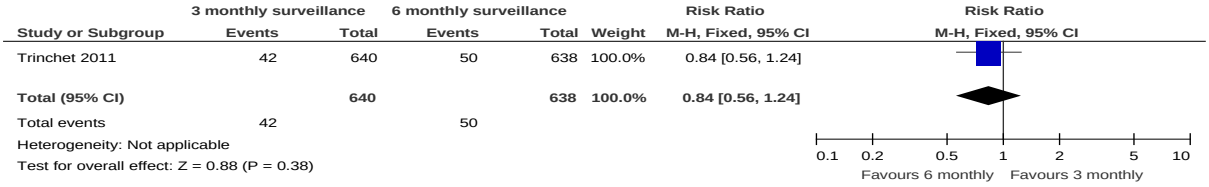


Figure 115: HCC stage (beyond Milan criteria: one nodule ≤50 mm or 2 or 3 nodules ≤30 mm; negative outcome, RR<1 indicates an advantage to the 3-monthly group)

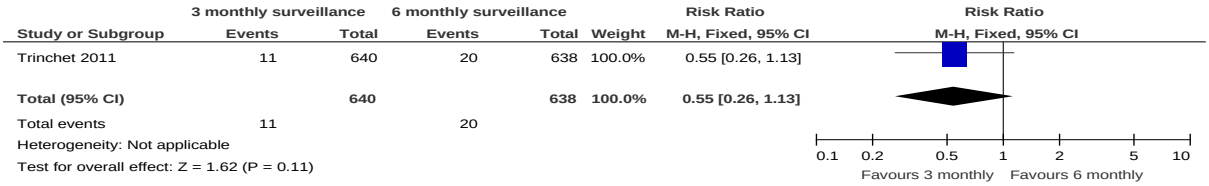
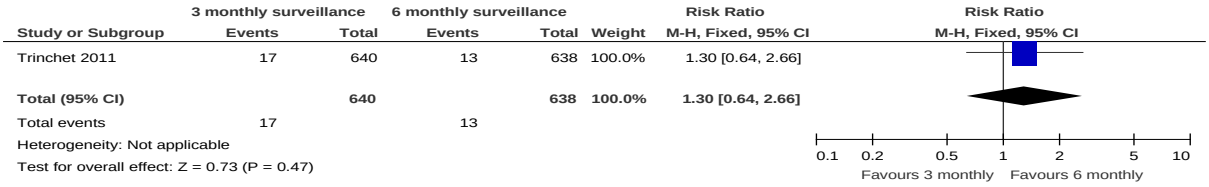


Figure 116: Liver transplant



K.5 Surveillance for the detection of varices

None

K.6 Prophylaxis of variceal haemorrhage

K.6.1 Non-selective beta-blockers versus placebo or no intervention

Size of varices (medium or large)

Figure 117: Survival

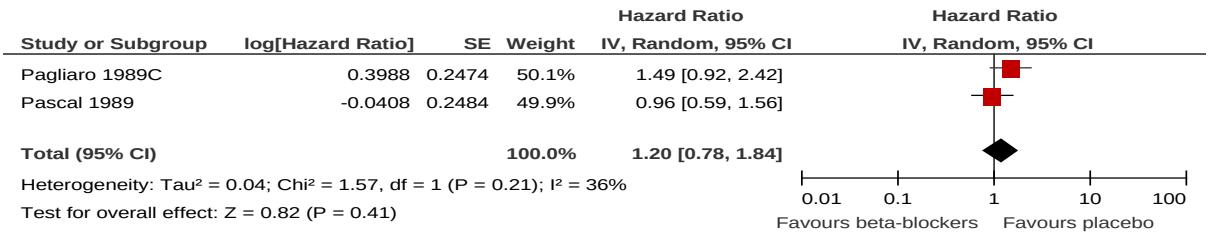


Figure 118: Variceal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andreani 1990	2	28	8	22	34.8%	0.20 [0.05, 0.83]
Conn 1991	0	25	9	22	18.8%	0.05 [0.00, 0.76]
Pagliaro 1989C	13	83	18	88	46.4%	0.77 [0.40, 1.46]
Total (95% CI)		**136**		**132**	**100.0%**	**0.28 [0.06, 1.30]**
Total events	15		35			

Heterogeneity: Tau² = 1.20; Chi² = 6.66, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 1.63 (P = 0.10)

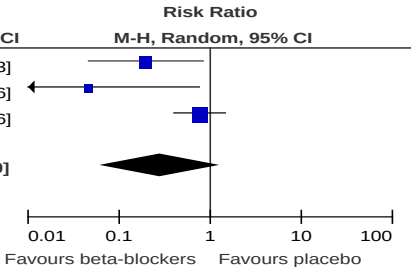


Figure 119: Upper gastrointestinal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andreani 1990	2	28	10	22	15.6%	0.16 [0.04, 0.64]
Pagliaro 1989C	18	83	31	88	41.8%	0.62 [0.37, 1.01]
Pascal 1989	20	116	30	111	42.6%	0.64 [0.39, 1.05]
Total (95% CI)		**227**		**221**	**100.0%**	**0.55 [0.39, 0.78]**
Total events	40		71			

Heterogeneity: Chi² = 3.54, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 3.42 (P = 0.0006)

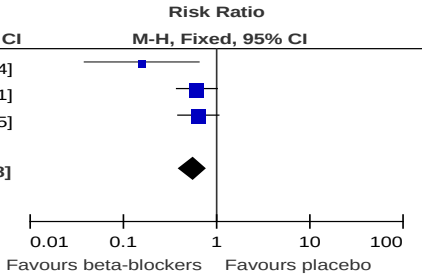
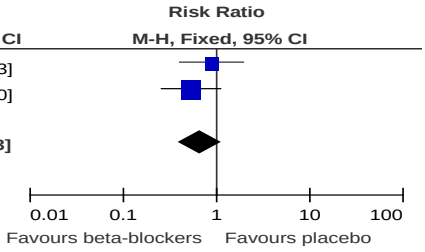


Figure 120: Bleeding-related mortality

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pagliaro 1989C	10	83	12	88	38.8%	0.88 [0.40, 1.93]
Pascal 1989	10	116	18	111	61.2%	0.53 [0.26, 1.10]
Total (95% CI)		**199**		**199**	**100.0%**	**0.67 [0.39, 1.13]**
Total events	20		30			

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



Size of varices (small)

Figure 121: Mortality

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2013	3	77	2	73	100.0%	1.42 [0.24, 8.27]
Total (95% CI)		**77**		**73**	**100.0%**	**1.42 [0.24, 8.27]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

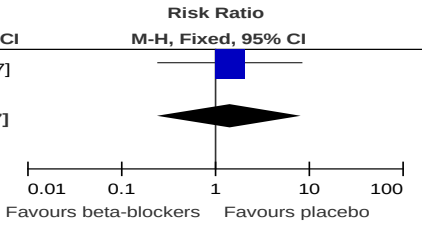


Figure 122: Variceal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andreani 1990	0	15	2	17	20.3%	0.23 [0.01, 4.35]
Conn 1991	2	26	2	29	44.4%	1.12 [0.17, 7.36]
Sarin 2013	4	77	1	73	35.3%	3.79 [0.43, 33.14]
Total (95% CI)		**118**		**119**	**100.0%**	**1.24 [0.31, 5.00]**
Total events	6		5			

Heterogeneity: Tau² = 0.21; Chi² = 2.31, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 0.30 (P = 0.76)

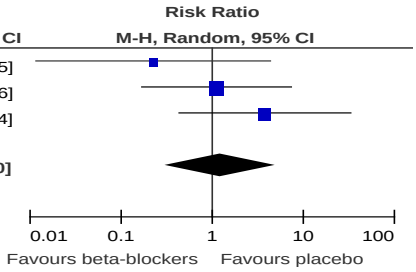
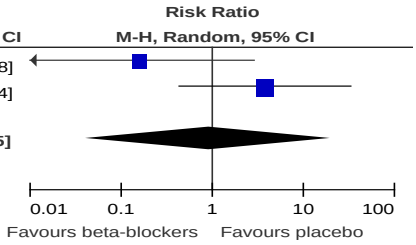


Figure 123: Upper gastrointestinal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andreani 1990	0	15	3	17	45.3%	0.16 [0.01, 2.88]
Sarin 2013	4	77	1	73	54.7%	3.79 [0.43, 33.14]
Total (95% CI)		**92**		**90**	**100.0%**	**0.90 [0.04, 20.15]**
Total events	4		4			

Heterogeneity: Tau² = 3.36; Chi² = 2.98, df = 1 (P = 0.08); I² = 66%
Test for overall effect: Z = 0.06 (P = 0.95)



K.6.2 Band ligation versus no intervention

Size of varices (medium or large)

Figure 124: Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Lay 1997	-0.8916	0.2729	57.5%	0.41 [0.24, 0.70]
Lo 1999	-0.4155	0.3176	42.5%	0.66 [0.35, 1.23]
Total (95% CI)			**100.0%**	**0.50 [0.33, 0.75]**

Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%
Test for overall effect: Z = 3.33 (P = 0.0009)

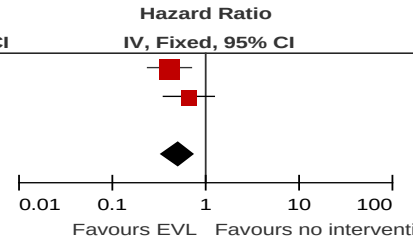


Figure 125: Mortality

Study or Subgroup	EVL Events	Total	no intervention Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 1996	4	35	8	33	29.8%	0.47 [0.16, 1.42]
Svoboda 1999	12	52	19	50	70.2%	0.61 [0.33, 1.12]
Total (95% CI)		**87**		**83**	**100.0%**	**0.57 [0.33, 0.97]**
Total events	16		27			

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

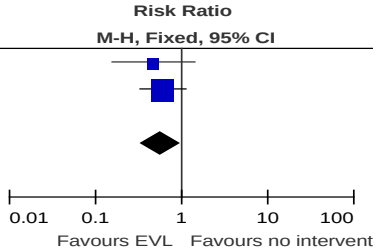


Figure 126: Free from variceal bleeding

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Lay 1997	-1.1087	0.2877	69.1%	0.33 [0.19, 0.58]
Lo 1999	-0.5276	0.4298	30.9%	0.59 [0.25, 1.37]
Total (95% CI)			**100.0%**	**0.39 [0.25, 0.63]**

Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 3.89 (P = 0.0001)

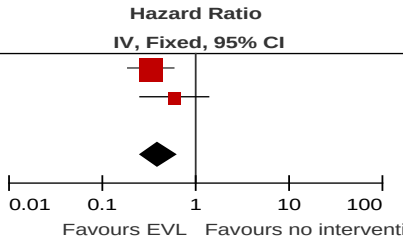


Figure 127: Variceal bleeding

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
Sarin 1996	3	35	13	33	33.1%	0.22 [0.07, 0.70]
Svoboda 1999	15	52	27	50	66.9%	0.53 [0.32, 0.88]
Total (95% CI)		**87**		**83**	**100.0%**	**0.40 [0.17, 0.93]**
Total events	18		40			

Heterogeneity: Tau² = 0.22; Chi² = 2.05, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.13 (P = 0.03)

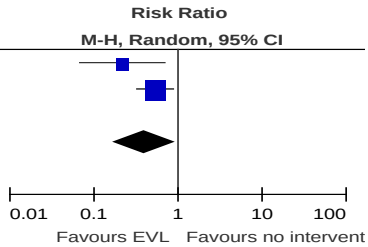


Figure 128: Upper gastrointestinal bleeding

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
Lay 1997	12	62	38	64	26.7%	0.33 [0.19, 0.56]
Lo 1999	14	64	22	63	25.7%	0.63 [0.35, 1.11]
Sarin 1996	3	35	13	33	11.3%	0.22 [0.07, 0.70]
Svoboda 1999	15	52	27	50	28.6%	0.53 [0.32, 0.88]
Triantos 2005	4	11	2	10	7.8%	1.82 [0.42, 7.87]
Total (95% CI)		**224**		**220**	**100.0%**	**0.49 [0.31, 0.76]**
Total events	48		102			

Heterogeneity: Tau² = 0.12; Chi² = 7.94, df = 4 (P = 0.09); I² = 50%
Test for overall effect: Z = 3.13 (P = 0.002)

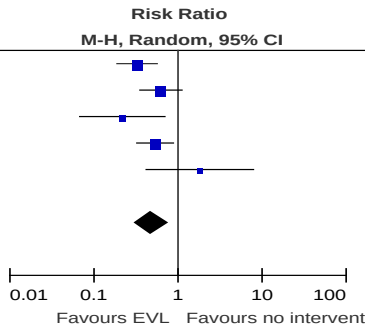
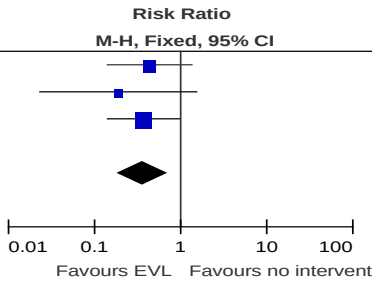


Figure 129: Bleeding-related mortality

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lo 1999	4	64	9	63	33.0%	0.44 [0.14, 1.35]
Sarin 1996	1	35	5	33	18.7%	0.19 [0.02, 1.53]
Svoboda 1999	5	52	13	50	48.2%	0.37 [0.14, 0.96]
Total (95% CI)		**151**		**146**	**100.0%**	**0.36 [0.18, 0.71]**
Total events	10		27			

Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.94 (P = 0.003)

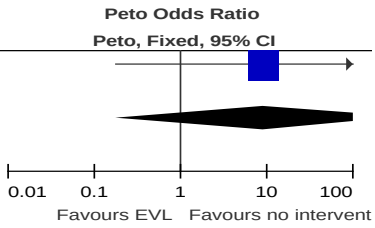


Size of varices (small)

Figure 130: Upper gastrointestinal bleeding

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Triantos 2005	1	14	0	17	100.0%	9.15 [0.18, 469.98]
Total (95% CI)		**14**		**17**	**100.0%**	**9.15 [0.18, 469.98]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



K.6.3 Band ligation versus non-selective beta-blockers

Size of varices (medium or large)

Figure 131: Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Drastich 2005	-0.2107	1.0017	1.7%	0.81 [0.11, 5.77]
Lui 2002	0.0862	0.3941	11.3%	1.09 [0.50, 2.36]
Perez 2010	0.392	0.3537	14.0%	1.48 [0.74, 2.96]
Psilopoulos 2005	-0.2357	0.4302	9.5%	0.79 [0.34, 1.84]
Schepke 2004	0.2151	0.2431	29.6%	1.24 [0.77, 2.00]
Shah 2014	-0.4308	0.3945	11.2%	0.65 [0.30, 1.41]
Tripathi 2009	-0.1054	0.2774	22.7%	0.90 [0.52, 1.55]
Total (95% CI)			**100.0%**	**1.03 [0.80, 1.34]**

Heterogeneity: Chi² = 3.69, df = 6 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

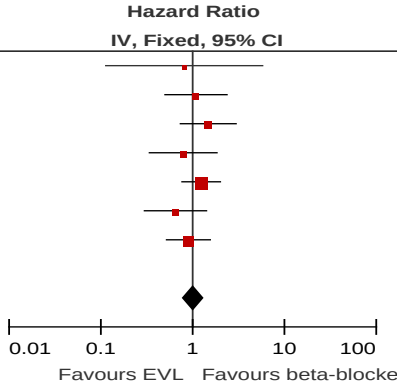


Figure 132: Mortality

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelfattah 2006	4	51	5	52	6.9%	0.82 [0.23, 2.87]
Abulfutuh 2003	13	44	24	66	26.7%	0.81 [0.47, 1.42]
Chen 1998	3	26	3	30	3.9%	1.15 [0.25, 5.23]
Gheorghe 2002	1	25	5	28	6.6%	0.22 [0.03, 1.79]
Jutabha 2005	0	31	4	31	6.3%	0.11 [0.01, 1.98]
Lay 2006	14	50	12	50	16.7%	1.17 [0.60, 2.27]
Mora 2000	0	12	1	12	2.1%	0.33 [0.01, 7.45]
Norberto 2007	3	31	3	31	4.2%	1.00 [0.22, 4.58]
Sarin 1999	5	46	5	44	7.1%	0.96 [0.30, 3.08]
Singh 2012	2	18	3	20	4.0%	0.74 [0.14, 3.94]
Song 2000	5	31	8	30	11.3%	0.60 [0.22, 1.64]
Thuluvath 2005	6	16	3	15	4.3%	1.88 [0.57, 6.19]
Total (95% CI)		**381**		**409**	**100.0%**	**0.83 [0.61, 1.13]**
Total events	56		76			

Heterogeneity: Chi² = 7.24, df = 11 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)

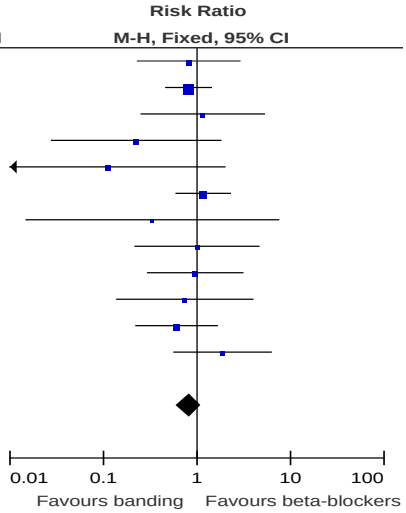


Figure 133: Free from variceal bleeding

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Drastich 2005	-0.4463	1.0063	7.9%	0.64 [0.09, 4.60]
Lui 2002	-0.7765	0.5928	14.4%	0.46 [0.14, 1.47]
Psilopoulos 2005	-1.5606	0.7701	11.1%	0.21 [0.05, 0.95]
Sarin 1999	-1.1087	0.4323	18.2%	0.33 [0.14, 0.77]
Schepke 2004	0.0488	0.3132	21.1%	1.05 [0.57, 1.94]
Shah 2014	-0.462	0.9033	9.1%	0.63 [0.11, 3.70]
Tripathi 2009	0.8755	0.4277	18.3%	2.40 [1.04, 5.55]
Total (95% CI)			**100.0%**	**0.68 [0.35, 1.31]**

Heterogeneity: Tau² = 0.45; Chi² = 15.55, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 1.16 (P = 0.25)

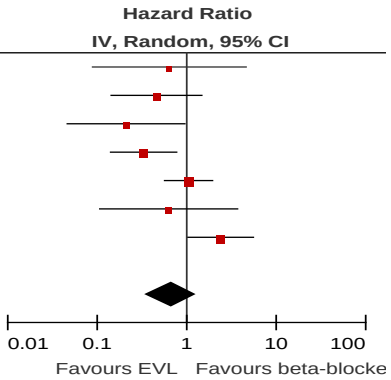


Figure 134: Variceal bleeding

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 1998	1	26	2	30	3.8%	0.58 [0.06, 6.00]
De 1999	2	15	1	15	2.0%	2.00 [0.20, 19.78]
Gheorghe 2002	3	25	13	28	25.0%	0.26 [0.08, 0.80]
Jutabha 2005	0	31	4	31	9.2%	0.11 [0.01, 1.98]
Lay 2006	5	50	8	50	16.3%	0.63 [0.22, 1.78]
Mora 2000	1	12	2	12	4.1%	0.50 [0.05, 4.81]
Norberto 2007	2	31	3	31	6.1%	0.67 [0.12, 3.72]
Perez 2010	2	39	9	36	19.1%	0.21 [0.05, 0.89]
Song 2000	3	31	6	30	12.4%	0.48 [0.13, 1.76]
Thuluvath 2005	2	16	1	15	2.1%	1.88 [0.19, 18.60]
Total (95% CI)		**276**		**278**	**100.0%**	**0.44 [0.27, 0.71]**
Total events	21		49			

Heterogeneity: Chi² = 6.72, df = 9 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)

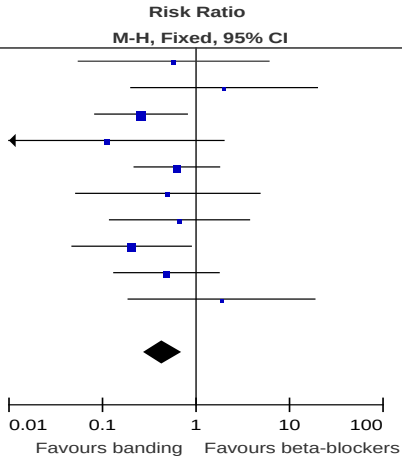


Figure 135: Upper gastrointestinal bleeding

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdelfattah 2006	4	51	13	52	5.5%	0.31 [0.11, 0.90]
Abulfutuh 2003	4	44	10	66	5.1%	0.60 [0.20, 1.79]
Chen 1998	1	26	2	30	1.3%	0.58 [0.06, 6.00]
De 1999	2	15	2	15	2.0%	1.00 [0.16, 6.20]
Drastich 2005	2	40	2	33	1.9%	0.82 [0.12, 5.54]
Gheorghe 2002	3	25	13	28	4.8%	0.26 [0.08, 0.80]
Jutabha 2005	0	31	4	31	0.8%	0.11 [0.01, 1.98]
Lay 2006	11	50	12	50	10.2%	0.92 [0.45, 1.88]
Lui 2002	3	44	9	66	4.1%	0.50 [0.14, 1.74]
Mora 2000	1	12	2	12	1.3%	0.50 [0.05, 4.81]
Norberto 2007	5	31	4	31	4.3%	1.25 [0.37, 4.22]
Perez 2010	5	39	9	36	6.1%	0.51 [0.19, 1.39]
Psilopoulos 2005	4	30	9	30	5.4%	0.44 [0.15, 1.29]
Sarin 1999	4	46	12	44	5.5%	0.32 [0.11, 0.91]
Schepke 2004	19	75	22	77	15.5%	0.89 [0.52, 1.50]
Shah 2014	6	86	7	82	5.6%	0.82 [0.29, 2.33]
Singh 2012	3	18	5	20	3.9%	0.67 [0.19, 2.40]
Song 2000	6	31	7	30	6.4%	0.83 [0.32, 2.18]
Thuluvath 2005	2	16	1	15	1.3%	1.88 [0.19, 18.60]
Tripathi 2009	17	75	8	77	9.0%	2.18 [1.00, 4.75]
Total (95% CI)		**785**		**825**	**100.0%**	**0.71 [0.54, 0.92]**
Total events	102		153			

Heterogeneity: Tau² = 0.05; Chi² = 21.96, df = 19 (P = 0.29); I² = 13%
Test for overall effect: Z = 2.56 (P = 0.01)

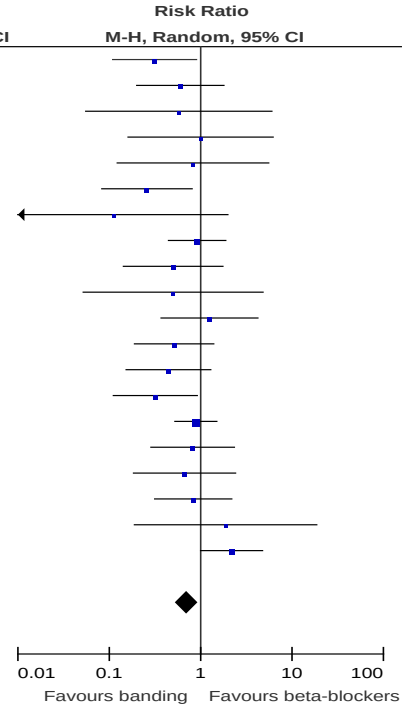


Figure 136: Bleeding-related mortality

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 1998	0	26	0	30		Not estimable
De 1999	0	15	0	15		Not estimable
Drastich 2005	1	40	1	33	2.7%	0.82 [0.05, 12.69]
Jutabha 2005	0	31	2	31	6.2%	0.20 [0.01, 4.00]
Lay 2006	1	50	2	50	5.0%	0.50 [0.05, 5.34]
Lui 2002	1	44	4	66	7.9%	0.38 [0.04, 3.24]
Norberto 2007	1	31	2	31	5.0%	0.50 [0.05, 5.23]
Perez 2010	2	39	3	36	7.7%	0.62 [0.11, 3.47]
Psilopoulos 2005	0	30	2	30	6.2%	0.20 [0.01, 4.00]
Sarin 1999	3	45	4	44	10.0%	0.73 [0.17, 3.09]
Schepke 2004	9	75	8	77	19.6%	1.16 [0.47, 2.83]
Shah 2014	4	86	4	82	10.2%	0.95 [0.25, 3.69]
Singh 2012	1	18	2	20	4.7%	0.56 [0.05, 5.62]
Thuluvath 2005	0	16	0	15		Not estimable
Tripathi 2009	3	75	6	77	14.7%	0.51 [0.13, 1.98]
Total (95% CI)		**621**		**637**	**100.0%**	**0.67 [0.42, 1.08]**
Total events	26		40			

Heterogeneity: Chi² = 3.54, df = 11 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

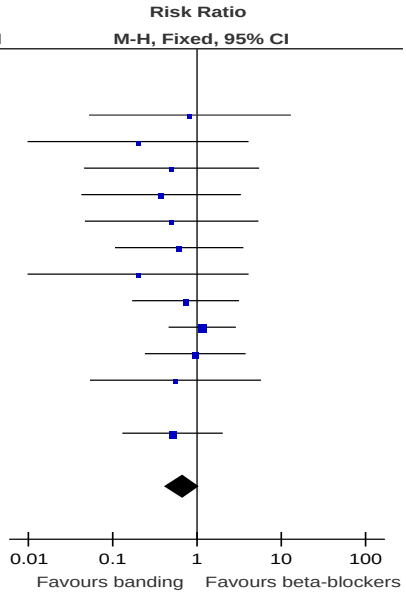


Figure 137: Hospitalisation

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 1999	5	45	12	44	100.0%	0.41 [0.16, 1.06]
Total (95% CI)		**45**		**44**	**100.0%**	**0.41 [0.16, 1.06]**
Total events	5		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

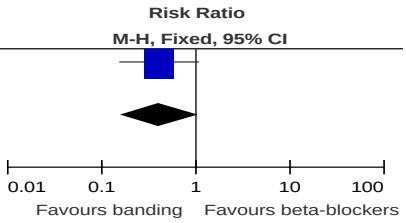
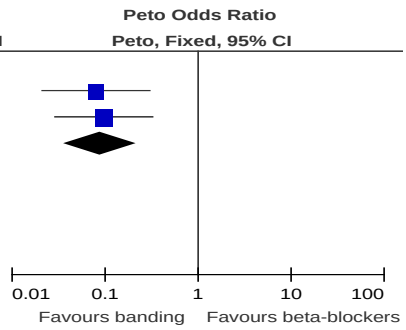


Figure 138: Adverse events: fatigue

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.14.9 Lethargy						
Drastich 2005	0	40	10	33	45.2%	0.08 [0.02, 0.30]
Sarin 1999	0	46	12	44	54.8%	0.10 [0.03, 0.32]
Subtotal (95% CI)		**86**		**77**	**100.0%**	**0.09 [0.04, 0.22]**
Total events	0		22			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 5.30 (P < 0.00001)



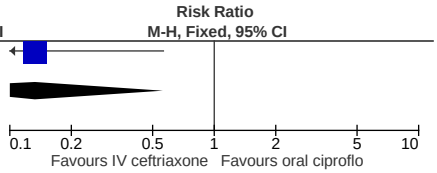
K.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

K.7.1 IV ceftriaxone 2 g versus oral ciprofloxacin 500 mg twice daily

Figure 139: Bacterial infections

Study or Subgroup	IV ceftriaxone 2g Events	Total	Oral ciprofloxacin 1000mg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2011	2	66	13	57	100.0%	0.13 [0.03, 0.56]
Total (95% CI)		**66**		**57**	**100.0%**	**0.13 [0.03, 0.56]**
Total events	2		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.74 (P = 0.006)



K.7.2 IV ceftriaxone 1 g versus oral norfloxacin 400 mg twice daily

Figure 140: Bacterial infections

Study or Subgroup	IV ceftriaxone 1g Events	Total	Oral norfloxacin 800 mg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez 2006	6	54	15	57	100.0%	0.42 [0.18, 1.01]
Total (95% CI)		**54**		**57**	**100.0%**	**0.42 [0.18, 1.01]**
Total events	6		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)

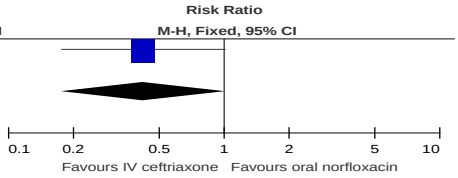
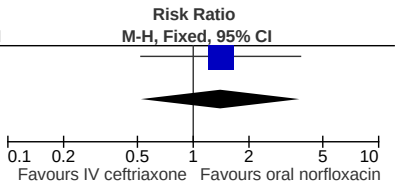


Figure 141: All-cause mortality (dichotomous)

Study or Subgroup	IV ceftriaxone 1g Events	Total	Oral norfloxacin 800 mg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez 2006	8	54	6	57	100.0%	1.41 [0.52, 3.79]
Total (95% CI)		**54**		**57**	**100.0%**	**1.41 [0.52, 3.79]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

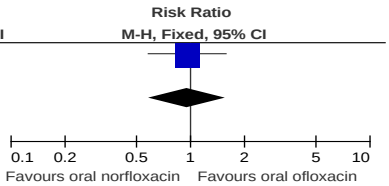


K.7.3 Oral norfloxacin 800 mg versus oral ofloxacin 400 mg

Figure 142: Bacterial infections

Study or Subgroup	Oral norfloxacin 800 mg Events	Total	Oral ofloxacin 400 mg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Spanish 1998	26	183	27	182	100.0%	0.96 [0.58, 1.58]
Total (95% CI)		**183**		**182**	**100.0%**	**0.96 [0.58, 1.58]**
Total events	26		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)



K.7.4 Oral norfloxacin 800 mg and IV ceftriaxone 2 g (combination) versus oral norfloxacin 800 mg (monotherapy)

Figure 143: Bacterial infections

Study or Subgroup	Oral norflox+IV ceftriax Events	Total	Oral norfloxacin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sabat 1998	3	24	4	22	100.0%	0.69 [0.17, 2.73]
Total (95% CI)		**24**		**22**	**100.0%**	**0.69 [0.17, 2.73]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)

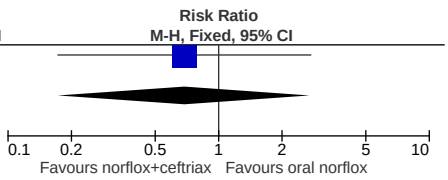


Figure 144: All-cause mortality (dichotomous)

Study or Subgroup	Oral norflox+IV ceftriax Events	Total	Oral norflox Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sabat 1998	1	24	2	22	100.0%	0.46 [0.04, 4.71]
Total (95% CI)		**24**		**22**	**100.0%**	**0.46 [0.04, 4.71]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)

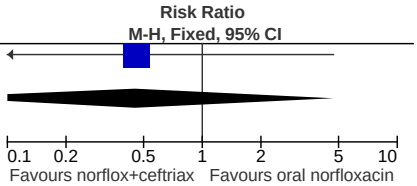
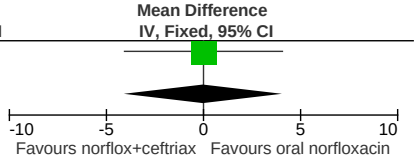


Figure 145: Length of hospital stay (days)

Study or Subgroup	Oral norflox+IV ceftriax Mean	SD	Total	Oral norflox Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sabat 1998	12	8	24	12	6	22	100.0%	0.00 [-4.07, 4.07]
Total (95% CI)			**24**			**22**	**100.0%**	**0.00 [-4.07, 4.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

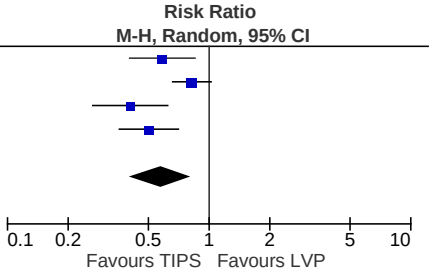


K.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Figure 146: Re-accumulation of ascites

Study or Subgroup	TIPS Events	Total	LVP Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gines 2002	17	35	29	35	23.9%	0.59 [0.40, 0.85]
Narahara 2011	23	30	28	30	28.9%	0.82 [0.66, 1.02]
Salerno 2004	13	33	32	33	22.1%	0.41 [0.26, 0.62]
Sanyal 2003	22	52	48	57	25.1%	0.50 [0.36, 0.70]
Total (95% CI)		**150**		**155**	**100.0%**	**0.57 [0.40, 0.82]**
Total events	75		137			

Heterogeneity: Tau² = 0.10; Chi² = 14.05, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 3.06 (P = 0.002)



Note: One study (Narahara 2011) defined complete response as the elimination of ascites – therefore the number of people that did not have a complete response were calculated as having recurrence of ascites

Figure 147: Health-related quality of life: SF-36 – physical and mental component

Study or Subgroup	TIPS Mean	SD	Total	LVP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.2.1 Physical score								
Sanyal 2003	2.33	12	52	5.69	10	57	100.0%	-3.36 [-7.53, 0.81]
Subtotal (95% CI)			**52**			**57**	**100.0%**	**-3.36 [-7.53, 0.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
3.2.2 Mental score								
Sanyal 2003	1.83	7.6	52	3.96	10	57	100.0%	-2.13 [-5.45, 1.19]
Subtotal (95% CI)			**52**			**57**	**100.0%**	**-2.13 [-5.45, 1.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.26 (P = 0.21)								

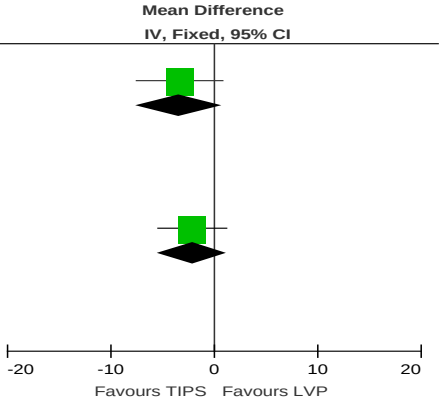
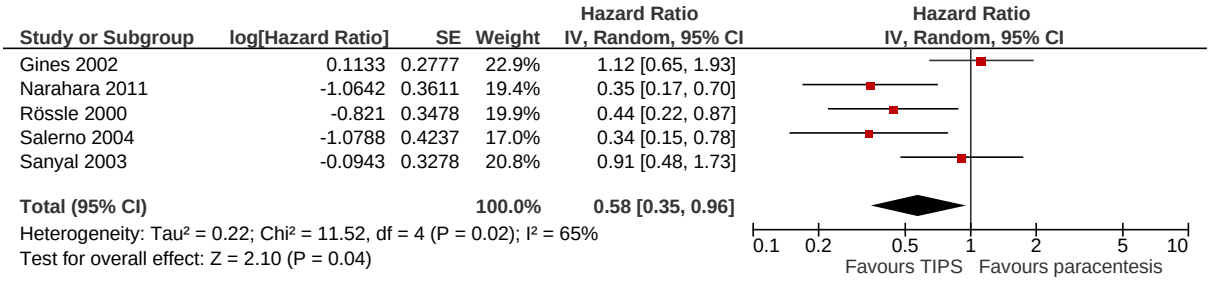


Figure 148: Transplant-free survival



Note: One study reported overall survival but no patients had transplantation (Narahara 2011).

Figure 149: Spontaneous bacterial peritonitis

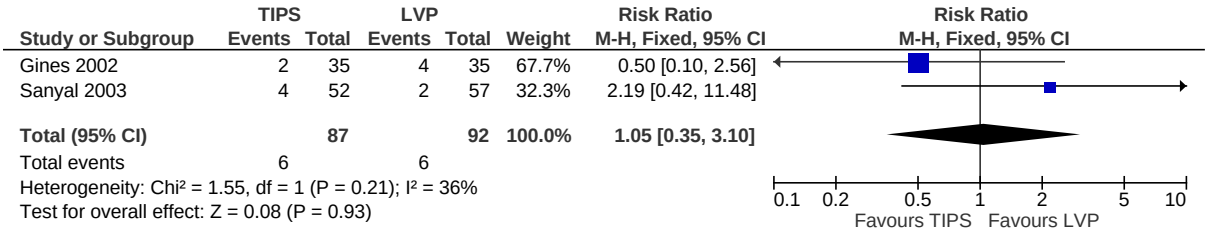


Figure 150: Renal failure

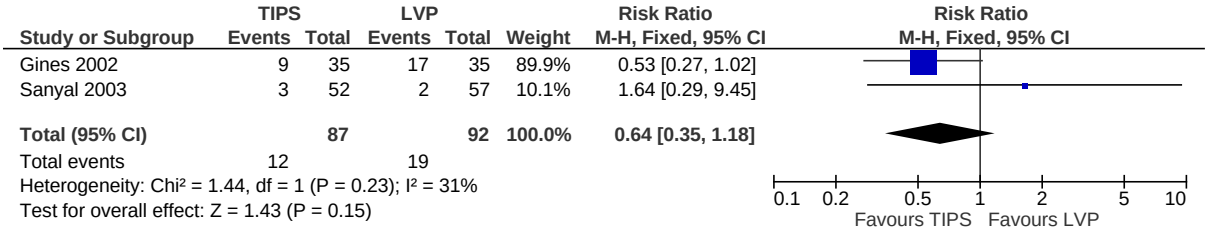
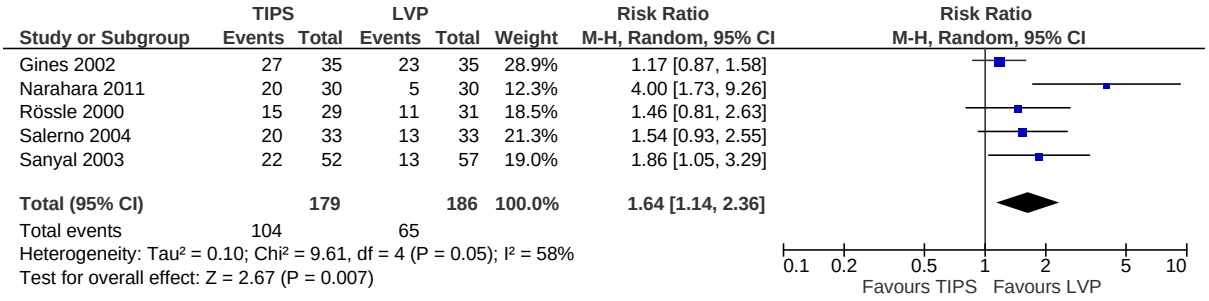


Figure 151: Hepatic encephalopathy

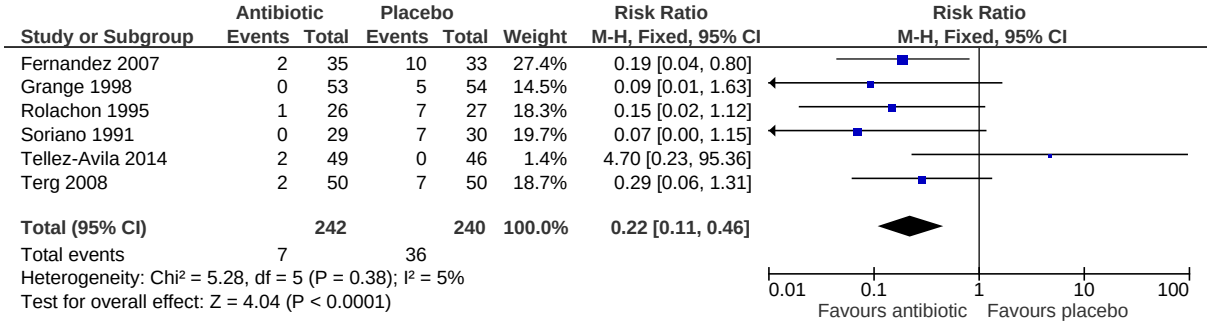


Hepatic encephalopathy (HE) was an exclusion criteria in all studies, however some studies reported new cases of HE, some worsening cases of HE and some relapse of HE

K.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

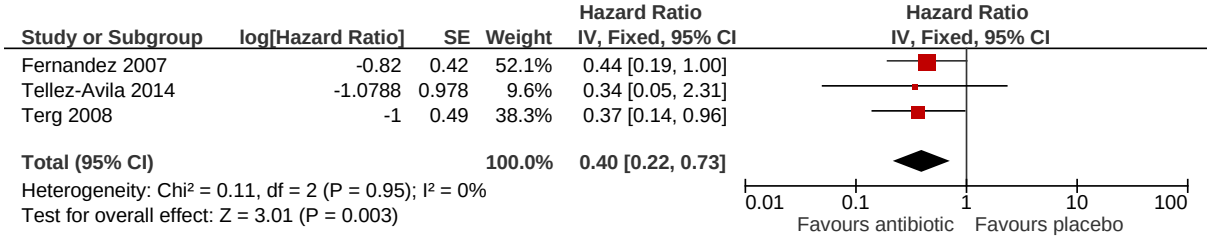
K.9.1 SBP

Figure 152: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites



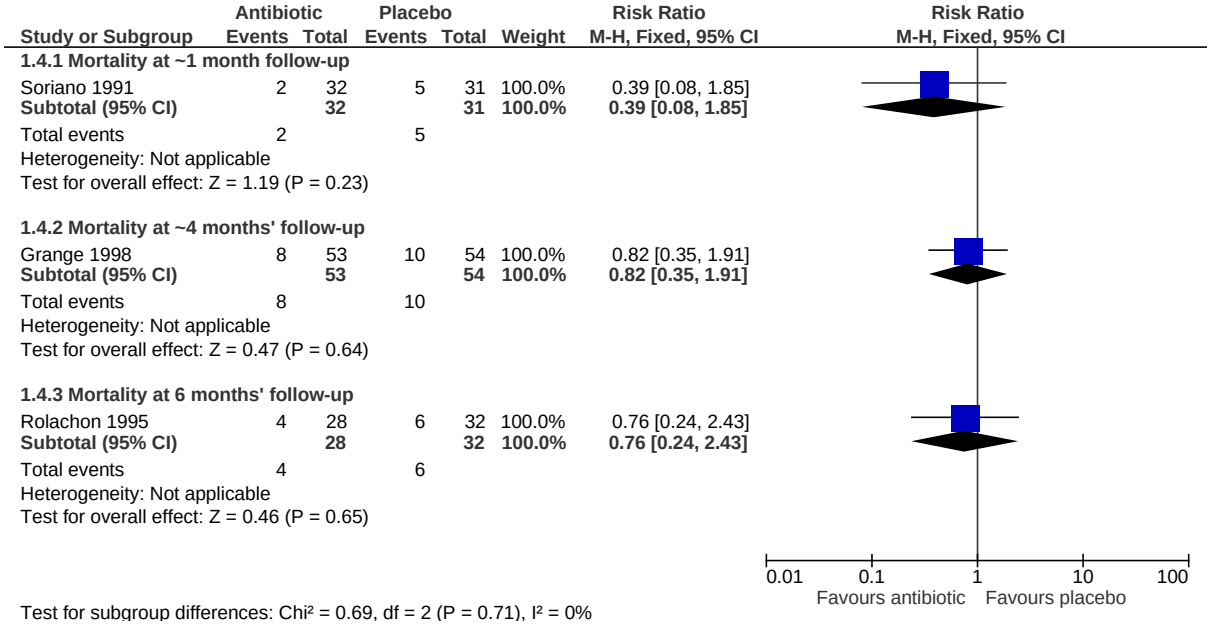
K.9.2 All-cause mortality (time-to-event)

Figure 153: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites



K.9.3 All-cause mortality (dichotomous)

Figure 154: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

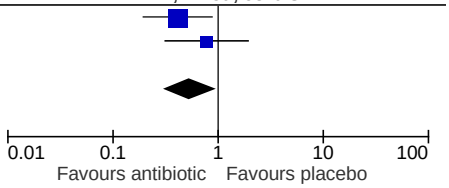


K.9.4 Adverse event: renal failure

Figure 155: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez 2007	7	35	16	33	64.7%	0.41 [0.19, 0.87]
Terg 2008	7	50	9	50	35.3%	0.78 [0.31, 1.93]
Total (95% CI)		**85**		**83**	**100.0%**	**0.54 [0.31, 0.96]**
Total events	14		25			

Heterogeneity: Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 2.10 (P = 0.04)

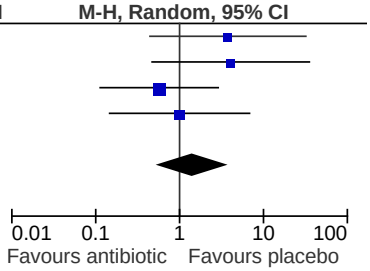


K.9.5 Adverse event: liver failure

Figure 156: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Fernandez 2007	4	35	1	33	20.3%	3.77 [0.44, 32.03]
Grange 1998	4	53	1	54	19.9%	4.08 [0.47, 35.28]
Rolachon 1995	2	28	4	32	34.7%	0.57 [0.11, 2.89]
Terg 2008	2	50	2	50	25.0%	1.00 [0.15, 6.82]
Total (95% CI)		**166**		**169**	**100.0%**	**1.43 [0.54, 3.79]**
Total events	12		8			

Heterogeneity: Tau² = 0.03; Chi² = 3.09, df = 3 (P = 0.38); I² = 3%
Test for overall effect: Z = 0.71 (P = 0.48)

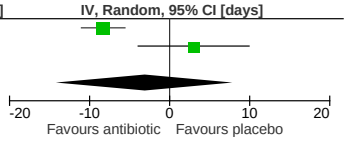


K.9.6 Length of hospital stay

Figure 157: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Mean [days]	Antibiotic SD [days]	Antibiotic Total	Placebo Mean [days]	Placebo SD [days]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [days]
Rolachon 1995	9.3	4.5	28	17.6	6.2	32	54.1%	-8.30 [-11.02, -5.58]
Soriano 1991	27	15	32	24	13	31	45.9%	3.00 [-3.92, 9.92]
Total (95% CI)			**60**			**63**	**100.0%**	**-3.12 [-14.15, 7.92]**

Heterogeneity: Tau² = 56.64; Chi² = 8.86, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.55 (P = 0.58)



K.10 Volume replacers in hepatorenal syndrome

None

K.11 Management of an episode of acute hepatic encephalopathy

K.11.1 Non-absorbable disaccharides versus single therapy

K.11.1.1 Non-absorbable disaccharides versus neomycin

Figure 158: Mortality

Study or Subgroup	Non-absorb disaccharides Events	Non-absorb disaccharides Total	Neomycin Events	Neomycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Uribe 1981	1	8	1	10	100.0%	1.25 [0.09, 17.02]
Total (95% CI)		**8**		**10**	**100.0%**	**1.25 [0.09, 17.02]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)

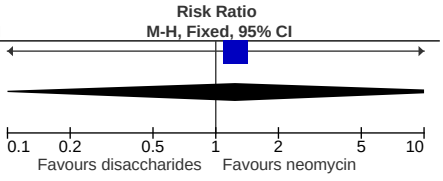


Figure 159: Clinical-biochemical improvement (improvement of 1 grade in mental state (Conn's grading 0-4), a reduction of 30s in time taken to perform the NCT and ammonia reduction of 50ug%)

Study or Subgroup	Non-absorb disaccharides Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Uribe 1981	7	8	7	10	100.0%	1.25 [0.77, 2.03]
Total (95% CI)		**8**		**10**	**100.0%**	**1.25 [0.77, 2.03]**
Total events	7		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.37)

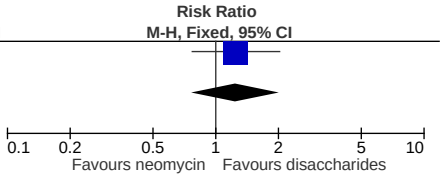
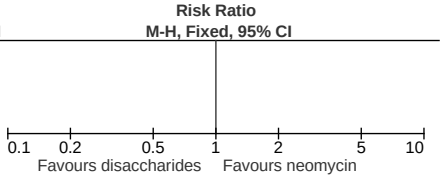


Figure 160: Side Effects

Study or Subgroup	Non-absorb disaccharides Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Uribe 1981	0	8	0	10		Not estimable
Total (95% CI)		**8**		**10**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



K.11.1.2 Non-absorbable disaccharides versus Rifaximin

Figure 161: Mortality (considered unrelated to medication; at 28 days)

Study or Subgroup	Non-absorb disacchrides Events	Total	Rifaximin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mas 2003	2	53	1	50	100.0%	1.89 [0.18, 20.17]
Total (95% CI)		**53**		**50**	**100.0%**	**1.89 [0.18, 20.17]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

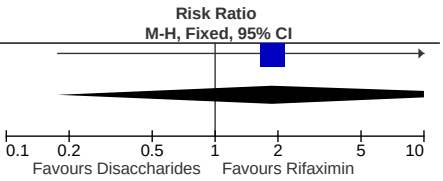


Figure 162: Unchanged/failure (hepatic encephalopathy clinical syndrome not improved and blood ammonia levels not decreased / increase in blood ammonia, increase in PSE index and/or a shift to a higher stage of hepatic encephalopathy)

Study or Subgroup	Non-absorb disacchrides Events	Total	Rifaximin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mas 2003	10	53	9	50	100.0%	1.05 [0.46, 2.36]
Total (95% CI)		**53**		**50**	**100.0%**	**1.05 [0.46, 2.36]**
Total events	10		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

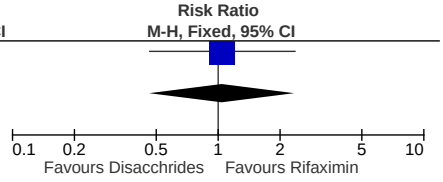


Figure 163: Improvement in hepatic encephalopathy grade (at 7 days)

Study or Subgroup	Non-absorb disacchrides Events	Total	Rifaximin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Paik 2005	16	22	26	32	100.0%	0.90 [0.66, 1.21]
Total (95% CI)		**22**		**32**	**100.0%**	**0.90 [0.66, 1.21]**
Total events	16		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

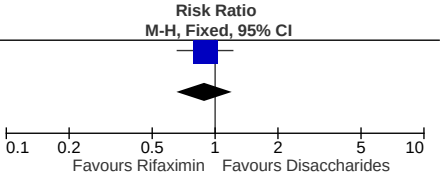


Figure 164: Improvement in hepatic encephalopathy index (taking into account hepatic encephalopathy grade, NCT, blood ammonia and severity of flapping tremor; at 7 days)

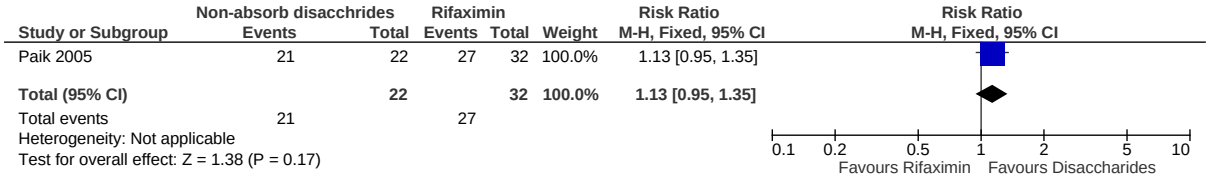
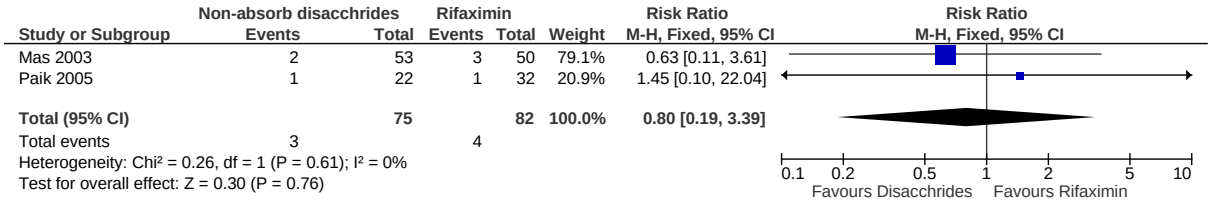


Figure 165: Adverse Events



K.11.1.3 Non-absorbable disaccharides versus BCAA

Figure 166: Mortality (up to 10 days after mental recovery)

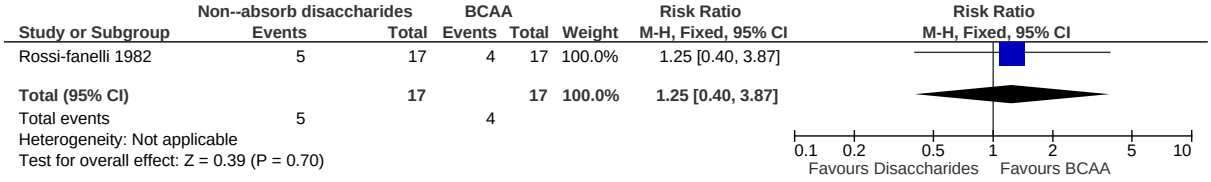


Figure 167: Complete mental recovery (study 1 defines as consciousness regained and returned to grade 0 hepatic encephalopathy; study 2 defines as come out of coma by day 7)

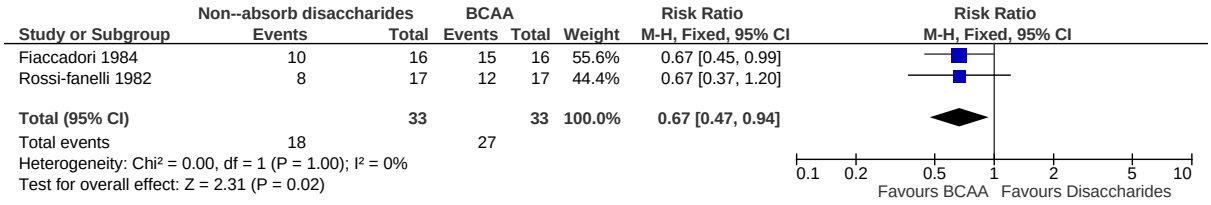
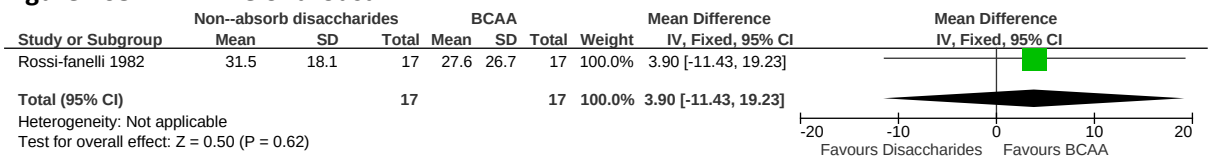


Figure 168: Time of arousal



K.11.1.4 Non-absorbable disaccharides versus PEG 3350

Figure 169: Mortality (at 24 hours)

Study or Subgroup	Non-absorb disaccharide Events	Total	PEG 3350 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rahimi 2014	2	25	1	25	100.0%	2.00 [0.19, 20.67]
Total (95% CI)		**25**		**25**	**100.0%**	**2.00 [0.19, 20.67]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

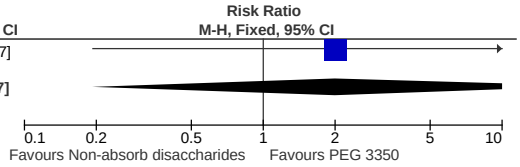


Figure 170: Hepatic encephalopathy resolution (defined as an improvement to grade 0, or two days at grade 1 after an initial improvement of at least 1 grade)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Rahimi 2014	-0.5621	0.3108	100.0%	0.57 [0.31, 1.05]
Total (95% CI)			**100.0%**	**0.57 [0.31, 1.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)

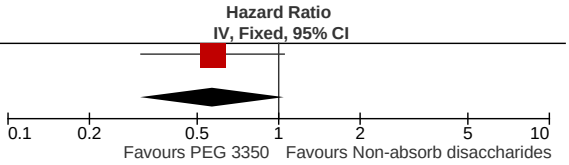


Figure 171: Improvement of 1 or more in hepatic encephalopathy grade (hepatic encephalopathy SA score; at 24 hours)

Study or Subgroup	Non-absorb disaccharides Events	Total	PEG 3350 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rahimi 2014	13	25	21	23	100.0%	0.57 [0.38, 0.85]
Total (95% CI)		**25**		**23**	**100.0%**	**0.57 [0.38, 0.85]**
Total events	13		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.78 (P = 0.005)

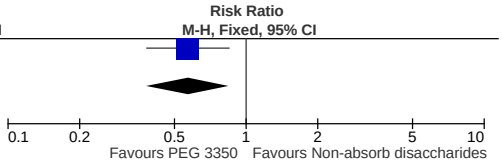


Figure 172: Length of hospital stay (days)

Study or Subgroup	Non-absorb disaccharides Mean	SD	Total	PEG 3350 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rahimi 2014	8	12	25	4	3	25	100.0%	4.00 [-0.85, 8.85]
Total (95% CI)			**25**			**25**	**100.0%**	**4.00 [-0.85, 8.85]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.11)

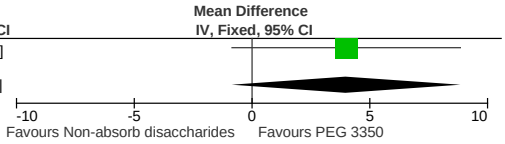
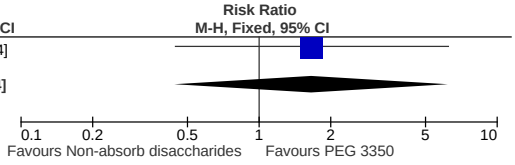


Figure 173: Adverse events (at 24 hours)

Study or Subgroup	Non-absorb disaccharides Events	Total	PEG 3350 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rahimi 2014	5	25	3	25	100.0%	1.67 [0.45, 6.24]
Total (95% CI)		**25**		**25**	**100.0%**	**1.67 [0.45, 6.24]**
Total events	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)



K.11.1.5 Non-absorbable disaccharides versus probiotics

Figure 174: Improvement in hepatic encephalopathy symptoms (at day 10)

Study or Subgroup	Non-absorb disaccharides Events	Total	Pro-biotics Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Loguercio 1987	14	19	15	19	100.0%	0.93 [0.65, 1.33]
Total (95% CI)		**19**		**19**	**100.0%**	**0.93 [0.65, 1.33]**
Total events	14		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

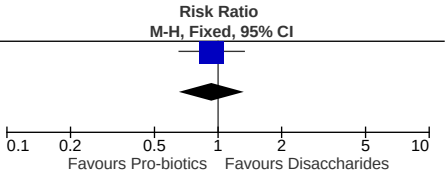
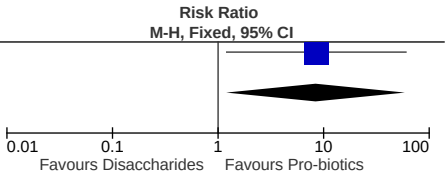


Figure 175: Adverse Events (at 20 days)

Study or Subgroup	Non-absorb disaccharides Events	Total	Pro-biotics Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Loguercio 1987	8	15	1	16	100.0%	8.53 [1.21, 60.33]
Total (95% CI)		**15**		**16**	**100.0%**	**8.53 [1.21, 60.33]**
Total events	8		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)



K.11.1.6 Non-absorbable disaccharides versus sodium benzoate

Figure 176: Mortality

Study or Subgroup	Non-absorb disaccharides Events	Total	Sodium benzoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sushma 1992	7	36	8	38	100.0%	0.92 [0.37, 2.29]
Total (95% CI)		**36**		**38**	**100.0%**	**0.92 [0.37, 2.29]**
Total events	7		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

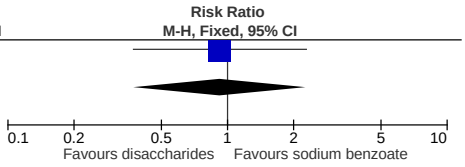


Figure 177: Complete response (recovery to normal mental status with no evidence of asterixis)

Study or Subgroup	Non-absorb disaccharides Events	Total	Sodium benzoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sushma 1992	29	36	30	38	100.0%	1.02 [0.81, 1.28]
Total (95% CI)		**36**		**38**	**100.0%**	**1.02 [0.81, 1.28]**
Total events	29		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

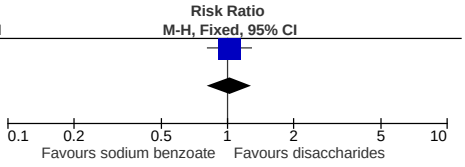


Figure 178: Continued in grade 1+ mental status despite therapy for 21 days

Study or Subgroup	Non-absorb disaccharides Events	Total	Sodium benzoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sushma 1992	1	36	3	38	100.0%	0.35 [0.04, 3.23]
Total (95% CI)		**36**		**38**	**100.0%**	**0.35 [0.04, 3.23]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)

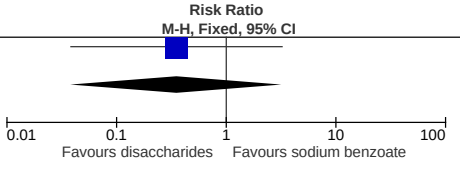
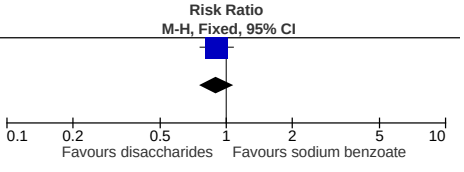


Figure 179: Complications during treatment

Study or Subgroup	Non-absorb disaccharides Events	Total	Sodium benzoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sushma 1992	30	36	35	38	100.0%	0.90 [0.76, 1.08]
Total (95% CI)		**36**		**38**	**100.0%**	**0.90 [0.76, 1.08]**
Total events	30		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)



K.11.2 Combination therapy (1 intervention + non-absorbable disaccharides) versus non-absorbable disaccharides

K.11.2.1 Rifaximin + non-absorbable disaccharides versus non-absorbable disaccharides

Figure 180: Mortality

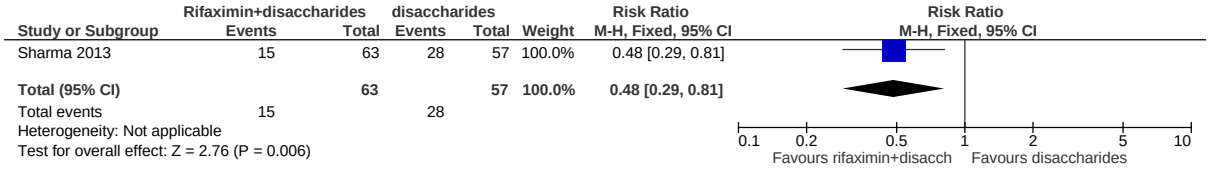


Figure 181: Complete reversal of hepatic encephalopathy (according to West Haven criteria; at 10 days)

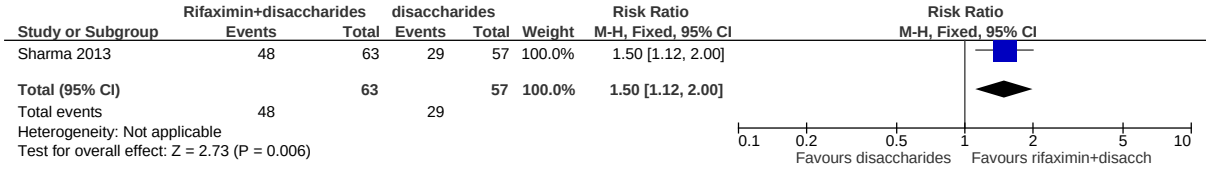


Figure 182: Length of Hospital Stay

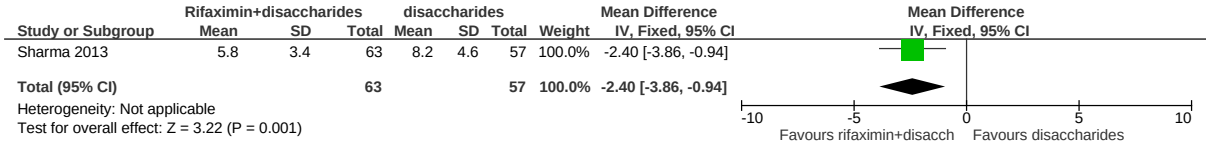
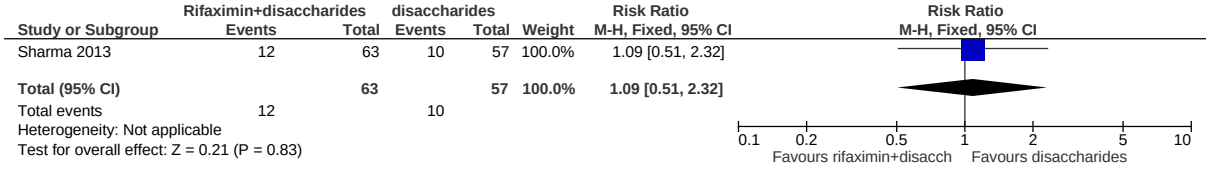


Figure 183: Side effects related to study medications



K.11.2.2 BCAA + non-absorbable disaccharides versus non-absorbable disaccharides

Figure 184: Mortality (at 16 days)

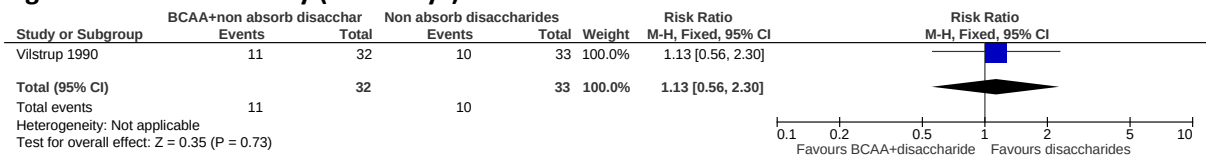


Figure 185: Wake up (study 1 defines as woke up to hepatic encephalopathy grade 0 or I by Fogarty classification at 16 days; study 2 defines as came out of coma by day 7)

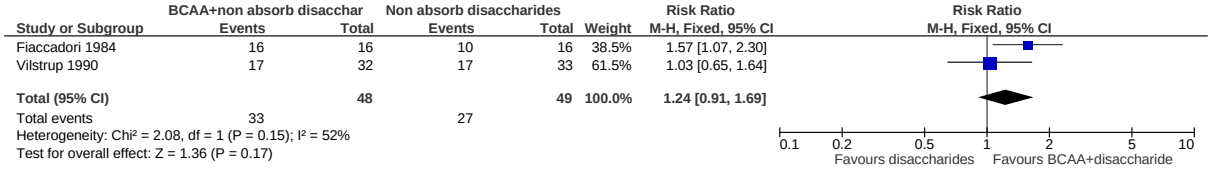
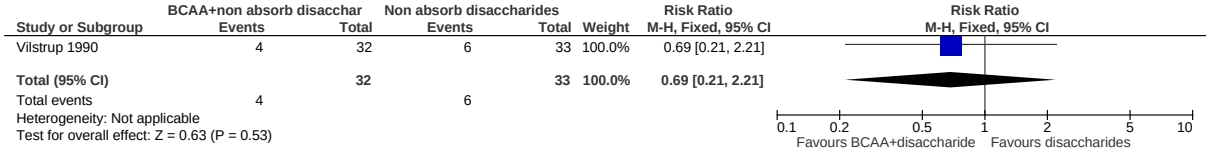


Figure 186: Treatment failures other than death (hepatic encephalopathy deeper than grade I (Fogarty classification) despite other improvements; at 16 days)



K.11.2.3 Flumazenil + non-absorbable disaccharides versus non-absorbable disaccharides

Figure 187: Mortality (during the observation period, 3hr treatment + 5hr observation)

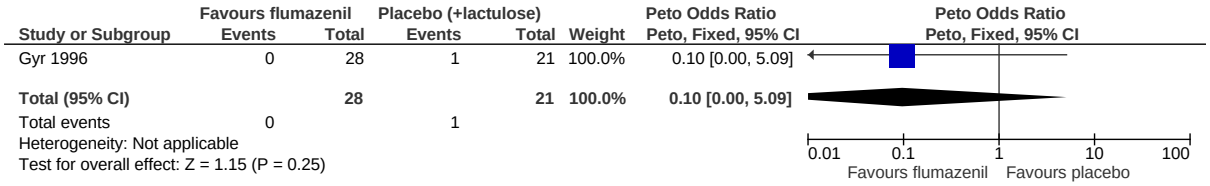


Figure 188: Clinically relevant response (improvement of at least 2 points in PSE score, PSE score on a 0-16 scale, at 8 hours)

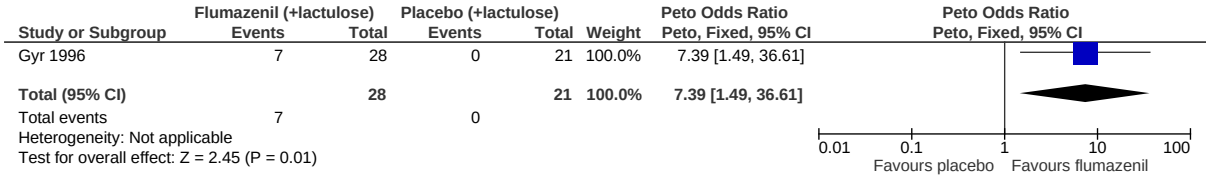
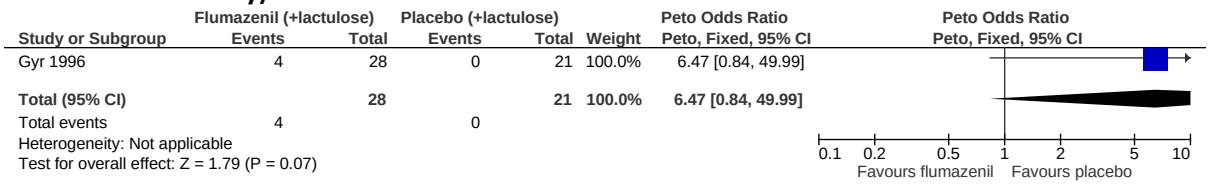


Figure 189: Adverse events ((at 8 hours) – flushing, nausea and vomiting, nausea and irritability)



K.11.3 Combination therapy (2 interventions + non-absorbable disaccharides) versus combination therapy (1 intervention + non-absorbable disaccharides)

K.11.3.1 Flumazenil + BCAA + non-absorbable disaccharides versus BCAA + non-absorbable disaccharides

Figure 190: Mortality at 24 hours

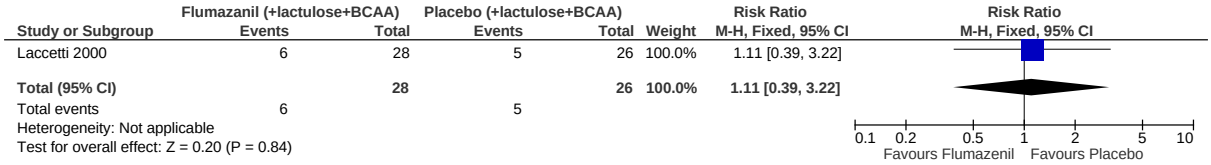


Figure 191: Improvement in neurological status (Increase in Glasgow coma score by 3 points; at 24 hours

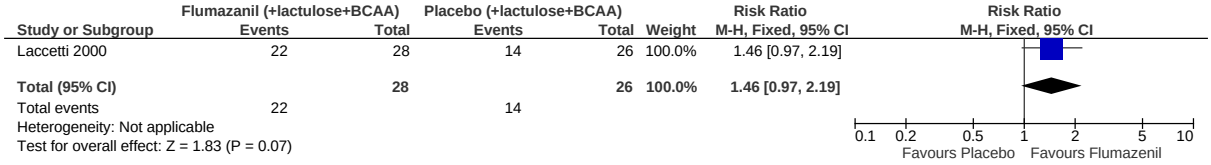
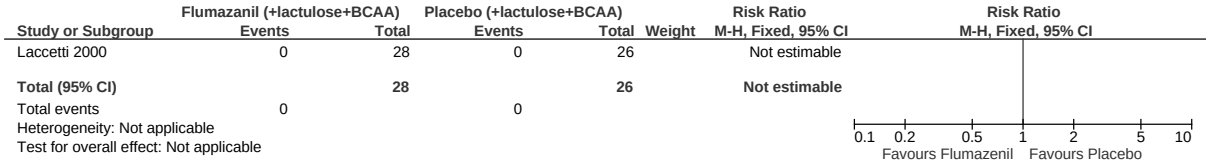


Figure 192: Side effects (at 24 hours)



K.11.3.2 LOLA + metronidazole + non-absorbable disaccharides versus metronidazole + non-absorbable disaccharides

Figure 193: Mortality during inpatient stay

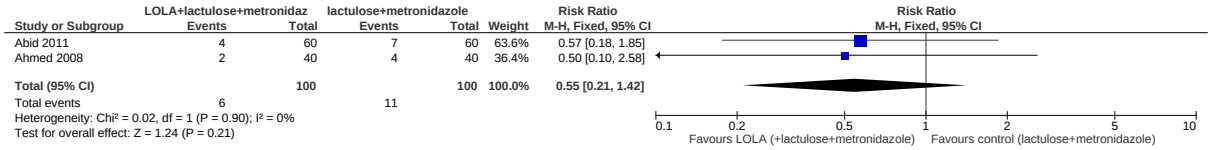


Figure 194: Complete improvement defined as improvement of 2 grades from baseline (day 3)

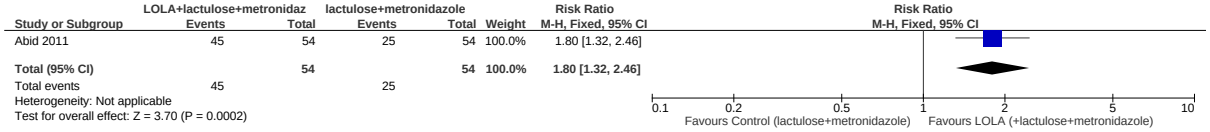


Figure 195: Achieved hepatic encephalopathy grade 0 (at 5 days)

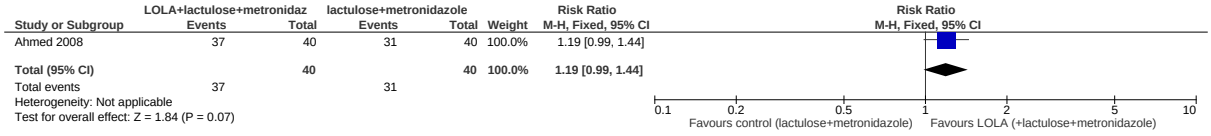
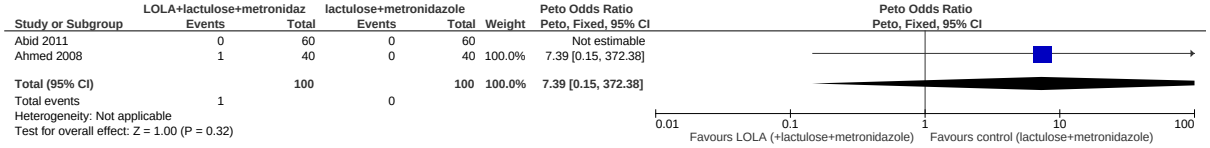


Figure 196: Adverse events



K.11.4 Single therapy versus placebo

K.11.4.1 Non-absorbable disaccharides versus placebo

Figure 197: Mortality (variable follow-up time and response dependent)

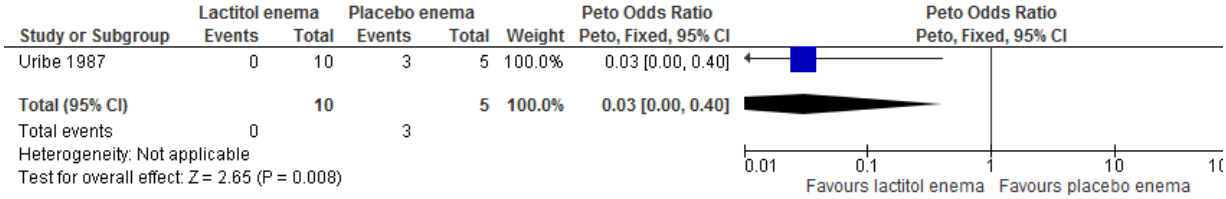
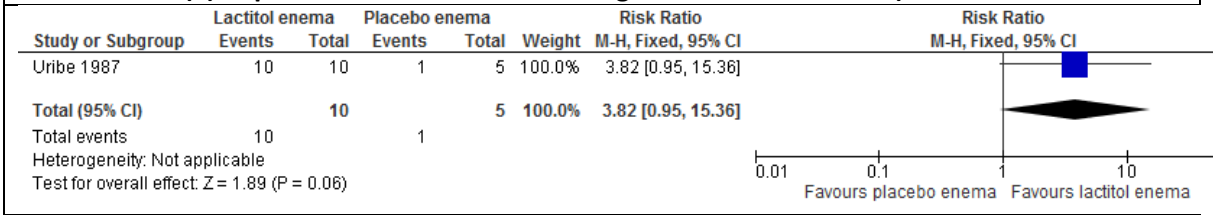


Figure 198: Therapeutic response (variable follow-up time and response dependent; defined as (i) sustained improvement of one grade in mental state during ≤48 hours or (ii) improvement of more than two grades in mental state.)



K.11.4.2 BCAA versus placebo

Figure 199: Mortality (at 5 days)

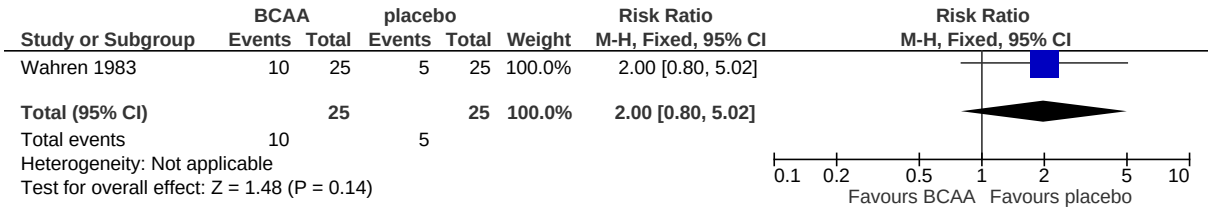
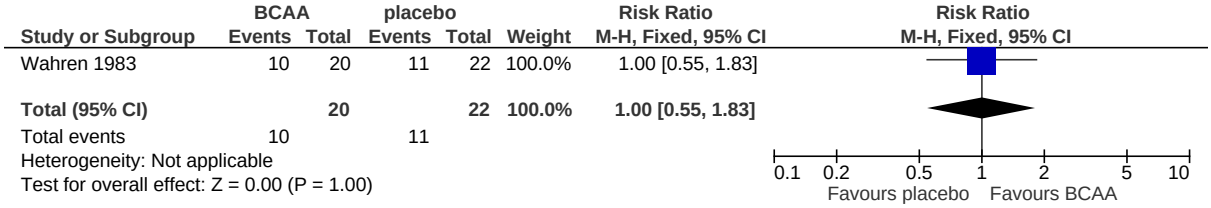


Figure 200: Positive response to treatment (at 5 days)



K.11.4.3 Neomycin (+BCAA in grades III and IV) versus placebo (+BCAA in grades III and IV)

Figure 201: Mortality (at 5 days)

Study or Subgroup	Neomycin (+/- BCAA) Events	Total	Placebo (+/- BCAA) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strauss 1992	2	20	2	19	100.0%	0.95 [0.15, 6.08]
Total (95% CI)		**20**		**19**	**100.0%**	**0.95 [0.15, 6.08]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

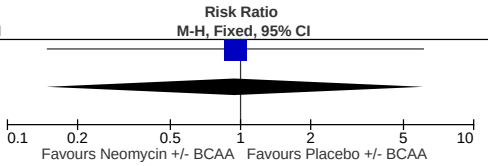
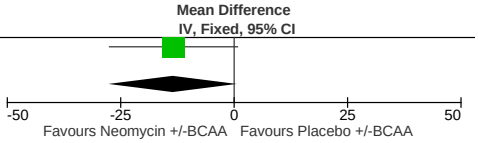


Figure 202: Time until regression to grade 0 hepatic encephalopathy

Study or Subgroup	Neomycin (+/- BCAA) Mean	SD	Total	Placebo (+/- BCAA) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Strauss 1992	36.11	23.04	20	49.47	21.92	19	100.0%	-13.36 [-27.47, 0.75]
Total (95% CI)			**20**			**19**	**100.0%**	**-13.36 [-27.47, 0.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)



K.11.5 Single therapy versus single therapy

K.11.5.1 BCAA versus neomycin

Figure 203: Mortality

Study or Subgroup	BCAA Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerra 1983	2	12	4	10	14.6%	0.42 [0.10, 1.82]
Cerra 1985	14	40	22	35	78.7%	0.56 [0.34, 0.91]
Strauss 1986	2	16	2	16	6.7%	1.00 [0.16, 6.25]
Total (95% CI)		**68**		**61**	**100.0%**	**0.57 [0.36, 0.89]**
Total events	18		28			

Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.44 (P = 0.01)

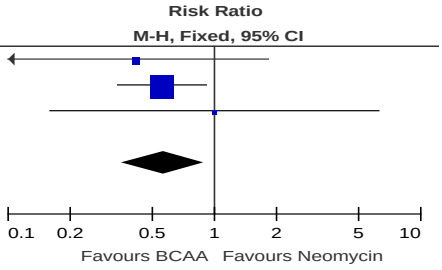


Figure 204: Improvement to grade 0 hepatic encephalopathy

Study or Subgroup	BCAA Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerra 1983	5	9	2	8	100.0%	2.22 [0.58, 8.44]
Total (95% CI)		**9**		**8**	**100.0%**	**2.22 [0.58, 8.44]**
Total events	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)

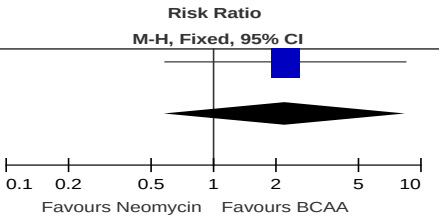


Figure 205: Improvement to grade 0 or 1 hepatic encephalopathy

Study or Subgroup	BCAA Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerra 1983	8	9	6	8	100.0%	1.19 [0.75, 1.88]
Total (95% CI)		**9**		**8**	**100.0%**	**1.19 [0.75, 1.88]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

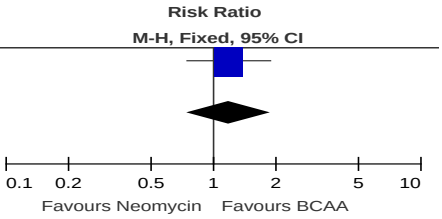
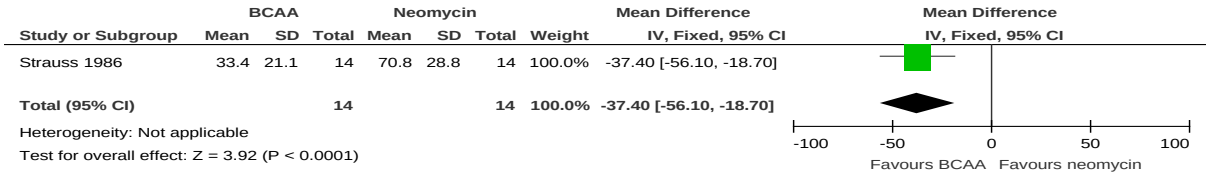


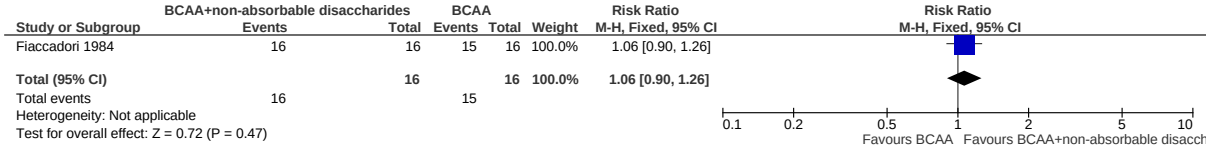
Figure 206: Time to recovery (hours)



K.11.6 Combination therapy (1 intervention + non-absorbable disaccharides) versus single therapy

K.11.6.1 BCAA + non-absorbable disaccharides versus BCAA

Figure 207: Came out of coma (at 7 days)



K.11.7 MARS versus standard medical therapy

K.11.7.1 MARS versus standard medical therapy

Figure 208: Mortality (at 5 days)

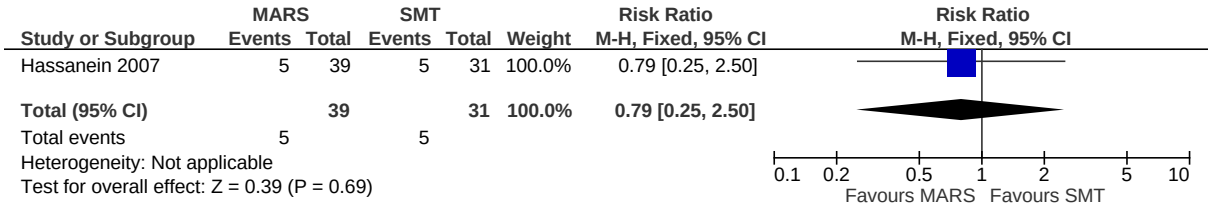


Figure 209: Responder (improvement of hepatic encephalopathy by 2 grades at any time; at 5 days)

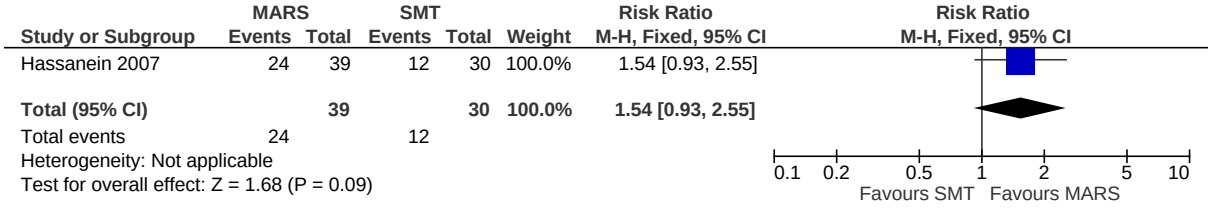
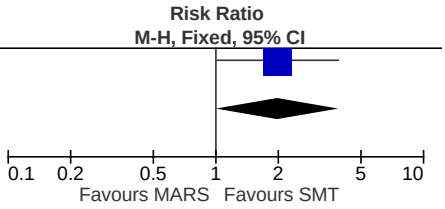


Figure 210: Serious adverse events (at 5 days)

Study or Subgroup	MARS Events	MARS Total	SMT Events	SMT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hassanein 2007	20	39	8	31	100.0%	1.99 [1.02, 3.89]
Total (95% CI)		**39**		**31**	**100.0%**	**1.99 [1.02, 3.89]**
Total events	20		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)



Appendix L: Excluded clinical studies

L.1 Risk factors and risk assessment tools

Table 54: Studies excluded from the clinical review

Reference	Reason for exclusion
Anon 2006[4]	Conference abstract. Genetic test to predict cirrhosis likelihood in people with hepatitis C.
Becker 1996[72]	Data incorporated in another included study
Bellentani 1997[75]	Incorrect study design: cross-sectional study with retrospective assessment of alcohol consumption for prediction of current cirrhosis
Bellentani 1999[74]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Carulli 2015[138]	Study pertains to genetic risk factors not identified in protocol
Chen 2011[166]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Chen 2014D[167]	Conference abstract of descriptive case-control study; no longitudinal follow-up; not prognostic study
Corrao 1998[198]	Systematic review, checked for references
Craxi 1987[200]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Curto 2011[207]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Day 2001[214]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Delahall 1992[216]	Review paper
Delahooke 2000[226]	Review containing studies of incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Deleuran 2012[227]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse versus a control group)
Demeulenaere 1977A[229]	Review paper
Dhyani 2015[232]	Narrative review
Dragosics 1987[238]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Durbec 1981[244]	Incorrect study design (case-control study)
Dyal 2015[245]	Conference abstract of a systematic review; not enough information provided
Ebell 2003[246]	Incorrect study design (cross-sectional study, diagnosis of cirrhosis)
Everhart 2009[259]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Fattovich 1991[265]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Fernandez-Rodriguez 2013[276]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Freeman 2001[298]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)

Reference	Reason for exclusion
Freeman 2003A[299]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Garceau 1964[317]	Incorrect study design (examines previous alcohol intake and hepatitis status in current cirrhosis patients)
Garcia-Compean 2014[319]	Incorrect population (patients already have cirrhosis)
Ge 2015A[322]	Incorrect study design (looking at genetic polymorphisms contributing to susceptibility rather than clinical risk factors)
Goodgame 2003[347]	Review containing studies of incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Gordon 2015[348]	Incorrect study population (patients all already have chronic hepatitis C) Incorrect study design (looking at the association of other characteristics (such as race, private health insurance cover and genotype) with the risk of cirrhosis, rather than the risk of cirrhosis in people with hepatitis C compared to those without)
Gordon 1984[349]	Reports the future incidence of cirrhosis in people with various alcohol consumption levels, however does not report the relative risk adjusted for confounding factors
Harkisoen 2014[372]	Incorrect study design (not prognostic; cross-sectional design and population not followed up over time)
Hashemi 2015[373]	Incorrect study design (case-control study; no longitudinal follow-up) Incorrect study population (patients already had cirrhosis matched with healthy controls)
He 2015[377]	Systematic review looking at implications of genetic polymorphisms on alcoholic liver cirrhosis risk
Huang 2007[388]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Huang 2013[390]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Hui 2004A[392]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Huo 2000[398]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Huo 2000A[399]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Hsiang 2015[385]	Incorrect study population (patients already have cirrhosis)
Ieluzzi 2014[411]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Ikeda 1998[412]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B and C)
Iloeje 2006[415]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Innes 2013[423]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Ioannou 2005[425]	Additional analysis of a study already included in this review (Ioannou 2003)
Ioannou 2015[424]	Incorrect study design (case-control study; not prognostic; no longitudinal follow-up)
Jamal 2005[431]	Review paper checked for references
Jerkeman 2014[435]	Incorrect study design (cross-sectional study of associations of different

Reference	Reason for exclusion
	factors with cirrhosis; not prognostic; no longitudinal follow-up)
Kage 1997[445]	Assessing time to progression to cirrhosis in people with the risk factor (not relative risk in people with and without the risk factor)
Kamper-Jorgensen 2004[448]	Incorrect comparison (reference group [group without risk factor] had a level of drinking consistent with harmful drinking)
Khullar 2015[463]	Narrative review on diagnosis and treatment of hepatitis C
Klatsky 1981[480]	Reports the future incidence of cirrhosis in people with various alcohol consumption levels, however does not report the relative risk adjusted for confounding factors
Kramer 2005[489]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Lagging 2002[498]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Laspada 2013[494]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Lee 2013[515]	Risk assessment tool does not contain any risk factors stated in the protocol
Lee 2015[512]	Incorrect study population (patients with chronic hepatitis C). Incorrect intervention (comparing anti-hepatitis C treatment versus no treatment).
Levy 2015[519]	Incorrect study design (not prognostic study; no longitudinal follow-up; study aims to make associations between characteristics and alcoholic liver disease)
Marbet 1987[564]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Marcolongo 2009[565]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Mathurin 2007[579]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Mcmahon 1990[584]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Mcmahon 2009[585]	Review paper discussing natural history of hepatitis B
Meikle 2015[590]	Incorrect comparison (study is looking at increase of susceptibility to cirrhosis in people who are already drinkers; no comparison to non-drinkers)
Mittal 2015[600]	Conference abstract of prognostic study but provides insufficient information for data extraction
Murakami 1999[614]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Naveau 1997[629]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Naveau 2010[628]	Narrative paper
Nyberg 2015[644]	Conference abstract of cross-sectional, descriptive study; no longitudinal follow-up; not prognostic study
Park 2014[671]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Parrish 1991[673]	Review article checked for references
Pequignot 1978[684]	Incorrect study design: case-control study recruiting a group with ascitic cirrhosis and a control group from the general population and

Reference	Reason for exclusion
	retrospective assessment of alcohol consumption
Petta 2015[688]	Incorrect study design (not prognostic but case-control study). Incorrect study population (all patients already have hepatitis C).
Poh 2015[695]	Incorrect study population (study population already being treated for hepatitis B; patients would only get treatment for hepatitis B if it is already known that they have cirrhosis)
Poynard 1997[700]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Poynard 2001[704]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Pradat 2010[709]	Narrative paper
Qian 2014[715]	Incorrect study design (looks at hepatitis B and cirrhosis as predictors of liver metastasis in colorectal cancer)
Rodriguez-Torres 2006[737]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Safdar 2004[753]	Review article checked for references
Sheen 1996[797]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Shen 2015[799]	Study pertains to genetic risk factors not identified in protocol
Skog 1984[819]	Incorrect study design (not primary research study)
Sorensen 1984[827]	Reports the future incidence of cirrhosis in people with various alcohol consumption levels, however does not report the relative risk adjusted for confounding factors
Sorensen 1989[826]	Review article checked for references
Takase 1993[855]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Thein 2008[868]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Thein 2008A[867]	Meta-analysis containing studies of incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Trepo 2011[876]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors and ELF score)
Tuyns 1984A[893]	Incorrect study design: case-control study recruiting a group with cirrhosis and a control group from the general population and retrospective assessment of alcohol consumption
Verbaan 1998[904]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Whitfield 2015[927]	Incorrect study design (case-control study; comparison between people with and without cirrhosis and their alcohol consumption)
Wu 2003[940]	Reports the incidence of cirrhosis in people with and without hepatitis B, but does not report the relative risk adjusted for confounders
Xiong 2015[942]	Incorrect study population (all patients have cirrhosis already). Incorrect study design (not longitudinal, prognostic study).
Yilmaz 2014B[952]	Incorrect study design (diagnostic study rather than prognostic; cross-sectional study without longitudinal follow-up)
Yu 1997[959]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Yu 2008[960]	Incorrect study design (assesses the added effect of other risk factors in

Reference	Reason for exclusion
	subjects with hepatitis B)

L.2 Diagnostic tests

Table 55: Studies excluded from the clinical review

Reference	Reason for exclusion
ABDELWAHAB 1993[8]	Population does not match protocol (schistosomal hepatic fibrosis without cirrhosis)
ABELWAHAB 1995[11]	Population does not match protocol (people presenting with splenomegaly)
ADAMS 2011[16]	Reference standard does not match protocol (biopsy length range 6-50mm)
AFDHAL 2015[19]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
AHMED 2009[23]	Index test does not match protocol (α2-macroglobulin, haptoglobin, apolipoprotein A1 and APRI, but sensitivity and specificity of APRI only provided for the diagnosis of significant fibrosis and advanced fibrosis, not cirrhosis).
ALLAN 2014[30]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, length of biopsy not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
ANASTASIOU 2010[39]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, only subgroups into viral (hep C and hep B, and non-viral (alcohol, autoimmune hepatitis and NASH)). Reference standard does not match protocol (included if biopsy >10mm in length, mean 17mm, median 1 fragment).
ANDERSON 2000[40]	Reference standard does not match protocol (fibrosis staging score not stated, length of biopsy not stated).
ASBACH 2010[49]	Reference standard does not match protocol (length of biopsy not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis)
AUBE 1999[54]	Reference standard does not match protocol (length of biopsy not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis, subgroups only provided for those with compensated alcohol and compensated viral disease).
AUBE 2004[55]	Reference standard does not match protocol (included if biopsy ≥10mm in length). Study aims to identify Doppler US variables predicative of cirrhosis. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
BAVU 2011[70]	Reference standard does not match protocol (reference standard was a predicted fibrosis score based on serum markers, with liver biopsy only taken into account in 39/108 people).
BECKEBAUM 2010[71]	Population does not match protocol (fibrosis staging in liver transplant recipients, inclusion of different aetiological groups within the same analysis). Reference standard fibrosis scoring system does not match protocol.
BEN 2009[76]	Diagnostic accuracy of serum fibrosis markers to predict significant

Reference	Reason for exclusion
	fibrosis (METAVIR ≥F2) not cirrhosis.
BERZIGOTTI 2010[85]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
BOOZARI 2010[97]	Population does not match protocol (inclusion of different aetiological groups within the same analysis: 68.5% hep C; 28.2% hep B; 2.4% both).
BOTA 2013B[106]	Does not give diagnostic accuracy of ARFI for cirrhosis (only gives the number of people with discordance – a difference of at least 2 stages of fibrosis between METAVIR and ARFI)
BOTA 2015A[103]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (transient elastography)
BOTTERO 2009[108]	Reference standard does not match protocol (no minimum length stated, only 60% had a biopsy length ≥15mm, mean 17.0 range 2–35mm, mean portal tracts 12.3 range 3–25)
BOURLIERE 2006[110]	Reference standard does not match protocol (only 117 ⁄ 235 (50%) patients had a biopsy ≥15 mm, mean 16(7.5) mm and mean number of portal tracts 9.4 (5).
BOURLIERE 2008A[109]	Reference standard does not match protocol (only 282 ⁄ 467 (59%) patients had a biopsy >15 mm, mean 19.7(8.4) mm and median number of portal tracts 9 (range 2–36).
BOURSIER 2009[116]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (reliable biopsy of ≥15mm and/or ≥8 portal tracts only in 89.5%).
BOURSIER 2009A[114]	Systematic review (not all included studies had a liver biopsy criteria of ≥15mm). Used for references to identify original papers with a liver biopsy criteria ≥15mm)
BOURSIER 2012A[115]	Reference standard does not match protocol (only 79% patients had a biopsy >15 mm, mean 23(9))
BOURSIER 2013[117]	Reference standard does not match protocol (reliable liver biopsy was length ≥15mm and/or portal tracts ≥8, biopsy reliable in only 93.8% of patients, median 24 (IQR 18-30) mm – subgroup analysis of TE accuracy in reliable and unreliable biopsies but data not shown).
CALES 2010[127]	Index test does not match protocol
CALES 2010A[126]	Validation study
CALES 2014[128]	Development and internal validation study for a combination of fibrometer and fibroscan
CALES 2014[128]	Reference standard does not match protocol (analysis of 2 datasets (overall 93.5% biopsies >15mm and 8 portal tracts), reference standard biopsy length criteria does not meet protocol for one dataset, other dataset (Zarski 2012) already included in this review)
CALES 2015D[125]	Reference standard does not match protocol (reliable liver biopsy was length ≥15mm and/or portal tracts ≥8, biopsy reliable in only 93.5% of patients)
CALVARUSO 2013[131]	Reference standard does not match protocol (length of biopsy not stated).
CARRION 2006[136]	Population does not match protocol (HCV recurrence after liver transplant). Reference standard does not match protocol (no minimum biopsy length stated).
CARTON 2011[137]	Reference standard does not match protocol (length of biopsy not stated).

Reference	Reason for exclusion
CASSINOTTO 2013[141]	Reference standard does not match protocol (no minimum biopsy length stated, median 25mm range 10-51)
CASSINOTTO 2014[142]	Population does not match protocol (inclusion of different aetiological groups within the same analysis – subgroup analysis provided but only for mixed viral hepatitis and mixed alcoholic/NASH).
CASTERA 2005[146]	Reference standard does not match protocol (no minimum biopsy length stated, median length 17mm and median number of fragments 2)
CASTERA 2009[145]	Reference standard does not match protocol (no minimum biopsy length stated, median length 19.5mm and median number of fragments 2.9, length was ≥15 in 69% of patients)
CASTERA 2014A[144]	Reference standard does not match protocol (no minimum biopsy length, median length 19.5mm and median number of portal tracts 14, length was ≥15 in 75% of patients, not reported if all have ≥6 portal tracts)
CHANG2008[156]	Reference standard does not match protocol (liver biopsy only performed in 79%). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 48% hepatitis B)
CHANTELOUP 2004[158]	Conference abstract, not a full paper. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
CHEN 2012A[170]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
CHOI 2013[174]	Reference standard does not match protocol (no minimum biopsy length). Population does not match protocol (inclusion of different aetiological groups within the same analysis.
CHOONG 2012[177]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, 87% hepatitis B). Reference standard does not match protocol (length of biopsy not stated).
CHUNG 2013[183]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
COBBOLD 2010[185]	Article not available for copyright reasons
COCO 2007[186]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (range 12-54mm).
COLLI 1994[189]	Index test does not match protocol (Doppler waveform of hepatic veins)
COLOMBO 2012[191]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
CORPECHOT 2006[196]	Reference standard does not match protocol (biopsy length median 17mm (8-40mm) and the median number of fragments was 2, number of portal tracts not reported)
CORPECHOT 2014[197]	Reference standard does not match protocol (included biopsies >8mm, median 18mm (8-42mm), number of portal tracts not reported)
CRESPO 2012[202]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
CROSS 2010[203]	Reference standard does not match protocol (included biopsies >10mm or >10 portal tracts, mean 15mm (13-17mm), unknown if those <15mm had at least 6 portal tracts)
CROSSON 2015[204]	HTA systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this HTA was checked for relevant studies but not updated itself.
D'AMBROSIO[209]	Reference standard does not match protocol (inclusion criteria >10mm

Reference	Reason for exclusion
	and/or ≥12 portal tracts, median 30mm (10-45mm), median number of portal tracts not reported – some biopsies <15mm may not have contained enough portal tracts).
DE LÉDINGHEN 2012[220]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (inclusion criteria ≥11mm, median 25mm (IQR 20-30mm), number of portal tracts unknown).
DEFFIEUX 2015[224]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length range 6-40mm and portal tracts range 3-20).
DEGOS 2010[225]	Population does not match protocol (inclusion of different aetiological groups within the same analysis – subgroup analysis provided for HCV population but included people with HCV and HBV co-infection).
DI MARCO 2010[233]	Population does not match protocol (all patients have thalassaemia and some also have hepatitis C but results from all patients, regardless of aetiology, are combined).
DINESEN 2008[235]	Reference standard does not match protocol (length of biopsy not stated).
EL GUESIRY 2011[248]	Reference standard does not match protocol (length of biopsy not stated).
FERLITSCH 2010[269]	Conference abstract, not a full paper. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FERRAL 1992[281]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
FERRANTE 1968[282]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (details about biopsy, including length, not stated).
FERRIAOLI 2012[277]	Reference standard does not match protocol (no minimum biopsy length stated, mean 27(SD 8.0)mm, range 10-55mm, >15mm in 117/121 cases, number of portal tracts not reported).
FERRIAOLI 2012a[280]	Reference standard does not match protocol (no minimum biopsy length stated, median 25 (IQR 20-35)mm, but range not reported, number of portal tracts not reported).
FERRIAOLI 2013[278]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (no minimum biopsy length stated, mean 27(SD 8.0)mm but range not reported).
FILLY2002[288]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
FORESTIER 2010[291]	Reference standard does not match protocol (length of biopsy not stated).
FOUAD 2012[292]	Reference standard does not match protocol (length of biopsy not stated).
FOUCHER 2006[293]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FOUCHER2005[294]	Conference abstract, not a full paper. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FRAQUELLI 2007[296]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).

Reference	Reason for exclusion
FRAQUELLI 2014[295]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FRIEDRICH-RUST 2007[303]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FRIEDRICH-RUST 2009[306]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, HCV and HBV).Reference standard does not match protocol (not all patients had liver biopsy as the reference standard – 16/86 had proven cirrhosis but no biopsy and these patients included in the diagnostic accuracy calculation for cirrhosis F4).
FRIEDRICH-RUST 2010[302]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, Ludwig scoring system).
FRIEDRICH-RUST 2012[304]	Reference standard does not match protocol (inclusion criteria at least 10mm or ≥6 portal tracts, range 10-60mm, median number of portal tracts not reported – some biopsies <15mm may not have contained enough portal tracts).
FRIEDRICH-RUST 2015[300]	Article not in English
FROSSARD 2013[307]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
GAIA 2015[313]	Diagnostic accuracy of transient elastography to predict advanced fibrosis (METAVIR ≥F3) not cirrhosis.
GAIANI 1997[314]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
GANNE-CARRIE 2006[315]	Reference standard does not match protocol (median liver biopsy length 17mm, range 5-40mm, number of portal tracts not mentioned)
GARA 2013[316]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, mean length 13.4 (SD 6.8) and mean number of portal tracts 13 (SD 6)).
GE 2015[322]	Population does not match protocol (chronic hepatitis: 111 out of 120 people had hepatitis B)
GIANNINI 2003b[329]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GIORGIO 1986[336]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GOBEL 2015[343]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GODFREY 2012[344]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GOERTZ 2010[345]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 37% hepatitis B)
GOMEZ-DOMINGUEZ 2008[346]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GOSINK 1979[350]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within

Reference	Reason for exclusion
	the same analysis).
GOTO 2014[351]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
GRGUREVIC 2011[357]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, 19% Hep B).
GUZELBULUT 2011[364]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
HAKTANIR 2005[367]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Does not give diagnostic accuracy of Doppler Sonography for cirrhosis
HAMBERG 1996[369]	Reference standard does not match protocol (fibrosis scoring system does not match protocol).
HAQUE 2010[371]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HEDIN 2000[378]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
HESS 1989[381]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HORNG 2002[383]	Incorrect study design. Does not compare index test to reference standard.
HSIEH 2009[386]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 19% Hep B).
HULTCRANTZ 1993[393]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
HUWART 2007[402]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HUWART 2008[401]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HUWART 2008A[403]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
IACOBELLIS 2005[405]	Reference standard does not match protocol (included if contained 5 or more portal tracts, average length not reported).
ICHIKAWA 2012[407]	Reference standard does not match protocol (no biopsy performed).
ICHIKAWA 2015[408]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (not all had liver biopsy).
ICHIKAWA 2015A[406]	Population does not match protocol (various aetiologies with fibrosis and healthy volunteers)
ICHINO 2010[409]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).

Reference	Reason for exclusion
ILIOPOULOS 2007[414]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
ILIOPOULOS 2008[413]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
IMBERT-BISMUT 2001[416]	Reference standard does not match protocol (included if biopsy ≥10mm in length, number of portal tracts not mentioned).
IMPERIALE 2000[420]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
ISHIBASHI 2010[427]	Diagnostic test does not match protocol (ultrasound using microbubble transit time).
ISHIBASHI 2012[428]	Diagnostic test does not match protocol (ultrasound using microbubble transit time).
ISLAM 2005[429]	Reference standard does not match protocol (included if biopsy ≥10mm in length and at least 4 portal tracts)
KAMPHUES 2010[449]	Population does not match protocol (post liver transplant).
KANEDA 2006[450]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
KAROUI 2012[454]	Non-English language publication
KHAN 2008[461]	Diagnosis of significant fibrosis and advanced fibrosis, not cirrhosis.
KIM 2011[467]	Population does not match protocol (inclusion of people with hepatitis B (78%), hepatitis C and five living liver donors within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated).
KIRK 2009[478]	Reference standard does not match protocol (median biopsy length 12mm, median portal tracts 11, range not stated).
KOBAYASHI 2015[483]	Systematic review protocol does not match protocol (minimum biopsy length for reference standard not an inclusion criteria).
KOIZUMI 2011[485]	Reference standard does not match protocol (included if biopsy ≥12mm in length and if ≥5 portal tracts).
KRAMER 2014[488]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
KUMAR 2013[491]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
KURODA 2010[493]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
LADERO 2010[497]	Reference standard does not match protocol (included if biopsy ≥10mm in length, subgroup analysis of biopsies >15mm but data not shown, 84.1% had biopsy ≥15mm).
LEE 2010[510]	Reference standard does not match protocol (included if biopsy ≥10mm in length). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 77% Hep B).
LEE 2010A[516]	Population does not match protocol (inclusion of people with hepatitis B (76%) and hepatitis C within the same analysis).
LI 2014[522]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
LICHTINGHAGEN 2013[523]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).

Reference	Reason for exclusion
LUCIDARME 2009[541]	Assessing the influence of TE success rate and IQR/median ratio on the diagnostic accuracy (accuracy reported for IQR/median >21 and <21 but overall values not reported)
LIM (2005)[525]	Diagnostic test does not match protocol (ultrasound using microbubble transit time).
LIU 2007A[527]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
LIU 2015B[529]	Systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this review was checked for relevant studies but not updated itself.
LIM 2011[524]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
LIU 2011A[528]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
LUO 2002[543]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported, included if ≥5 portal tracts).
LUPSOR 2008[547]	Presumed overlap in patients with more recent larger study already included in this review (Lupsorplanten 2013). Both recruited from the same centre and recruitment started in May 2007.
LUPSOR 2010[546]	Diagnostic accuracy of transient elastography for cirrhosis Brunt F4 not reported as no patients in the population were diagnosed as F4.
LUTZ 2012[549]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
MACIAS-RODRIGUEZ 2011[553]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
MAHADEVA 2013[554]	Reference standard does not match protocol (no minimum biopsy criteria, median 13 (IQR 8-15)mm, number of portal tracts not stated).
MALIK 2010[560]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
MARMO 1993[567]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
MARTIN 2015[570]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
MARUYAMA 2009[573]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
MARUYAMA 2012A[572]	Diagnostic test does not match protocol (ultrasound using microbubble transit time). Reference standard does not match protocol (length of biopsy not stated).
MATHIESEN 2002[578]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
MAZUZAKI 2008[576]	Population does not match protocol (inclusion of hepatocellular carcinoma patients within the same analysis).
MCPHERSON 2010[587]	Reference standard does not match protocol (no minimum biopsy criteria, mean 22(±8)mm, range not reported, number of portal tracts not reported)

Reference	Reason for exclusion
MCPHERSON 2013[586]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
MEEK 1984[588]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
MOON 2013[605]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
MORIKAWA 2011[609]	Reference standard does not match protocol (median length of biopsy 18mm, range 10-25).
MOROSAN 2014[610]	Reference standard does not match protocol (no minimum biopsy criteria stated and mean not reported).
MYERS 2010[615]	Reference standard does not match protocol (no minimum biopsy criteria stated, median 2.4 (IQR 1.7–2.8) mm, 87% of biopsies were at least 1.5 cm long, number of portal tracts not reported).
NAALEINI 2013[617]	Non-English language publication
NAGATA 2003[619]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
NAHON 2006[621]	Reference standard does not match protocol (no minimum biopsy criteria, mean 15.8 (7.6)mm, range 4-50mm, number of portal tracts not stated).
NAHON 2008[620]	Reference standard does not match protocol (median length of biopsy 14mm, range 4-50).
NAVEAU 2005[633]	Reference standard does not match protocol (no minimum biopsy criteria, mean 15(0.5)mm, portal tracts 14.4(0.7), range not reported).
NAVEAU 2009[631]	Reference standard does not match protocol (no minimum biopsy criteria, mean 15(5)mm, portal tracts 14.4(0.7), range not reported).
NAVEAU 2014[632]	Reference standard does not match protocol (inclusion criteria at least 10mm or 10 portal tracts, average not stated, some biopsies could be <15mm and not have 6 portal tracts).
NAVEAU 2014[630]	Reference standard does not match protocol (no minimum biopsy criteria, mean 12 (SEM 0.4)mm, number of portal tracts not reported).
NGUYEN-KHAC 2008[635]	Reference standard does not match protocol (no minimum biopsy criteria, mean 12.2 (3)mm and 7.8 (2.7) portal tracts, range not reported).
NISHIURA 2005[636]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (details about biopsy, including length, not stated).
NITTA 2009[637]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
NUDO 2008[641]	Reference standard does not match protocol (Batts and Ludwig fibrosis scoring system in hepatitis C population).
NUNES 2005[642]	Reference standard does not match protocol (no minimum biopsy criteria, average 14.5mm).
OCHI 2012[645]	Reference standard does not match protocol (included if biopsy ≥12mm).
OGAWA 2012[649]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
ONG 2003[651]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
OSAKI 2010[656]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).

Reference	Reason for exclusion
PAPAGEORGIOU 2011[666]	Study does not report any outcomes that can be combined in the analysis (only ROC AUC for of transient elastography in Hepatitis C population, no CIs reported)
PARISE 2006[668]	Reference standard does not match protocol (Ludwig fibrosis scoring system)
PARK 2000[669]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, minimum length of biopsy not stated in inclusion criteria and average not reported).
PAVLOV 2015[680]	Review protocol only
PAVLOV 2015[679]	Systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this review was checked for relevant studies but not updated itself.
PEDERSEN 2008[681]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Index test does not match protocol (hepatic vein Doppler waveform). Reference standard does not match protocol (length of biopsy not stated).
PETTA 2011[687]	Diagnostic accuracy of transient elastography for significant (≥F2) and severe (≥F3) fibrosis, but not for diagnosis of cirrhosis.
PFEIFER 2014[689]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
POUSTCHI 2013[699]	Population does not match protocol (people with beta thatassemia and chronic hepatitis C)
POYNARD 2007B[702]	Diagnostic accuracy of FibroTest adjusted for liver biopsy size (inclusion criterium for biopsy length does not match protocol).
POYNARD 2011A[706]	Retrospective review of data from 3 studies (reference standard biopsy length criteria does not meet protocol with the exception of Zarski study already included in this review)
POYNARD 2012D[703]	FibroTest for assessing liver fibrosis progression, not diagnosis of cirrhosis.
POYNARD 2012[705]	Retrospective review of data from 3 studies (reference standard biopsy length criteria does not meet protocol with the exception of Zarski study already included in this review)
PROCOPET 2015[711]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
RATZIU 2006[719]	Reference standard does not match protocol (no minimum biopsy length in inclusion criteria, mean (SE): group 1: 20 (0.5)mm and 16.3 (0.6) portal tracts, group 2: 17.8 (0.7)mm and 13.6 (0.6) portal tracts, ranges not reported). Sensitivity analysis performed for biopsies ≥25mm, but only for the diagnosis of significant fibrosis not cirrhosis).
REIBERGER 2012[722]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
RESINO 2010[725]	Reference standard does not match protocol (only states 'only 5 out of 297 biopsies yielded insufficient liver tissue for pathological diagnosis', minimum size not stated)
RICCI 2013[727]	Population does not match protocol (inclusion of people with hepatitis B and hepatitis C within the same analysis). Reference standard does not match protocol (no minimum biopsy length stated).
RUNGE 2014[747]	Aim to compare interobserver agreement of MR elastography (used data

Reference	Reason for exclusion
	from the primary study KIM 2011A)
SAID 2010[755]	Reference standard does not match protocol (biopsy length range 10-35mm and 2-25 portal tracts).
SANDRIN 2003[764]	Study does not report any outcomes that can be combined in the analysis (only ROC AUC for of transient elastography in Hepatitis C population, no CIs reported)
SANFORD 1985[765]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
SAMIR 2015[761]	Reference standard does not match protocol (minimum length of biopsy was 10mm, range 10-53mm and minimum number of portal tracts was 3).
SASSO 2012[777]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
SCHWABL[786]	Unable to access full text article
SEBASTIANI 2006[789]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
SEBASTIANI 2011[787]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
SEBASTIANI 2012[788]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported).
SHEN 2006[800]	Reference standard does not match protocol (included if biopsy ≥10mm, number of portal tracts not stated).
SHETH 1998[803]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
SCHNEIDER 2005[783]	Index test does not match protocol (Doppler ultrasound variables: splenic artery pulsatile index, hepatic vein dampening index, portal vein flow, portal vein undulations)
SHARMA 2014[796]	Reference standard does not match protocol (minimum length of biopsy not stated (only stated 'adequate' specimens) in inclusion criteria and range not reported).
SINGH 2015[814]	Systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length.
SPOREA2010A[837]	Population does not match protocol (inclusion of people with hepatitis B and hepatitis C within the same analysis).
STEVENSON 2012[842]	HTA systematic review protocol did not match review protocol. Only included the ALD population and included studies assessing all stages of fibrosis, not just cirrhosis. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this HTA was checked for relevant studies but not updated itself.
SU 2014[849]	Systematic review. Unable to obtain full paper.
SUGIMOTO 2010[850]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
TAKAHASHI 2010[854]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, mean 18.2mm and 6.8 portal tracts, range not reported).
TATSUMI 2008[858]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
TAWADA 2013[860]	Reference standard does not match protocol (biopsy length range 11-28mm, number of portal tracts not stated). Population does not match

Reference	Reason for exclusion
	protocol (inclusion of different aetiological groups within the same analysis).
TOSHIMA 2015[874]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (histology on hepatectomy or living donor liver transplantation).
TSOCHATZIS 2014[889]	Systematic review. Reference standard does not match protocol (accuracy of index tests for diagnosis of fibrosis stage ≥F2).
VALLET-PRICHARD 2007[898]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
VENKATESH 2015[902]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (some patients were undergoing MRI and biopsy for investigation of liver masses).
VERVEER 2012[908]	Study does not report any outcomes that can be combined in the analysis (only ROC AUC for of transient elastography in Hepatitis C population, no CIs reported)
WAHL2012[913]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, mean 22.1 (SEM 2.2)).
WAI2003[915]	Development study for APRI (training and validation set). Reference standard biopsy length not stated.
WANG 2009[920]	Reference standard does not match protocol (included if biopsy ≥10mm in length, biopsy length range 10-28mm, number of portal tracts not stated).
WANG 2010[922]	Reference standard does not match protocol (length of biopsy not stated). Population does not match protocol (presumed inclusion of different aetiological groups within the same analysis, aetiologies not stated).
WANG2011[925]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (only states 'all patients had adequate size biopsies', minimum size not stated)
WONG 2008a[936]	Population does not match protocol (inclusion of different aetiological groups within the same analysis).
WONG 2013A[935]	Diagnostic accuracy of cirrhosis not reported, only of significant fibrosis.
YAKOOB 2015[944]	Reference standard does not match protocol (<50% of biopsies were >15mm and 6 portal tracts).
YONEDA 2015[953]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
YOON 2012[956]	Reference standard does not match protocol (included if biopsy ≥10mm in length). Population does not match protocol (inclusion of different aetiological groups, including 64% hepatitis B within the same analysis
ZHANG 2014[967]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, Ludwig scoring system).
ZHENG2003[971]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, 92.4% hep B). Reference standard does not match protocol (fibrosis scoring system does not match protocol and biopsy size not stated)
ZIOL 2005[974]	Population does not match protocol (included patients with mixed aetiologies, included 251 patients with HCV but 13 had a human

Reference	Reason for exclusion
	immunodeficiency virus co-infection, 5 had a hepatitis B virus co-infection, 18 had a current daily alcohol intake of at least 60 g/d, and 2 had undergone a liver transplantation)

Table 56: Studies identified by the GDG which were picked up in the search but excluded from the clinical review during the first sift, prior to ordering full papers

Reference	Reason for exclusion
BARDOUJACQUET 2013[66]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
BOURSIER 2011[113]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, overall 93.5% biopsies >15mm and 8 portal tracts)
BOURSIER 2014[111]	Incorrect study design – prognostic study (prognostic accuracy of blood fibrosis tests for the prediction of future liver related complications or death, not diagnostic accuracy for current cirrhosis)
CARL 2012[135]	Conference abstract only Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
DOLMAN 2013[236]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, average length 23mm IQR 16-29mm, mean portal tracts 15 range 3-53, 84% of biopsies were greater than 15mm).
FERNANDEZ 2012[275]	Conference abstract only Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
KIM 2009[470]	Article not in English Reference standard does not match protocol (fibrosis scoring system does not match protocol, Batts-Ludwig scoring system) Included in Stevenson HTA
LANNERSTEDT 2013[501]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
LEMOINE 2008[517]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, average length 14mm, range not reported).
MELIN 2005[591]	Article not in English Reference standard biopsy length not stated Not identified in search due to incorrect referencing Included in Stevenson HTA (data obtained direct from manufacturers)

L.3 Severity risk tools

Table 57: Studies excluded from the clinical review

Reference	Reason for exclusion
Addario 2006[17]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Albers 1989[25]	Population does not match protocol (some patients had decompensated cirrhosis at baseline). No prognostic accuracy data reported.
Alhasani 2014[24]	Population does not match protocol: people with HCC (86.9% cirrhosis)

Reference	Reason for exclusion
	but with mixed aetiology (26.8% HBV)
Attia 2008a[53]	Population does not match protocol (57% Child-Pugh C at baseline)
Berzigotti 2011[84]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Beuers 1991[86]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Bhise 2007[88]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Botta 2003[107]	Population does not match protocol (some patients had ascites at baseline)
Boursier 2009b[112]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Chan 2015[154]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Chawla 2011[162]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Choi 2009[173]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Cholongitas 2005[175]	Review paper checked for references
Chon 2012a[176]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Christensen 1984[180]	Population does not match protocol (27% of patients had minimal hepatic encephalopathy at baseline)
Christensen 2004[179]	Review paper checked for references
Christensen 2014[181]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Colecchia 2014[188]	Severity risk tool does not match protocol (prognostic accuracy of spleen stiffness)
Corpechot 2012[195]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Prognostic accuracy measures not reported.
Corpechot 2014[197]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Crespo 2014[201]	Population does not match protocol (post-transplant patients)
De ledinghen 2013[219]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Dultz 2013[242]	Unclear if subjects compensated at baseline. Prognostic accuracy measures not reported.
Dultz 2015[241]	Population does not match protocol (199 out of 272 patients were decompensated at baseline). Prognostic accuracy measures not reported.
Forestier 2010[291]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Gianni 2002[328]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Giannini 2004[327]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Giannini 2005[330]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Gotzberger 2012[352]	Population does not match protocol (some patients had decompensated

Reference	Reason for exclusion
	cirrhosis at baseline)
Hassan 2013[374]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Huo 2005[397]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Huo 2005a[400]	Unclear if patients were compensated at baseline
Huo 2008a[396]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Huo 2010[395]	Severity risk tool does not match protocol (prognostic accuracy of different creatinine cut-off levels to calculate MELD score). Population does not match protocol (presumed some patients had decompensated cirrhosis at baseline as diagnosis of cirrhosis could be made based on the presence of ascites).
Infante-rivard 1987[422]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Jung 2011[441]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Kamath 2001[447]	Populations do not match protocol (some patients had decompensated cirrhosis at baseline)
Kang 2014[451]	Systematic review checked for references
Karagiannakis 2014[453]	Populations do not match protocol (48.9% patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Kim 1999[472]	Populations do not match protocol (some patients had decompensated cirrhosis at baseline). No prognostic accuracy data.
Kim 2012c[468]	Population does not match protocol (some patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Kim 2012i[471]	Population does not match protocol (recruited patients with F3 and F4 fibrosis stages, not all patients had cirrhosis at baseline)
Koo 2013[486]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Lee 2014c[511]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Longheval 2003[535]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Lv 2009[550]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Macias 2013a[552]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Mallaiyappan 2013[561]	Population does not match protocol (patients had decompensated cirrhosis at baseline)
Masuzaki 2009[577]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Mayo 2008[580]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Mishra 2007a[598]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Montagnese 2015[602]	Population does not match protocol (cirrhosis with previous decompensation)
Montano 2014[603]	Review paper checked for references

Reference	Reason for exclusion
Moreno 2013a[607]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Nunes 2010[643]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Pang 2014[665]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Park 2015[670]	Unable to access full text article
Pasqualetti 1992[677]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Prognostic accuracy measures not reported.
Poynard 2011[707]	Systematic review. One included study assessed the prognostic accuracy of transient elastography but in the wrong population (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline).
Poynard 2014[708]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Data presented for those with cirrhosis at baseline (EPIC cohort) for prognostic accuracy of fibrotest but not transient elastography.
Reichel 2000[723]	Population does not match protocol (some patients Child-Pugh C at baseline)
Ripoll 2005[730]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Ripoll 2007[731]	Population does not match protocol (9% of subjects had HCC at baseline)
Ripoll 2012a[732]	Population does not match protocol (29% of subjects had HCC at baseline)
Ripoll 2014[733]	Unable to access full text article
Ripoll 2015[734]	Prognostic accuracy only reported for albumin in the people with compensated cirrhosis
Ruiz-del-arbol 2013[746]	Population does not match protocol (some patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Singh 2013[813]	Systematic review. Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline or some patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Somsouk 2009[824]	Prognostic accuracy measures not reported. Population does not match protocol (some patients had decompensated cirrhosis at baseline).
Stokes 2014[844]	Prognostic accuracy measures not reported
Strauber 2014[838]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Testa 1999[866]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Tsochatzis 2014b[888]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Tuma 2010[890]	Prognostic accuracy measures not reported
Urbain 1995[894]	Population does not match protocol (some patients Child-Pugh C at baseline). Prognostic accuracy measures not reported. Severity risk tool does not match protocol (prognostic accuracy of thallium-201 per rectal scintigraphy).
Vandam 1999[899]	Population does not match protocol (included patients who died of primary biliary cirrhosis)

Reference	Reason for exclusion
Vergniol 2011[906]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Vergniol 2014[905]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Verma 2006[907]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Wang 2007[924]	Population does not match protocol (47% of patients had ascites at baseline)
Wang 2012a[923]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Wang 2013a[917]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Prognostic accuracy measures not reported.
Weinmann 2015[926]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
WONG 2014C[934]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Xie 2013[941]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Yang 2012[949]	Population does not match protocol (all patients had decompensated cirrhosis at baseline)
Zhang 2012b[968]	Population does not match protocol (patients had decompensated cirrhosis at baseline)
Zheng 2011[970]	Population does not match protocol (patients had acute-on-chronic liver failure at baseline)
Zipprich 2010[976]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Zipprich 2012a[975]	Severity risk tool does not match protocol (prognostic accuracy of HVPG alone)

L.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Table 58: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdelgawad 2015[10]	Incorrect intervention/comparison: study looks at diagnostic accuracy not surveillance
Ando 2006[41]	Intervention does not match protocol: surveillance consisted of combinations of ultrasound, AFP, des-ɣ-carboxyprothrombin and CT. Population does not match protocol: chronic liver disease irrespective of cirrhosis (unclear proportion with cirrhosis).
Berretta 2011[83]	Population does not match protocol: people with HCC and chronic liver disease but with mixed aetiology (23.1% HBV)
Bischof 2014[90]	Incorrect study design (commentary of Singal 2014)
Biselli 2015[91]	Incorrect intervention/comparison: study looks at diagnostic accuracy not surveillance
Bolondi 2001[96]	Population does not match protocol: people with HCC and chronic liver

Reference	Reason for exclusion
	disease but with mixed aetiology (17.6% HBV)
Borzio 2013 [99]	Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed)
Chandna 2015[155]	Conference abstract; no relevant comparison
Chang 2015[157]	Incorrect intervention/comparison: study looks at diagnostic test accuracy not surveillance
Chen 2003[168]	Population does not match protocol: surveillance versus no surveillance in HBV carriers, at risk of HCC irrespective of cirrhosis (unclear proportion with cirrhosis). Intervention does not match protocol: surveillance group had 6-monthly surveillance testing using alpha-fetoprotein only, not ultrasound.
Chou 2015[178]	Systematic review; incorrect intervention/comparison: study looks at diagnostic accuracy instead of surveillance frequency
Colombo 2007[190]	Review article and retrospective analysis (non-systematic)
Cucchetti 2014[206]	Non-randomised study comparing 12-monthly versus 6-monthly surveillance (multivariate analysis not performed)
El-Serag 2011[250]	Intervention does not match protocol: surveillance was ultrasound or alpha-fetoprotein. Population does not match protocol: chronic liver disease irrespective of cirrhosis (cirrhosis 40.5%).
Eltabbakh 2015[255]	Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed)
Elzayadi 2010[251]	Population does not match protocol: people with HCC and chronic liver disease but with mixed aetiology (20% HBV). Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed).
Fasani 1999[263]	Non-randomised study comparing 12-monthly versus 6-monthly surveillance (multivariate analysis not performed)
Gaba 2013[311]	Population does not match protocol:recruited people with HCC but unclear if they all had cirrhosis. Intervention does not match protocol: surveillance defined as a history of more than one imaging investigation (type of imaging not specified).
Gebo 2002[323]	Systematic review. Protocol included studies in people with all chronic liver disease not just cirrhosis. Protocol did not restrict surveillance to ultrasound with or without alpha-fetoprotein.
Han 2013[370]	Population does not match protocol: people with HCC (84.3% cirrhosis) but with mixed aetiology (72.3% HBV)
Hucke 2011[391]	Comparison does not match protocol: comparison of outcomes between two time periods before and after introduction of the EASL HCC surveillance guidelines. Non-randomised study (multivariate analysis not performed).
Hung 2015[394]	Incorrect intervention: study looks at screening rather than surveillance. Incorrect population: not just patients with cirrhosis.
Izzo 1997[430]	No comparator group: incidence of HCC in patients undergoing 3-monthly surveillance. Population does not match protocol: people with viral hepatitis irrespective of cirrhosis.
Jan 2005[432]	Incorrect study design: conference abstract. Population does not match protocol: people without cirrhosis (surveillance versus no surveillance)
Jou 2010[440]	Intervention does not match protocol: surveillance versus no surveillance but surveillance method and frequency unclear ("an imaging exam for the detection of HCC in the year before diagnosis")

Reference	Reason for exclusion
Kalman 2014[446]	Incorrect intervention: investigated any imaging not just ultrasound
Kansagara 2014[452]	Systematic review. Protocol included studies in people with all chronic liver disease not just cirrhosis. Surveillance method of included studies was ultrasound or other methods such as alpha-fetoprotein alone or an alternative scanning method.
Kemp 2005[456]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 19% hepatitis B.
Kim 2003[473]	Population does not match protocol: people with cirrhosis, mixed aetiologies with predominantly hepatitis B (58%), surveillance every 3 months versus 6 months
Khalili 2015[459]	Correct intervention but interval not relevant: effectiveness of ultrasound surveillance of ≤12 months was compared to >12 months
Kohli 2014[484]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 31% hepatitis B
Kuo 2010[492]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 55.6% hepatitis B or hepatitis B co-infection
Leykum 2007[520]	Population does not match protocol: population was people with HCV but not all people had cirrhosis. Coinfection with HBV in 40%.
Liu 2015B[529]	Incorrect intervention: study uses CT scan instead of ultrasound
Manini 2014[563]	Descriptive study, not comparing between intervals of surveillance
Marks 2015[566]	Incorrect intervention: study uses MRI instead of ultrasound
Marrero 2002[568]	Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed)
McGowan 2015[583]	No comparison: practice and knowledge of GPs adherence to recommendations
Noda 2010[638]	Population does not match protocol: chronic liver disease irrespective of cirrhosis (cirrhosis 68.8%). Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed).
Onodera 1994[652]	Population does not match protocol: people with HCC but unclear if all people had cirrhosis and the proportion of people with HBV not clear. Non-randomised study (multivariate analysis not performed).
Panda 2014[663]	Narrative review
Prapruttam 2014[710]	Incorrect population: many patients with Hepatitis B and not necessarily cirrhosis. No comparison – just descriptive.
Sangio 2004[766]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 25.9% hepatitis B
Santago 2003[767]	Population does not match protocol: population was people with haemophilia and HCV but not all people had cirrhosis
Saquib 2015[771]	Incorrect population: asymptomatic patients, not having cirrhosis
Sherman 1991[802]	Incorrect study design: abstract
SHERMAN 2014[801]	Incorrect study design (review, non-systematic)
Shoreibah 2014[804]	Review article
Silveira 2008[807]	Intervention does not match protocol (surveillance test that prompted further investigation was not ultrasound in all cases due to variations in patient and physician preference)
Singal 2014 [809]	Systematic review. Protocol included studies in people with all chronic liver disease not just cirrhosis.

Reference	Reason for exclusion
Singal 2015[810]	No comparison: study investigates reasons for inconsistent surveillance in a hospital in Dallas, USA
Solmi 1996[823]	Population does not match protocol: people with HCC and chronic liver disease but only 70.6% had cirrhosis
Stravitz 2008[847]	Comparison does not match protocol: standard surveillance versus substandard surveillance (standard surveillance consisted of ultrasound or another imaging at least once in the year prior to HCC diagnosis)
Tanaka 2006[856]	Population does not match protocol: people with HCC and HCV but only 79.4% had cirrhosis
Taura 2005[859]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 18.5% hepatitis B or hepatitis B co-infection. Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed). Surveillance was based on ultrasound or alpha-fetoprotein results.
Thompson 2007[870]	Systematic review: protocol only included RCTs and not observational studies. No RCTs identified for comparison of surveillance versus no surveillance in people with cirrhosis.
Tomiyama 2013[873]	Incorrect study design: prognostic study assessing the risk factors for the development of HCC in people with PBC (all received the same HCC surveillance frequency with no comparator group)
Toyoda 2006[875]	Population does not match protocol: presumed mixed population, not only people with cirrhosis. Coinfection with HBV in 21%, no surveillance versus surveillance.
Trevisani 2002[878]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 26.8% hepatitis B
Trevisani 2007[879]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 20.8% hepatitis B
Trinchet 2007[883]	Conference abstract
TRIVEDI 2015[887]	Incorrect study design: prognostic study assessing the risk factors for the development of HCC in people with PBC (all received the same HCC surveillance frequency with no comparator group)
Vanvlier 2005[901]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 17% hepatitis B. Surveillance method for the surveillance group was not reported.
Villalvazo 2015[909]	Conference abstract; intervention does not match review protocol
Wang 2011[918]	Conference abstract. Population does not match protocol: people with HBV and HCV but not all had cirrhosis.
Wang 2013[919]	Population does not match protocol: people with HBV and HCV but not all had cirrhosis (31.9% with cirrhosis and 34.9% hepatitis B)
Wang 2015A[916]	Conference abstract; incorrect population – mainly patients with Hepatitis B that are excluded from review protocol
Wong 2013[937]	Population does not match protocol: mixed aetiologies with 22.7% hepatitis B. Surveillance method for the surveillance group was CT or ultrasound.
Yang 1997[946]	Population does not match protocol: people with HBV
Yang 2011[947]	Surveillance method for the surveillance group was CT, MRI or ultrasound. Population does not match protocol: cirrhosis 83%.
YEH 2014[951]	Population does not match protocol: people at risk for HCC but not all people had cirrhosis

Reference	Reason for exclusion
Yuen 2003[962]	Review (non-systematic)
Zapata 2010[963]	Population does not match protocol: people with chronic liver disease but unclear if they all had cirrhosis and proportion of HBV unclear. Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed).
Zhang 1997[965]	Incorrect study design: abstract
Zhang 2004[966]	Population does not match protocol: people with HBV

L.5 Surveillance for the detection of varices

Table 59: Studies excluded from the clinical review

Reference	Reason for exclusion
Amarapurkar 2013[38]	Conference abstract. Incorrect study design: adherence to guidelines in India.
Barritt 2009[67]	Incorrect study design: adherence to guidelines for screening for gastroesophageal varices in the US
Cales 1990[129]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
Cestari 1996[153]	Review article (non-systematic)
Chasalani 1999[159]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
Dagradi 1972[211]	Population does not match protocol: varices at baseline. Incorrect study design: not comparing different frequencies of surveillance.
D' Ambrosio 2011[208]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
De Franchis 2010[215]	EASL guidelines on the diagnosis of portal hypertension and its treatment
Debernardi 2014[223]	Population does not match protocol: treatment with endoscopic control following oesophageal variceal eradication by band ligation
Elia 2012[253]	Conference abstract. Population does not match protocol: assessment of frequency of endoscopic control after variceal obliteration.
Ferruzzi 2011[284]	Conference abstract. Population does not match protocol: assessment of frequency of endoscopic control after variceal obliteration.
Garcia-Tsao 2007[320]	AASLD guidelines on the prevention and management of varices
Giannini 2005[326]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
Giraldez 2003[337]	Incorrect study design: prognostic study assessing the risk factors for variceal haemorrhage
Hsu 2013[387]	Incorrect study design: prognostic study assessing the risk factors for variceal bleeding
Jensen 2002[434]	Incorrect study design: review (non-systematic)
Khambaty 2014[460]	Incorrect study population: patients already had varices. Incorrect study design: aims to characterise compliance rates with surveillance; does not define 'timely surveillance'.
Krystallis 2012[490]	Incorrect study design: review (non-systematic)
Moodley 2010[604]	Incorrect study design: adherence to guidelines for screening and treatment of varices

Reference	Reason for exclusion
Ooi 2013[653]	Conference abstract. Incorrect study design: prevalence of endoscopic screening and outcomes.
Riley 1999[729]	Review article: does not address review question
Saab 2003[748]	Incorrect study design: cost-effectiveness model
Sacher- Huvelin 2015[752]	Incorrect study design: study compares two endoscopy methods in terms of diagnostic test accuracy
Sort 2014[831]	Incorrect study design: study looks at diagnostic test accuracy rather than comparing different frequencies of surveillance
Spiegel 2003[833]	Incorrect study design: cost-effectiveness model
Zoli 1990[977]	Incorrect study design: not comparing different frequencies of surveillance

L.6 Prophylaxis of variceal haemorrhage

Table 60: Studies excluded from the clinical review

Study	Exclusion reason
Agrawal 2002[20]	Conference abstract
Anon 1995[2]	Conference abstract
Anon 2012[5]	Review
Banares 1999[62]	Not review population. No relevant outcomes.
Bendtsen 1991[77]	No relevant outcomes
Berges 1983[79]	Not in English
Bhardwaj 2013[87]	Conference abstract
Bosch 1988[102]	Conference abstract
Bosch 1990[101]	Conference abstract
Bosch 2005[100]	Commentary on Merkel 2004 (assessed for eligibility in this review)
Burroughs 1992[122]	Commentary on Sorensen 1991
Cales 1999[130]	Not review population. Patients with no or small oesophageal varices at endoscopy.
Chen 1993[172]	Not in English
Chen 1999[164]	Conference abstract
Chen 2000[165]	Conference abstract
Deschenes 2000[230]	Commentary on Sarin 1999 (included in this review)
Drastich 2005[240]	Not in English
Elder 1992[252]	Review article
Elta 1991[254]	Commentary on Andreani 1990 (included in this review)
Feng 2012[267]	Not in English
Ferrarese 2014[283]	Conference abstract
Funakoshi 2012[310]	Systematic review: same studies included in the Cochrane review which has already been included
Gawrieh 2005[321]	Commentary on Schepke 2004 (included in this review)
Gluud 2007[339]	Systematic review: same studies included in the Cochrane review which has already been included
Grace 1988[354]	Conference abstract

Grace 1990[355]	Conference abstract
Hayes 1990[376]	Systematic review: methods are not adequate/unclear
Huang 2007[389]	Not in English
Ideo 1998[410]	Not review intervention (nadolol)
Imperiale 1992[419]	Commentary on Poynard 1991 (assessed for eligibility in this review)
Imperiale 2001[417]	Systematic review: methods are not adequate/unclear
Imperiale 2007[418]	Cost-effectiveness analysis. No relevant clinical outcomes.
Khuroo 2005[464]	Systematic review: same studies included in the Cochrane review which has already been included
Korula 1991[487]	Commentary on Groszmann 1990 (assessed for eligibility in this review)
Lebrec 1988[508]	Not review intervention (nadolol)
Lebrec 1990[509]	Systematic review: methods are not adequate/unclear
Lebrec 1993[505]	Systematic review: methods are not adequate/unclear
Lebrec 1994[506]	Review article
Li 2011[521]	Systematic review: same studies included in the Cochrane review which has already been included
Lo 2004[531]	Not review intervention (nadolol). Included in Cochrane review but excluded from this review.
Lopez-Acosta 2002[539]	Conference abstract
Manera 2012[562]	Conference abstract
Merkel 2003[592]	Conference abstract (full text article assessed for eligibility Merkel 2004)
Merkel 2004[593]	Not review intervention (nadolol)
Mishra 2007[599]	Conference abstract
Omar 1998[650]	Conference abstract
Pagliaro 1986[660]	Not full paper (letter to the editor). Full paper included in this review (Pagliaro 1989).
Pagliaro 1992[659]	Systematic review: methods are not adequate/unclear
Pedrosa 1992[683]	Systematic review: methods are not adequate/unclear
Plevris 1994[694]	Not review population. Patients with and without varices.
Poynard 1991[701]	Systematic review: methods are not adequate/unclear
Psilopoulos 2002[713]	Preliminary report (study included in this review)
Ricca Rosellini 1991[726]	Systematic review: methods are not adequate/unclear
Romero 2011[740]	Conference abstract
Saab 2003[748]	Not RCT:decision analytic model
Salami 2011[756]	Conference abstract
Sarin 2000[774]	Review
Sorensen 1991[828]	Population is people with all sizes of varices and no subgroup analyses to match the population strata of this protocol
Shah 2012[792]	Conference abstract
Sussman 2003[852]	Commentary on Lui 2002 (assessed for eligibility in this review)
Teran 1997[862]	Not RCT (cost-effectiveness model)
Tripathi 2007[886]	Systematic review: same studies included in the Cochrane review which has already been included
Vlachogiannakos 2000[911]	Review

L.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Table 61: Studies excluded from the clinical review

Study	Exclusion reason
Ali 2014[29]	Not relevant intervention, comparison and population (patients in remission from recurrent hepatic encephalopathy
Ahmed 2014[22]	Purpose of study is treatment of SBP, not prevention of bacterial infections
Albillos 2004[27]	Not review population (not upper gastrointestinal bleeding). Incorrect interventions (antibiotic compared to placebo).
Alvarez 2005[37]	Not review population (not variceal bleeding)
Bernard 1998[80]	Not review population (not upper gastrointestinal bleeding)
Bernard 1999[81]	Incorrect interventions (antibiotic compared to placebo)
Casper 2015[140]	Protocol only; incorrect study population (patients with cirrhosis and ascites)
Dever 2015[231]	Narrative review
Fagiuoli 2014[260]	Consensus conference recommendations; no data
Gulberg 1999[363]	Incorrect interventions (study comparing dosages for the same antibiotic)
Jindal 2014[438]	Conference abstract of population not matching the study protocol
Jindal 2014A[439]	Not review population (patients have spontaneous bacterial peritonitis)
Lata 2005[502]	Drug unlicensed in UK
Londono 2015[534]	Conference summary
Loomba 2009[538]	Not review population (not variceal bleeding). Incorrect interventions (antibiotic compared to placebo).
Piano 2014[691]	Poster without abstract or any information
Rao 2014[717]	Conference abstract of observational study
Saab 2009[750]	Not review population (not variceal bleeding). Incorrect interventions.
Schubert 1991[784]	Commentary
Soares-weiser 2002[820]	This is the original Cochrane review which has since been updated (Chavez-Tapia 2010) and included
Soares-weiser 2003[821]	Incorrect interventions (antibiotic compared to placebo)
Soriano 1992[830]	Incorrect interventions (antibiotic compared to placebo)
Tellez-avila 2013[861]	Incorrect interventions (antibiotic compared to placebo). Not review population (not upper gastrointestinal bleeding).
Thevenot 2015[869]	Incorrect study population (people with cirrhosis and sepsis)
Tuncer 2003[891]	Purpose of study is treatment of SBP, not prevention of bacterial infections

L.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 62: Studies excluded from the clinical review

Study	Exclusion reason

Abou-Assi 2004[14]	Incorrect study design: abstract
Adebayo 2015[18]	Incorrect intervention and comparison: trial looking at new pump system versus large volume paracentesis
Albillos 2005[26]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included
Bai 2014[59]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included
Campbell 2005[132]	Incorrect study design. Secondary analysis of Sanyal 2003 study (included).
Chen 2014[169]	Systematic review: most of studies included in this review were included in the Cochrane review which has already been included
D'Amico 2005[210]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included
Deltenre 2005[228]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included
Engelmann 2015[257]	Incorrect comparison: trial looking at new pump system versus large volume paracentesis and TIPS; Poster of study protocol only, no data yet
Gines 1991[333]	Incorrect interventions: peritoneovenous shunting
Gines 1995[331]	Incorrect interventions: LVP compared to shunt with titanium tip
Gough 1993[353]	Not review population: malignant ascites
Lebrec 1996[507]	TIPS intervention not performed according to current UK practice
Luo 2015[544]	Incorrect study population: participants all have portal vein thrombosis Incorrect comparison: trial is looking at prevention of bleeding
Qi 2015A[714]	Systematic review looking at treatments for bleeding rather than ascites
Salerno 2007[760]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included

L.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 63: Studies excluded from the clinical review

Study	Exclusion reason
Ahmed 2014[22]	Not review population (management of patients with SBP). Inappropriate comparison.
Ali 2014[29]	Not relevant intervention, comparison and population (use of antibiotics to prevent occurrence of hepatic encephalopathy in patients with cirrhosis)
Alvarez 2005[37]	Inappropriate comparison (head-to-head trial). Study population includes more than 15% of patients who previously had SBP.
Bauer 2002[69]	Inappropriate comparison (head-to-head trial). Study population includes more than 15% of patients who previously had SBP.
Bernard 1998[80]	Systematic review. Relevant included papers in Cochrane review . Study population includes more than 15% of patients who previously had SBP.
Casper 2015[140]	Relevant RCT but protocol only; results will not be published before the guideline
Casper 2015A[139]	Relevant RCT but conference abstract of protocol only; results will not be published before the guideline
Das 1998[212]	Cost analyses, not from a unique RCT
Dever 2015[231]	Narrative review

Study	Exclusion reason
Fagiuoli 2014[260]	Consensus conference recommendations; no data
Frazee 2005[297]	Systematic review. Relevant included papers in Cochrane review.
Gines 2010[332]	Systematic review. Relevant included papers in Cochrane review.
Gines 1990[334]	Study population includes more than 15% of patients who previously had SBP.
Inadomi 1997[421]	Cost analyses, not from a unique RCT
Jindal 2014[438]	Conference abstract; study population not matching the review protocol
Jindal 2014A[439]	Conference abstract; study population already has SBP
Londono 2015[534]	Conference summary
Lontos 2008[536]	Published as an abstract
Lontos 2014[537]	Inappropriate comparison. Unable to obtain full paper.
Loomba 2009[538]	Systematic review. Relevant included papers in Cochrane review.
Mostafa 2014[611]	Inappropriate comparison. Incorrect interventions.
Navasa 1996[627]	Inappropriate comparison
Navasa 2005[626]	Published as an abstract
Novella 1997[640]	People with variceal bleeding (includes significant proportion of patients with upper GI haemorrhage). Inappropriate comparison (not versus placebo or no treatment).
Piano 2014[691]	Poster without abstract or any information
Rao 2014[717]	Conference abstract of observational study (RCTs only in this review)
Saab 2009[750]	Systematic review. Included papers in Cochrane review. People with previous SBP (meta-analysis includes studies on secondary prophylaxis).
Sandhu 2005[763]	Incorrect interventions. Inappropriate comparison.
Segarra-Newnham 2010[790]	Systematic review. Included papers in Cochrane review. No meta-analysis of results performed.
Singh 1995[812]	Study population includes more than 15% of patients who previously had SBP
Singh 2013[815]	Incorrect interventions. Inappropriate comparison.
Terg 2000[863]	Not review population (management of patients with SBP)
Thevenot 2015[869]	Incorrect study population (people with cirrhosis and sepsis)

L.10 Volume replacers in hepatorenal syndrome

Table 64: Studies excluded from the clinical review

Study	Exclusion reason
Altman 1998[36]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome). Not receiving vasoconstrictors.
Angeli 2008[44]	Incorrect study design (non-systematic review)
Angeli 2013[43]	Incorrect study design (non-systematic review)
Arroyo 2003[48]	Incorrect study design (non-systematic review)
Bagshaw 2010[58]	Incorrect study design (non-systematic review)
Barada 2004[65]	Incorrect study design (non-systematic review)
Boyer 2012[118]	Incorrect interventions (IV terlipressin versus placebo in people with

Study	Exclusion reason
	type I hepatorenal syndrome also receiving IV albumin)
Boyer 2012A[119]	Incorrect interventions (IV terlipressin versus placebo in people with type I hepatorenal syndrome also receiving IV albumin)
Boyer 2015[120]	Incorrect comparison: trial looking at effect of vasopressin rather than volume replacer
Burroughs 2003[123]	Incorrect study design (non-systematic review)
Cavallin 2015[149]	Incorrect comparison: both groups received the same volume replacer plus vasopressins
Cavallin 2015A[148]	Incorrect intervention: narrative review looking at vasopressins rather than volume replacers
Clewell 1994[184]	Incorrect interventions (prostaglandins)
Davenport 2012[213]	Incorrect study design (non-systematic review)
Fassio 1992[264]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Fernandez 2005[274]	Population does not match protocol (people with cirrhosis and SBP, not hepatorenal syndrome)
Garcia-Compean 2002[318]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Gines 2010[332]	Systematic review: study designs inappropriate
Hadengue 1995[366]	Incorrect interventions (terlipressin)
Junge 2010[442]	Conference abstract. Could not obtain full details of study.
Landoni 2013[499]	Systematic review is not relevant to review question or unclear PICO
Lee 2009[513]	Systematic review: study designs inappropriate
Lee 2012[514]	Incorrect study design (non-systematic review)
Liu 2014[530]	Not in English
Lu 1999[540]	Incorrect interventions
Moreau 2006[606]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Mudireddy 2013[612]	Systematic review: study designs inappropriate
Nadim 2012[618]	Systematic review: study designs inappropriate
Phillips 2003[690]	Conference abstract. Could not obtain full details of study.
Planas 1990[693]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Reddy 2012[721]	Incorrect study design (non-systematic review)
Rena 2010[724]	Incorrect study design (non-systematic review)
Salerno 1991[757]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Sanyal 2008[769]	Inappropriate comparison. Both groups receiving albumin.
Schepke 2007[780]	Incorrect study design (non-systematic review)
Schewior 2008[781]	Conference abstract. Could not obtain full details.
Schmidt 2006[782]	Incorrect study design (non-systematic review)
Singla 2011[816]	Incorrect study design
Skagen 2010[818]	Systematic review is not relevant to review question or unclear PICO
Sola-Vera 2003[822]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Tandon 2007[857]	Systematic review is not relevant to review question or unclear PICO

Study	Exclusion reason
Turban 2007[892]	Incorrect study design (non-systematic review)
Whittman 2007[928]	Inappropriate comparison
Wong 2015[932]	Incorrect comparison: trial looking at effect of vasopressin rather than volume replacer
Wong 2001[931]	Incorrect study design (non-systematic review)
Wong 2007[933]	Incorrect study design (non-systematic review)
Yang 2001[950]	Not in English
Yang 2014[948]	Not in English
Yu 2013[958]	Inappropriate comparison
Zhang 2009[969]	Not in English

L.11 Management of an episode of acute hepatic encephalopathy

Table 65: Studies excluded from the clinical review

Reference	Reason for exclusion
Abid 2005[12]	Conference abstract
Alexander 1992[28]	Not review population (no hepatic encephalopathy)
Als-Nielsen 2001[31]	Review paper checked for references
Als-Nielsen 2003[35]	Cochrane review - checked for references
Als-Nielsen 2004[33]	Review - checked for references
Als-Nielsen 2004[34]	Review paper checked for references
Als-Nielsen 2004[32]	Review paper checked for references
Anon 1976[1]	Review paper checked for references
Atterbury 1976[51]	Conference abstract
Atterbury 1978[52]	Twenty episodes of acute hepatic encephalopathy occurred in people in a trial of the same comparison (lactulose versus neomycin) for chronic hepatic encephalopathy (so these patients were already undergoing treatment)
Avery 1972[56]	Review (non-systematic)
Bai 2013[60]	Review - checked for references
Bajaj 2015[61]	Prevention of recurrence of overt hepatic encephalopathy episodes
Banares 2013[63]	Incorrect population (looking at the improvement of acute hepatic encephalopathy in people with acute on chronic liver failure - deterioration of liver function which included HRS and circulatory failure as well as acute hepatic encephalopathy)
Bansky 1989[64]	Not a comparative study. All subjects received flumazenil
Bass 2004[68]	Conference abstract
Berenguer 1971[78]	Not in English
Bircher 1966[89]	People with chronic hepatic encephalopathy
Blanc 1994[93]	Non-English language paper
Blanco 2011[94]	Conference abstract
Block 2010[95]	Primary or secondary prevention of hepatic encephalopathy. Incorrect line of therapy
Bucci 1993[121]	Incorrect population. Unclear if patients had acute or chronic hepatic

Reference	Reason for exclusion
	encephalopathy.
Cadranel 1995[124]	For the 8 episodes of hepatic encephalopathy randomised to the placebo arm, if there was no improvement after 10 minutes infusion, flumazenil was given. This occurred for all 8 episodes and the effectiveness of flumazenil was assessed in both arms of the trial, in a before and after manner.
Corazza 1982[194]	Population is people with clinical evidence of grade 1 chronic hepatic encephalopathy.
Conn 1977[193]	People with chronic hepatic encephalopathy. Crossover study
Cowan 1986[199]	Conference abstract
DeMarco 1984[221]	Comparison between paromomycin (a drug not licenced in the UK) and rifaximin
DuPont 2015[243]	Narrative review of therapeutic effects and mechanism of action of rifaximin (references checked)
Eltawil 2012[256]	Systematic review – not all acute hepatic encephalopathy (checked for references)
Falavigna 2007[262]	Cochrane review – checked for references
Feher 1997[266]	Not review population
Fera 1993[268]	People with minimal hepatic encephalopathy (sometimes called latent or subclinical)
Gluud 1983[338]	Conference abstract
Gluud 2015[342]	Systematic review – not all acute hepatic encephalopathy (checked for references)
Gluud 2015A[341]	Poster of unpublished systematic review; uncertain if studies included are acute or chronic hepatic encephalopathy
Grimm 1988[358]	Not a comparative study (all patients received flumazenil)
Groeneweg 1996[359]	Incorrect study design. An ancillary study of a RCT (Gyr 1996, included in this review)
Grungreiff 1993[361]	Not in English
Held 1987[380]	Not in English
Held 1988[379]	Not in English
Hirayama 1982[382]	Some (17.5%) of the participants did not have cirrhosis but had hepatic carcinoma.
Howard 1993[384]	Letter – checked for references
Hwang 1988[404]	Not in English
Jiang 2008[437]	Review – checked for references
Jiang 2009[436]	Review paper checked for references
Kersh 1973[457]	Incorrect study design
Khokhar 2015[462]	Secondary prevention of recurrence of hepatic encephalopathy
Kimer 2014[474]	Review – checked for references
Kimer 2015[475]	Review protocol only
Kircheis 1992[476]	Not in English
Kircheis 2002[477]	Review paper checked for references
Klotz 1989[482]	Commentary
Lang 1995[500]	Not in English
Maharsh 2015[555]	Trial for prevention rather than treatment of acute hepatic encephalopathy

Reference	Reason for exclusion
	Incorrect study population: patients with acute variceal bleed
Malaguarnera 2003[556]	Duration of intervention longer than 2 weeks
Malaguarnera 2005[558]	Duration of treatment longer than 2 weeks
Malaguarnera 2006[557]	Incorrect interventions
Malaguarnera 2009[559]	(BCAA + L-acetylcarnitine) is compared against BCAA only, and all participants received lactulose.
Martí-carvajal 2014[569]	Cochrane review protocol
Massa 1993[575]	People with chronic hepatic encephalopathy
Mazariegos 1998[581]	Conference abstract
Mcgee 2011[582]	Cochrane review – checked for references
Meier 1988[589]	Not a comparative study (all patients received flumazenil)
Michel 1984[595]	Incorrect interventions. Branched chain amino acids infusion is compared with aromatic amino acids infusion
Michel 1985[594]	Incorrect interventions. Branched chain amino acids infusion compared with conventional amino acids infusion
Miglio 1997[596]	Treatment period > 14 days
Mohammad 2012[601]	Review – checked for references
Morgan 1982[608]	Crossover study (results also presented for first treatment only, but only for one arm of the study – metronidazole before neomycin but not for neomycin before metronidazole). Some patients on treatment for chronic hepatic encephalopathy symptoms before the start of the trial
Neff 2006[634]	Incorrect line of therapy. The participants had suffered from hepatic encephalopathy related to poor compliance or ineffective therapy for hepatic encephalopathy prior to entering the study.
Orlandi 1981[655]	Recruits people with chronic hepatic encephalopathy and an acute episode, washout period of 15 days but unclear treatment for chronic hepatic encephalopathy prior to this (recruited both inpatients and outpatients, the mean duration of hepatic encephalopathy was 14.1 months). The mean duration of the current hepatic encephalopathy episode prior to trial treatment was 14-18 days, therefore the intervention was not first line treatment of the acute episode.
Panella 1993[664]	Conference abstract
Parini 1992[667]	Comparison between paromomycin (a drug not licenced in the UK) and rifaximin
Patel 2015[678]	Conference abstract clinical trial protocol involving patients with chronic hepatic encephalopathy
Pedretti 1991[682]	People with chronic hepatic encephalopathy
Pomier-layrargues 1994[696]	Crossover study
Poo 2006[698]	Review paper checked for references
Poo 2007[697]	Conference abstract
Ratnaike 1975[718]	Not a comparative study (all patients received lactulose)
Raza 2004[720]	Lactulose enema with oral lactulose was compared against tap water enema with oral lactulose: same drug class compared
Rigali 2006[728]	Review (drug information update) - references checked
Romeiro 2013[739]	Incorrect interventions
Sen 2004[791]	Incorrect population (looking at the improvement of acute hepatic encephalopathy in people with acute on chronic liver failure - deterioration of liver function which included HRS and circulatory failure

Reference	Reason for exclusion
	as well as acute hepatic encephalopathy)
Sharma 2013[794]	Commentary
Simmons 1970[808]	Incorrect line of therapy. Half the participants had hepatic encephalopathy for between 4 and 93 days prior to the start of the study (and unclear prior treatment, therefore treatment may not be first line). Type of hepatic encephalopathy defined as chronic in 4/26 patients (according to Zieve et al. 1960 criteria) and all patients pooled for analysis.
Stauch 1992[839]	Not in English
Sterling 1994[841]	Crossover study. Not full paper (summary/commentary)
Testa 1985[865]	People with minimal hepatic encephalopathy (sometimes called latent or subclinical)
Trey 1970[881]	Mechanisms of action study
Uribe 1980[897]	Conference abstract
Van der rijt 1995[900]	Crossover study. Incorrect population – patients had acute or chronic underlying liver disease.
Venturini 2005[903]	Population does not match protocol - people with cirrhosis but without hepatic encephalopathy
Wahib 2014[912]	Unable to obtain full text article
Williams 2000[930]	Not a comparative study (all patients received rifaximin)
Xue 2010[943]	Commentary
Younsi 1991[957]	Not in English
Yuan 2008[961]	Cochrane review protocol
Zhu 1998[972]	Not in English
Zhu 2015[973]	Systematic review protocol – acute and chronic hepatic encephalopathy

Appendix M: Excluded health economic studies

M.1 Risk factors and risk assessment tools

None.

M.2 Diagnostic tests

Table 66: Studies excluded from the economic review

Reference	Reason for exclusion
Crossan 2015[204]	Population does not match protocol: diagnostic tests for cirrhosis were assessed for a population with mixed aetiology; protocol specifies testing of people with different aetiologies must be analysed separately.

M.3 Severity risk tools

None.

M.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Table 67: Studies excluded from the economic review

Reference	Reason for exclusion
Ruelas 2004[745]	Population does not match protocol: study included people without cirrhosis.

M.5 Surveillance for the detection of varices

None.

M.6 Prophylaxis of variceal haemorrhage

Table 68: Studies excluded from the economic review

Study	Exclusion reason
Dipascoli 2014[234]	Intervention does not match protocol: beta-blocker used was nadolol.

M.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

None.

M.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 69: Studies excluded from the economic review

Reference	Reason for exclusion
Parker 2013[672]	This study was assessed as not applicable due to the study design: it compared costs of the same patients before and after TIPS was carried out; no randomisation.

M.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

None.

M.10 Volume replacers in hepatorenal syndrome

None.

M.11 Management of an episode of acute hepatic encephalopathy

None.

Appendix N: Cost-effectiveness analysis: diagnostic tests and surveillance strategies for cirrhosis

N.1 Introduction

Diagnosing cirrhosis in people with liver disease is a crucial point in a patient's disease pathway as it triggers a more intensive clinical path that includes surveillance for the cirrhosis complications of hepatocellular carcinoma (HCC) and oesophageal varices. Failing to detect cirrhosis at an early stage can have detrimental clinical effects for patients. Amongst hepatologists and gastroenterologists, the only commonly agreed reference standard for the diagnosis of advanced fibrosis or cirrhosis is liver biopsy. By nature liver biopsy is an invasive test associated with adverse clinical events and disutility for some people. In addition, it is a resource-intensive procedure, conducted with the guidance of ultrasound, which usually requires a day-case admission and has a considerable cost.

With the rising popularity of blood biomarkers associated with liver function and the increasing use of imaging tests that can stage liver fibrosis, without carrying the disadvantages of liver biopsy, these non-invasive liver tests (NILTs) have found their way into current clinical practice. However, the availability of the tests and the way that these are embedded into clinical practice vary substantially across NHS providers. For these reasons the GDG prioritised original economic analysis to be conducted for the review questions that address objective diagnostic tests for the diagnosis of cirrhosis and who should be offered such a test.

The economic review identified 3 studies (Canavan 2013, Steadman 2013, Stevenson 2012) that reported cost-effectiveness results in patients with different stages of fibrosis. However these studies reported outcomes for mixed populations at different stages of liver disease; none of the studies reported outcomes for only people with cirrhosis. A recently published NIHR HTA was also identified (Crossan 2015) that reported results for a population of people with cirrhosis, but this looked only at a population with mixed liver disease aetiology (including patients with viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease together).

Other areas of uncertainty identified in the clinical review questions were the optimal frequencies of surveillance for HCC and for oesophageal varices in people with cirrhosis, as regular surveillance for these complications is believed to lead to clinical benefits for patients but the best frequencies are unclear. These 2 review questions were hence also examined using the same whole disease pathway model.

N.2 Methods

N.2.1 Model overview

N.2.1.1 Comparators

The model compares 23 tests and 4 combinations of tests, identified in the relevant clinical review, across all the different cirrhosis aetiologies. These are summarised below. Several tests were not considered for modelling due to the absence of sensitivity/specificity data in the relevant papers (only area under the curve figures reported). For each aetiology population the diagnostic tests are also compared against the reference standard, liver biopsy.

Two further strategies were also considered which did not include any tests:

- no test, monitor all patients in the relevant population assuming they have cirrhosis
- no test, monitor no-one, assuming none have cirrhosis until later clinical presentation.

In the hepatitis C cohort, for modelling purposes, there was an additional no test strategy which did not include HCV treatment.

Table 70: Tests included in the model by disease aetiology

Hepatitis B	Hepatitis C	Alcohol-related liver disease	Non-alcoholic fatty liver disease
Fibrotest at 0.74	Platelet count	APRI at 1.5 – 2.5	TE at 10.0 – <13.0 kPa
Transient elastography (TE) at 11.kPa	Fibrotest at a 0.56 – 0.75	TE at 11.0 – <13.0 kPa	TE at >15 kPa
APRI at 2.0	ELF at 9.3 – 10.44	TE at 15+ kPa	ARFI at 1.636 – 1.9
APRI at 1.0	APRI at 0.5 – <1.5		
	APRI at 1.5 – 2.5		
	FIB4 at 2.3122		
	AST/ALT ratio at 1.0		
	TE at 9.0 – <13.0 kPa		
	TE at 13.0 – <15.0 kPa		
	TE at 15+ kPa		
	ARFI at 1.55 – 2.0		
	pSWE at optimal level		
	TE and ARFI (at 12.2kPa and 1.8m/s)		
	TE or ARFI (at 12.2kPa and 1.8m/s)		
	SAFE algorithm		
	Castera algorithm		

***APRI**: AST, ALT, platelet count; **ARFI**: acoustic radiation force impulse; **Castera algorithm**: combination of TE and FibroTest, liver biopsy as confirmation when needed; **ELF**: enhanced liver fibrosis test including a serum concentration of procollagen-III aminoterminal-propeptide, tissue inhibitor of matrix metalloproteinase-1 and hyaluronic acid; **FIB4:** age, AST, ALT, platelets count; **Fibrotest**: Alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, alanine transaminase; **pSWE:** point shear wave elastography; **SAFE algorithm**: sequential use of APRI, FibroTest and liver biopsy; **TE:** Transient elastography*

N.2.1.1.1 Combinations of more than 1 test

In planning the model structure, the inclusion of combinations of tests was considered. Four algorithms were identified in papers included for the hepatitis C population (at the bottom of Table 70 above) and these were included alongside the single tests. The GDG also considered using 2 of the single tests (excluding liver biopsy) consecutively. The GDG considered that combinations should include 1 blood test and 1 imaging test as these would be likely to give independent results. The most promising combination would be one using a blood test with high sensitivity (to maximise true positives and minimise false negatives) followed by an imaging test with high specificity (to rule out true negatives). However, when viewing the diagnostic accuracy values found in the clinical review (see Section N.2.3.2 below) no such combination could be found. Consequently there was no reason to believe any combination of 2 tests would give more accurate results than the best single tests, but with an increased cost for using 2 tests instead of 1. Therefore no such combinations were modelled.

N.2.1.2 Population

The model considers people aged 50 years at the start of the model with one of the 4 major underlying causes of cirrhosis (hepatitis B, hepatitis C, alcohol-related liver disease, non-alcoholic fatty liver disease) who are therefore at risk of developing cirrhosis. Patients with different aetiologies are treated as separate patient cohorts in the model. Hepatitis B patients are further separated in 2 cohorts (positive or negative hepatitis B e Antigen, HBeAg). Hepatitis C patients are further separated by disease genotype (Genotypes 1–4).

N.2.1.3 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and the perspective of the UK NHS and personal social services. A sensitivity analysis will also be conducted using a discount rate of 1.5% for costs and health benefits. A lifetime horizon has been chosen to fully capture the adverse outcomes derived from incorrect diagnosis.

N.2.2 Approach to modelling

The model is based on 2 phases:

- **Decision tree:** Using the sensitivity and specificity, combined with data on the prevalence of cirrhosis in each of the target populations, the model identifies the proportion of people who receive a true positive (TP), true negative (TN), false positive (FP) or false negative (FN) diagnosis.
- **Markov model:** Once the diagnosis is made the people move into the second part of the model which involves a Markov model to fully evaluate long-term health and cost outcomes for people starting with each diagnosis. The model has 6-monthly cycles and continues until death or age 100 years.

Further information and technical details are provided below.

N.2.2.1 Model structure

Figure 211: Graphical depiction of the decision tree

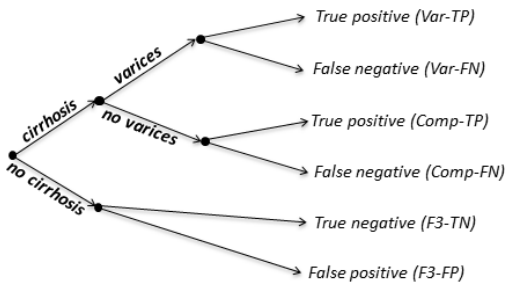
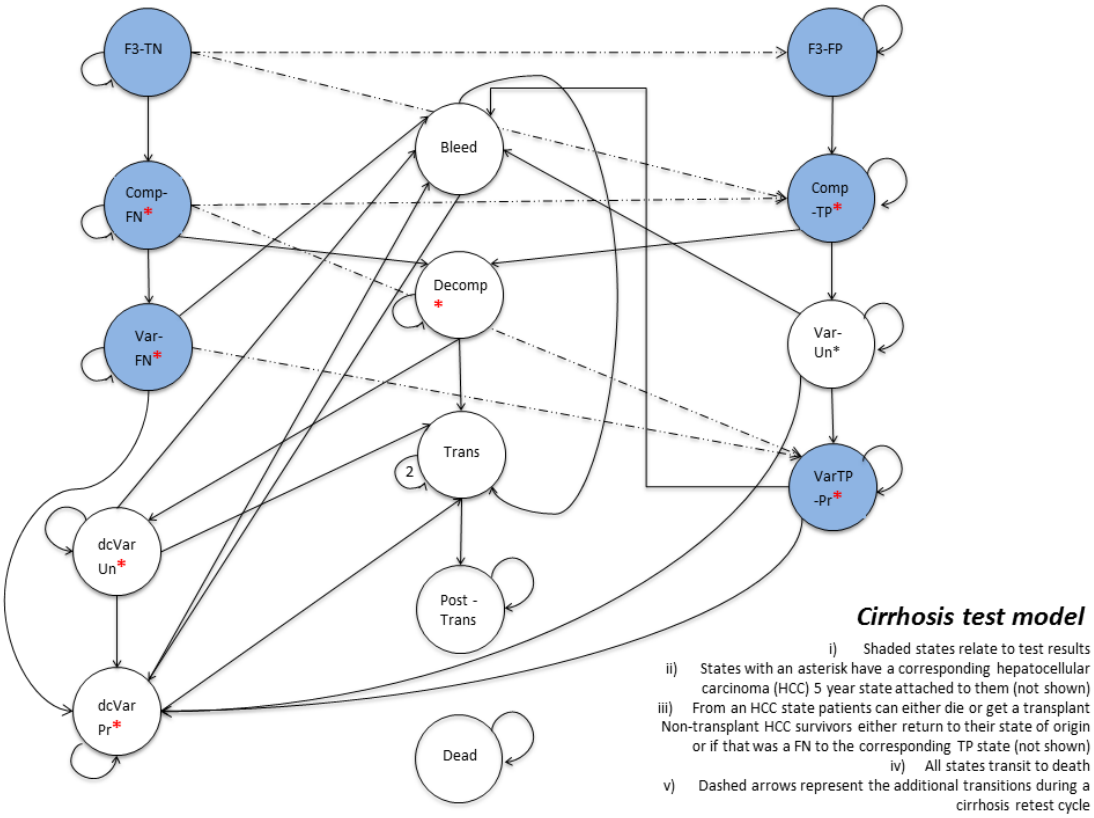


Figure 212: Graphical depiction of the Markov model



N.2.2.2 High-level model structure

Initially, a decision tree determines the proportion of people with cirrhosis who receive a correct diagnosis (true positive - TP) and an incorrect diagnosis (false negative - FN); and the proportion of people without cirrhosis who receive a correct diagnosis (true negative – TN) and an incorrect diagnosis (false positive – FP) depending on the diagnostic accuracy of every test. People diagnosed as not having cirrhosis were assumed to have advanced fibrosis (F3 on the METAVIR scale).

It is assumed that 27% of people with cirrhosis will already have medium or large varices at the time when they are first diagnosed with cirrhosis. People will receive endoscopic surveillance for oesophageal varices immediately following a positive diagnosis of cirrhosis. It is assumed that this is 100% successful at identifying medium or large varices.

Consequently, patients enter the Markov model through 6 health states:

- advanced fibrosis with a true negative diagnosis – (F3-TN)
- advanced fibrosis with a false positive diagnosis of cirrhosis– (F3-FP)
- compensated cirrhosis with a true positive diagnosis – (comp-TP)
- compensated cirrhosis with a false negative diagnosis of advanced fibrosis only – (comp-FN)
- compensated cirrhosis with oesophageal varices with a true positive diagnosis, hence immediately receiving prophylactic measures to prevent variceal bleeding – (VarTP-Pr)
- compensated cirrhosis with oesophageal varices with a false negative diagnosis of advanced fibrosis only, and hence not assess or receiving treatment for varices – (Var-FN)

It is assumed that everyone with cirrhosis at the start of the model has compensated cirrhosis, as decompensated cirrhosis would have previously been identified by a clinician's observations without

the need for the diagnostic tests examined here. Under GDG guidance, retesting for those with a negative diagnosis was set at 2 years for NAFLD, HBV and HCV and 1 year for ALD.

Overall, the model attempts to represent the natural history of the disease, from compensated cirrhosis without varices to the development of varices (which may lead to bleeding), HCC and other decompensation events, and finally to a post-liver transplant state or to death.

N.2.2.2.1 Surveillance for hepatocellular carcinoma (HCC)

Patients with cirrhosis run an increased risk of developing hepatocellular carcinoma. It is widely believed that a comprehensive HCC surveillance package can reduce the morbidity and mortality associated with HCC. However, there is a lot of uncertainty around the optimal surveillance frequency.

In the model, most of the health states depicted have a corresponding 5-year HCC state attached to them. Survivors from this cancer tunnel state that do not receive a liver transplant either return to their state of origin or are transferred to their corresponding true positive state in the cases where patients originally received an FN cirrhosis diagnosis. This is because it is assumed that if HCC is detected this would be directly attributed to cirrhosis and therefore patients would immediately receive a positive cirrhosis diagnosis without the need for further diagnostic testing.

As a model base case all patients diagnosed with cirrhosis will be monitored yearly for HCC. This was set after agreement with the GDG that this reflects common current practice in the NHS and in view of the GDG's opinion that having a no-surveillance strategy for HCC would not be appropriate. A 6-monthly surveillance strategy will also be tested for its cost-effectiveness compared with annual surveillance to contribute to the relevant clinical review question.

To apply the clinical benefit of HCC surveillance, figures from 2 different sources, identified by the clinical review (one included in the review: Santi 2010), were combined. A study by Zhang 2004 with a 5-year follow up on 18,816 hepatitis patients reported that 6-monthly surveillance (using alpha-fetoprotein [AFP] blood test plus ultrasound) was associated with a 37% reduction in HCC mortality in comparison to a no-monitor control group. This number was combined with an increased risk of death figure (1.39 hazard ratio) for patients under annual surveillance (AFP blood test plus imaging test) when compared to a 6-monthly surveillance strategy reported by Santi 2010 (649 patients of mixed disease aetiology). Therefore, for use in the model, 6-monthly and yearly surveillance were associated with a risk ratio of 0.63 and 0.88 respectively. These risk ratios were applied to the liver associated mortality of every true positive HCC health state.

The costs of an AFP blood test and an ultrasound were added accordingly to the model as those tests were considered by the GDG to be the current HCC surveillance practice across the NHS.

Two relevant economic evaluations were identified in our systematic literature review. One that compared annual surveillance and 6-monthly surveillance in people with cirrhosis of mixed aetiology[205] and one that compared no surveillance, annual AFP, annual ultrasound, annual AFP plus ultrasound, 6-monthly AFP, 6-monthly ultrasound, and 6-monthly AFP plus ultrasound in people with cirrhosis with either alcohol-related liver disease or hepatitis C.[870,871]

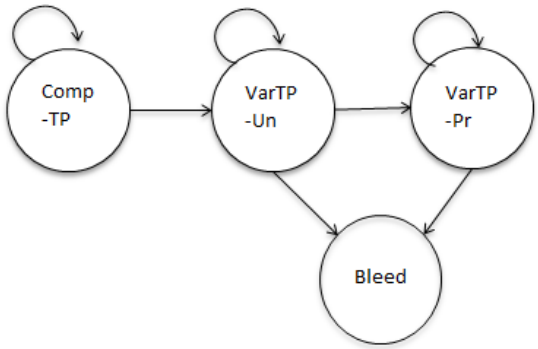
N.2.2.2.2 Surveillance for oesophageal varices

Variceal bleeding is one the most common complications of cirrhosis and is considered a decompensating event. Endoscopic surveillance for the development and the size estimation of oesophageal varices is believed to have a substantial patient benefit as those identified with medium and large varices receive a band ligation procedure that offers prophylactic benefits against variceal bleeding.

In the model base case, all patients diagnosed with cirrhosis will be monitored every 3 years for varices. This was set after agreement with the GDG that this reflects common current practice in the NHS. A 2 yearly and an annual surveillance strategy will also be tested for their cost-effectiveness compared to a 3-yearly strategy to contribute to the relevant clinical review question.

People who developed medium or large varices whilst in either compensated or decompensated cirrhosis states were represented in separate health states (depicted as Var and dcVar respectively in the model structure, Figure 212). As presented in Figure 213 below, people with cirrhosis are separated between those who have developed varices since their most recent endoscopy and so have not been yet been identified as having varices or offered a prophylactic band ligation (VarTP-Un, dcVar-Un) and those who have received an endoscopy since they have developed varices and so are assumed to have been correctly identified as having varices and consequently protected against bleeding by prophylactic band ligation (VarTP-Pr, dcVar-Pr). Similarly bleeding has been separated from the other decompensating events (ascites, hepatic encephalopathy, jaundice) and is represented as a separate state, which individuals are in for a single Markov cycle, after which if still alive they are transferred to a decompensated state, but with their varices now protected (dcVar-Pr). Prophylactic band ligation was taken to reduce the risk of bleeding by 50%, as found by a literature review provided by the GDG (Berzigotti 2013). The prevalence of varices (of any size) in people diagnosed with cirrhosis (40%) and annual rates of varices development in people with compensated or decompensated cirrhosis but without varices of 6% and 10% respectively were also sourced from this study. Those figures were adjusted accordingly to represent the proportion of people with cirrhosis with medium or large varices, which was set to 67% of the overall cohort of people with cirrhosis with varices of any size (assumption by Stevenson 2012).

Figure 213: Surveillance for varices structure



The cost of a diagnostic endoscopy is accordingly added to any Markov cycle during which surveillance for varices is conducted, depending on the frequency chosen. Under GDG guidance it was also assumed that if the endoscopy identified medium to large varices, a band ligation was offered immediately at the same visit. In the described scenario the cost of endoscopy was not applied to avoid double counting as band ligation is conducted endoscopically.

No relevant economic evaluations were identified in our systematic literature review.

N.2.2.3 Population cohorts

N.2.2.3.1 Non-alcoholic fatty liver disease (NAFLD)

This cohort has the simplest representation in the model. As for all populations, people with NAFLD diagnosed with cirrhosis will receive surveillance for HCC and varices. People with NAFLD will be offered lifestyle interventions and pharmacological treatment using pioglitazone or vitamin E regardless of whether they have advanced fibrosis (F3) or cirrhosis, and so diagnosis of cirrhosis will

not lead to any change in the treatment for the underlying NAFLD. Baseline probabilities are applied to model the progression of liver disease.

N.2.2.3.2 Alcohol-related liver disease (ALD)

All patients presenting with alcohol-related cirrhosis will need to undergo medically assisted withdrawal from alcohol as specified in NICE CG100 and CG115. Such treatment is not however different depending on whether the patient has cirrhosis or not and therefore is not represented in the current model. Instead, the model examines the effect of a positive cirrhosis test result on a patient's alcohol abstinence. A similar approach was also followed by 2 recently published NIHR HTAs on ALD cohorts (Crossan 2015, Stevenson 2012). NILTs were assumed to have a smaller effect compared to liver biopsy due to the latter's invasive nature. Figures on the abstinence effect of liver biopsy were sourced from Crossan 2015 (authors cite a published abstract) while the abstinence effect of NILTs was based on authors' assumptions. Figures are tested in deterministic sensitivity analysis in the current model.

In addition, following assumptions made by the Stevenson 2012 HTA, we attached a different bleeding rate for abstainers and drinkers.

N.2.2.3.3 Hepatitis B (HBV)

Following guidance from the GDG, we assumed that all patients referred for a cirrhosis test are also receiving treatment with antiviral drugs. This was considered a rational assumption as for patients to be suspected for cirrhosis they must have been new referrals and therefore not been appropriately treated for the underlying cirrhosis cause before.

The GDG agreed that first line treatment would be pegylated interferon alfa-2a for 1 year. Patients who do not respond to first line treatment are switched to either tenofovir or entecavir from the second year onwards indefinitely. For modelling purposes we set 75% of the referrals for second line treatment for tenofovir and the remaining 25% for entecavir as the GDG felt that this reflects current NHS practice. The rates by which patients respond to first line treatment were different for patients with positive and negative e antigen. Relevant figures were sourced from the NICE Hepatitis B guideline (CG165). The therapeutic effect of the HBV antiviral drugs was applied through a relative risk ratio attached to the patient's mortality. The model also included a different progression rate from advanced fibrosis (F3) to cirrhosis for patients with positive and negative e antigen, an approach also adopted by the Crossan 2015 HTA.

N.2.2.3.4 Hepatitis C (HCV)

A new generation of polymerase inhibitor drugs for hepatitis C has been recently assessed by NICE in technology appraisals and are entering NHS practice. In order for the present economic model to reflect the most up to date NICE recommendations, 2 recently published drug combinations (part of TA330 and TA ID742) covering the 4 most prevalent UK HCV genotypes are included in the modelling of the cirrhosis patient pathway. Ombitasvir-paritaprevir-ritonavir is also an option for genotypes 1 and 4. We chose ledipasvir-sofosbuvir as that is at least as effective and with similar price. Note that the economic results would not be altered by this choice of drug as both effectiveness and cost are very similar. People with HCV without cirrhosis are assumed to receive the appropriate pegylated interferon/ribavirin regimes since polymerase inhibitor drugs are not currently recommended for these patients.

With the introduction of the new antiviral treatments and their inclusion to the present model, the GDG has made a similar assumption as the one described for the HBV model cohort, that for patients to be suspected for cirrhosis they must be new referrals and therefore not appropriately treated before for the underlying cirrhosis cause (since antiviral treatments would dramatically decrease the

progression rate to cirrhosis). Therefore all of the patients in the model cohort will be treated with an antiviral agent.

The treatment effectiveness of the antiviral drugs is represented in the model by their sustained viral response (SVR). This figure is the rate of patients who have responded to treatment and therefore were 'cured' of the virus. The SVR was consequently applied to the probability of a patient progressing to the next state in the Markov model as patients that are free from the virus are assumed not to progress to more severe liver disease states. They were also assumed to only receive HCC surveillance and not varices surveillance, this was based on GDG guidance that there is still high uncertainty over the risk of HCC in 'cured' patients treated with the new drug combinations. SVRs per genotype where sourced from the evidence reports of TA330 and TA ID742.

Table 71: Sustained viral response per genotype

Genotype	People with **fibrosis**			People with **cirrhosis**		
	Drug combination	Duration	SVR	Drug combination	Duration	SVR
Genotype 1 – treatment naive	Ledipasvir-sofosbuvir	8 wks	0.94	Ledipasvir-sofosbuvir	12 wks	0.941
Genotype 2 – treatment naive	Pega-2a with ribavirin	24 wks	0.815	Soforbuvir with ribavirin	12wks	0.857
Genotype 3 – treatment naive	Pega-2a with ribavirin	24 wks	0.712	Sofosbuvir with pega-2a & ribavirin	12 wks	0.833
Genotype 4 – treatment naive	Pega-2a with ribavirin	48 wks	0.436	Ledipasvir-sofosbuvir	12 wks	0.941

In addition, under GDG guidance it was assumed that, for patients falsely identified as having cirrhosis, the drug effectiveness to be identical as for the correctly diagnosed with cirrhosis patients. For patients falsely diagnosed as negative, the drug effectiveness of the fibrosis-HCV treatment options was adjusted to 50% in order to depict their lower efficacy in patients with cirrhosis.

N.2.2.4 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base case and 5,000 times for each sensitivity analysis – and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 72 and in the relevant input summary tables in Section N.2.3. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 72: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Specificity	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and Beta values were calculated as follows: Alpha=(True negatives) Beta=(Number of patients)-(True negatives)
Diagnostic odds ratio	Lognormal	Derived from the ln(DOR) and Se(ln(DOR))
Utility	Lognormal applied on utility decrements	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2
Costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. SE was set at deterministic cost/4. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = SE^2/Mean
Hepatitis B treatment effect – Relative risk ratio	Log-normal	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2
Hepatitis C treatment effect – Proportion of people who responded to treatment	Beta	Bounded between 0 and 1. Derived from the number of responders and non-responders. Alpha and Beta values were calculated as follows: Alpha = n responded to treatment Beta = n not responded to treatment
HCC surveillance - Relative risk ratio	Log-normal	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, 1 or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

N.2.2.4.1 Deterministic sensitivity analysis

Apart from assigning distributions to most of the model parameters, deterministic sensitivity analysis was also performed for a variety of variables.

Table 73: Summary of parameters tested in DSA

Parameter	Base case	DSA values
NAFLD		
NAFLD prevalence (50% lower/higher)	13%	6.5%, 19.5%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
Fibroscan unit cost (20%	£68	£54.4 £81.6

Parameter	Base case	DSA values
lower/higher)		
ARFI unit cost (20% lower/higher)	£51	£40.8, £61.2
Discount rate	3.5%	1.5%
TE>15 diagnostic accuracy (low CI)	Sens=99, Spec=96	Sens=66, Spec=90
ALD		
ALD prevalence(50% lower/higher)	34%	17%, 51%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
Abstinence after diagnosis with NILT	Neg=0.31, Pos=0.52	Neg=0, Pos=0
TE at 11.0 - <13.0 diagnostic accuracy (low/high CI)	Sens=98, Spec=79	Sens=54, 100; Spec=54, 94
Fibroscan unit cost (20% lower/higher)	£68	£54.4, £81.6
Cirrhosis retesting	1 year	2 years
HBV (neg e antigen)		
HBV prevalence (50% lower/higher)	13%	6.5%, 19.5%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
TE at 11.0 diagnostic accuracy (low/high CI)	Sens=75, Spec=90	Sens=48, 93; Spec=85, 94
Fibroscan unit cost (20% lower/higher)	£68	£54.4, £81.6
Drug treatment effectiveness – second line treatment (low/high CI)	0.65	0.06, 0.95
HCV (only genotype 3)		
HCV prevalence (50% lower/higher)	18%	9%, 27%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
TE at 13.0 - <15.0 diagnostic accuracy (high CI)	Sens=93, Spec=93	Sens=97; Spec=97
Fibroscan unit cost (20% lower)	£68	£54.4
HCV treatment	yes	no
HCC surveillance in SVR patients	yes	no
Drug treatment effectiveness – fibrosis patients	0.71	0.63, 0.79
Drug treatment effectiveness – cirrhosis patients	0.83	0.63, 0.95
Drug treatment cost (50%, 60% lower)	37,162.88	14,865, 18,581
HCC surveillance frequency		

Parameter	Base case	DSA values
Surveillance costs (20% lower)	£50.42	£40.3
HR comparing 6-monthly and annual surveillance (20% higher)	1.39	1.67
Varices surveillance frequency		
Surveillance costs (20% lower)	£205.66	£164.5
RR on bleeding probability (20% higher/lower)	0.50	0.40, 0.60

N.2.3 Model inputs

N.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated by clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 74 and Table 75 below. Health state costs are presented separately in the relevant cost section. More details about sources, calculations and rationales for selection can be found in the sections following this summary table.

Table 74: Summary of base case model inputs

Input	Value	Source
Patient age at cirrhosis diagnosis	50 years	GDG assumption
Time horizon	Lifetime	NICE reference case
Discount rate	Costs = 3.5%; effects = 3.5%	NICE reference case

Table 75: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimates		Probability distribution	Distribution parameters
Prevalence of cirrhosis				
Hepatitis B (HBV)	0.13		95% CI 0.07-0.22	
Hepatitis C (HCV)	0.18		95% CI 0.14-0.22	
Alcohol related liver disease (ALD)	0.34		95% CI 0.19-0.53	
Non-alcoholic fatty liver disease (NAFLD)	0.13		95% CI 0.09-0.20	
Diagnostic accuracy (HBV)	Sensitivity	Specificity	Lognormal distribution	
Fibrotest at 0.74	0.47	0.91	DOR= 8.97	SE=0.74
TE at 11.kPa	0.75	0.90	DOR=26.37	SE=0.63
APRI at 2.0	0.20	0.84	DOR=1.28	SE=0.42
APRI at 1.0	0.67	0.81	DOR=8.38	SE=0.65
Diagnostic accuracy (HCV)	Sensitivity	Specificity	Lognormal distribution where applicable	
Platelet count	0.87	0.84	DOR=33.39	SE=0.79
Fibrotest at 0.56 - 0.75	0.80	0.70	Sampled from the joint posterior distribution (WinBUGS iterations)	
ELF at 9.3 – 10.44	0.81	0.80	Sampled from the joint posterior distribution (WinBUGS iterations)	

Parameter description	Point estimates		Probability distribution	Distribution parameters
APRI at 0.5 - <1.5	0.84	0.78	Sampled from the joint posterior distribution (WinBUGS iterations)	
APRI at 1.5 – 2.5	0.36	0.95	Sampled from the joint posterior distribution (WinBUGS iterations)	
FIB-4 at 2.3122	0.80	0.78	DOR=14.00	SE=0.68
AST/ALT ratio at 1.0	0.32	0.97	DOR=15.08	SE=0.57
TE at 9.0 - <13.0	0.82	0.90	Sampled from the joint posterior distribution (WinBUGS iterations)	
TE at 13.0 - <15.0	0.93	0.93	Sampled from the joint posterior distribution (WinBUGS iterations)	
TE at 15+	0.86	0.91	DOR=60.75	SE=0.73
ARFI at 1.55 – 2.0	0.88	0.84	Sampled from the joint posterior distribution (WinBUGS iterations)	
pSWE (optimal cut-off)	0.90	0.89	DOR=69.75	SE=1.10
TE+ARFI (12.2kPa and 1.8m/s)	0.85	0.94	DOR=95.63	SE=0.53
TE or ARFI (12.2kPa or 1.8m/s)	0.96	0.83	DOR=127.50	SE=0.75
SAFE algorithm	0.86	0.90	DOR=52.58	SE=0.37
Castera algorithm	0.90	0.98	DOR=492.75	SE=0.61
Diagnostic accuracy (ALD)	Sensitivity	Specificity	Lognormal distribution	
APRI at 1.5 – 2.5	0.40	0.61	DOR=1.03	0.60
TE at 11.0 - <13.0	0.98	0.79	DOR=224.66	3.24
TE at 15+	0.80	0.76	DOR=12.57	0.71
Diagnostic accuracy (NAFLD)	Sensitivity	Specificity	Lognormal distribution	
TE at 10.0 - <13.0	0.78	0.95	DOR=70.00	1.00
TE at >15	0.99	0.96	DOR=2498.10	3.23
ARFI at 1.636 – 1.9	0.92	0.92	DOR=132.00	1.17
Utilities (NAFLD)				
Fibrosis F3	0.72		Lognormal	SE=utility decrement/4
Compensated cirrhosis	0.60		Lognormal	SE=utility decrement/4
Decompensated cirrhosis	0.54		Lognormal	SE=utility decrement/4
Varices	0.60		Lognormal	SE=utility decrement/4
Variceal bleeding	0.54		Lognormal	SE=utility decrement/4
Hepatocellular carcinoma	0.54		Lognormal	SE=utility decrement/4
Liver transplant	0.80		Lognormal	SE=utility decrement/4
Post liver transplant	0.85		Lognormal	SE=utility decrement/4
Utilities (HBV)				
Fibrosis F3	0.66		Lognormal	0.024
Compensated cirrhosis	0.55		Lognormal	0.037

Parameter description	Point estimates		Probability distribution	Distribution parameters
Decompensated cirrhosis	0.49		Lognormal	0.064
Hepatocellular carcinoma	0.49		Lognormal	0.064
Varices	0.55		Lognormal	0.037
Variceal bleeding	0.49		Lognormal	0.064
Liver transplant	0.73		Lognormal	0.066
Post liver transplant	0.78		Lognormal	0.064
Utilities (HCV)				
Fibrosis F3	0.66		Lognormal	0.018
Compensated cirrhosis	0.55		Lognormal	0.037
Decompensated cirrhosis	0.49		Lognormal	0.077
Hepatocellular carcinoma	0.49		Lognormal	0.077
Varices	0.55		Lognormal	0.037
Variceal bleeding	0.49		Lognormal	0.077
Liver transplant	0.51		Lognormal	0.081
Post liver transplant	0.52		Lognormal	0.069
Utilities (ALD)				
Fibrosis F3	0.62		Lognormal	SE=utility decrement/4
Compensated cirrhosis	0.52		Lognormal	SE=utility decrement/4
Decompensated cirrhosis	0.46		Lognormal	SE=utility decrement/4
Hepatocellular carcinoma	0.46		Lognormal	SE=utility decrement/4
Varices	0.52		Lognormal	SE=utility decrement/4
Variceal bleeding	0.46		Lognormal	SE=utility decrement/4
Liver transplant	0.69		Lognormal	SE=utility decrement/4
Post liver tranplant	0.74		Lognormal	SE=utility decrement/4
Test costs (£)				
Transient elastography	68.00		gamma	SE=mean/4
ARFI-VTq	50.96		gamma	SE=mean/4
pSWE	50.96		gamma	SE=mean/4
ELF	111.06		gamma	SE=mean/4
Fibrotest (one threshold)	44.83		gamma	SE=mean/4
Fib4 (one threshold)	4.52		gamma	SE=mean/4
AST/ALT ratio	5.41		gamma	SE=mean/4
APRI	4.16		gamma	SE=mean/4
Platelets	2.71		gamma	SE=mean/4
Liver biopsy	639.61		gamma	SE=mean/4
SAFE algorithm	193.09		gamma	SE=mean/4

Parameter description	Point estimates		Probability distribution	Distribution parameters
Castera algorithm	248.42		gamma	SE=mean/4
Other test costs (£)				
HBV-DNA test	66.37		gamma	SE=mean/4
HCV-RNA test	79.43		gamma	SE=mean/4
Full blood count	2.71		gamma	SE=mean/4
INR	2.94		gamma	SE=mean/4
Urea-electrolytes	3.00		gamma	SE=mean/4
LFT	4.48		gamma	SE=mean/4
Surveillance test costs (£)				
Diagnostic Endoscopy	205.66		gamma	SE=mean/4
Ultrasound	49.00		gamma	SE=mean/4
AFP	1.42		gamma	SE=mean/4
Staff costs (£)				
GP consultation	67.00		gamma	SE=mean/4
GP practice nurse consultation	17.67		gamma	SE=mean/4
Hepatologist - first appointment	217.00		gamma	SE=mean/4
Hepatologist - follow up	176.00		gamma	SE=mean/4
Hospital nurse	19.33		gamma	SE=mean/4
Hospital dietitian	12.33		gamma	SE=mean/4
Hospital pharmacist	32.00		gamma	SE=mean/4
Procedure and Drug costs (£)				
Band Ligation	1325.83		gamma	SE=mean/4
Variceal bleeding treatment	2653.29		gamma	SE=mean/4
***Decompensation costs* (6-monthly)**				
Inpatient days	4568.89		gamma	SE=mean/4
Procedures	1204.42		gamma	SE=mean/4
Drugs	163.81		gamma	SE=mean/4
HBV drug treatments				
Pega-2a Pegasys (per year)	6499.90		fixed	
Entecavir (per year)	4419.66		fixed	
Tenofovir (per year)	2486.75		fixed	
HCV drug treatments				
Sofosbuvir (Sovaldi	11,660.98		Fixed	
ribavirin (Copegus)	246.65		Fixed	
Sofosbuvir/Ledipasvir (Harvoni)	12,993.33		Fixed	
Sofosbuvir/Ribavirin 12 weeks	36,092.87		Fixed	
Sofosbuvir/Ledipasvir 12 weeks	38,979.99		Fixed	
Sofosbuvir/Ledipasvir 8 weeks	25,986.66		Fixed	
Pega-2a/ribavirin 24 weeks	4359.88		fixed	
Pega-2a/ribavirin 48 weeks	8719.75		fixed	
Liver Transplant state costs (£) – 6-monthly				
HBV				

Parameter description	Point estimates	Probability distribution	Distribution parameters
Liver transplant - Year 1	34,854.82	gamma	SE=mean 4
Liver transplant - Year 2	11,943.02	gamma	SE=mean 4
Post liver transplant	7454.69	gamma	SE=mean 4
HCV			
Liver transplant - Year 1	24,294.20	gamma	SE=mean 4
Liver transplant - Year 2	6428.52	gamma	SE=mean 4
Post liver transplant	941.37	gamma	SE=mean 4
ALD			
Liver transplant - Year 1	29,574.51	gamma	SE=mean 4
Liver transplant - Year 2	9185.77	gamma	SE=mean 4
Post liver transplant	4198.03	gamma	SE=mean 4
NAFLD			
Liver transplant - Year 1	29,574.51	gamma	SE=mean 4
Liver transplant - Year 2	9185.77	gamma	SE=mean 4
Post liver transplant	4198.03	gamma	SE=mean 4

Abbreviations: AFP: alpha-fetoprotein blood test; APRI: Aspartate aminotransferase to platelet ratio index; ARFI: Acoustic radiation force impulse imaging; AST/ALT: Aspartate aminotransferase to alanine aminotransferase; Castera algorithm: combination of transient elastography, Fibrotest and liver biopsy; ELF: Enhanced liver fibrosis test; INR: International normalized ratio; LFT: liver function blood test; SAFE algorithm: combination of Fibrotest, APRI and liver biopsy; TE: Transient elastography

N.2.3.2 Diagnostic accuracy

The characteristics of liver biopsy, when serving as a reference standard, were carefully specified in the diagnostic review protocol. Therefore, after agreement with the GDG, only studies reporting a liver biopsy with at least 6 portal tracts and a length of 15 mm or more were considered in the review of the literature. When there were not enough studies (fewer than 3) around the diagnostic accuracy of a specific test for pooled sensitivity and specificity estimates, the corresponding 2×2 diagnostic table was selected from a single study that was believed to represent the best quality evidence. For the ALD cohort and TE at a 11- <13 threshold, to represent the uncertainty around its diagnostic accuracy and because the log-normal distribution could not fit onto a test with a 100% sensitivity, its 2×2 table was adjusted by adding 0.1 patients in each of the four diagnostic outcomes. This brought down its sensitivity from 100 to 99. A similar approach was followed for the NAFLD cohort and TE at a 15 threshold. Selection criteria for the chosen sources are presented in Table 76 below.

Table 76: Source selection when <3 studies identified

Aetiology	Test	Source	Reason
HCV	Platelet count	Sirli 2010	Higher quality reference standard (compared to Lackner 2005)
HCV	AST/ALT ratio	Borroni 2006	Higher quality reference standard and larger patient cohort (compared to Lackner 2005)
NAFLD	TE (at 10.0 -<13.0)	Gaia 2011	Higher quality reference standard and more representative patient cohort (compared to Wong 2010b)
NAFLD	TE (at 15.0)	Yoneda 2008	Larger patient cohort and smaller time gap between TE and liver biopsy (compared to Yoneda 2010)

Aetiology	Test	Source	Reason
NAFLD	ARFI	Fierbinteanu 2013	Larger patient cohort and smaller time gap between TE and liver biopsy (compared to Yoneda 2010)

To account for uncertainty around diagnostic accuracies and correlation between sensitivity and specificity a joint distribution was used when making diagnostic accuracies probabilistic. First of all the diagnostic odds ratio (DOR) was calculated for the diagnostic test:

$$DOR = \frac{sensitivity}{1 - sensitivity} * \frac{specificity}{1 - specificity}$$

The standard error of the log DOR was calculated using the absolute values for the number of TP, TN, FP and FN:

$$SE(\ln(DOR)) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Using these equations a normal distribution was fitted around the log of the DOR.

Once the DOR is calculated the sensitivity can become a function of the DOR and the specificity:

$$sensitivity = 1 - \frac{specificity}{specificity + (1 - specificity) * DOR}$$

Finally a beta distribution was fitted around the specificity therefore when probabilistic sensitivity analysis is conducted the specificity will change in accordance to the overall diagnostic uncertainty and its relationship with the sensitivity.

When reviewers identified more than 2 studies for a specific test, pooled diagnostic accuracy figures were estimated with the use of Bayesian methods. To account for uncertainty around these figures random samples were drawn from the original joint posterior distribution (WinBUGS iterations) for the purposes of probabilistic sensitivity analysis.

Diagnostic accuracy data for the HBV cohort were sourced from the NICE Hepatitis B guideline (CG165).

N.2.3.3 Baseline transition probabilities

Relevant transition rates were sought in the literature and were confirmed by the GDG as appropriate for use in the current model. All transition rates were transformed to 6-monthly transition probabilities.

N.2.3.3.1 Hepatitis B and hepatitis C

Table 77: HBV – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3 (HBeAg pos)	Compensated cirrhosis	0.019	Wright 2006
Fibrosis F3 (HBeAg neg)	Compensated cirrhosis	0.046	Dakin 2010
Compensated cirrhosis	Decompensated cirrhosis	0.025 (a)	Dakin 2010
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with	0.033 (c)	Berzigotti 2013

From	To	Value	Source
	varices		
Compensated cirrhosis with varices	Bleeding	0.064	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.154	NIEC 1988
Compensated/Decompensated cirrhosis/Bleeding	HCC	0.012	Dakin 2010
Decompensated cirrhosis/ bleeding	Transplant	0.008	Wright 2006
HCC	Transplant	0.008	Wright 2006
Compensated cirrhosis	Death	0.026	Dakin 2010
Decompensated cirrhosis	Death	0.163	Dakin 2010
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010
Transplant	Death	0.111	Dakin 2010
Post-transplant	Death	0.029	Dakin 2010

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices.
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices.
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices.

Table 78: HCV – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3	Compensated cirrhosis	0.019	Wright 2006
Compensated cirrhosis	Decompensated cirrhosis	0.020 (a)	Wright 2006
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices	Bleeding	0.065	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.154	NIEC 1988
Compensated/Decompensated cirrhosis/Bleeding	HCC	0.073	Wright 2006
Decompensated cirrhosis/HCC/bleeding	Transplant	0.010	Wright 2006
Compensated cirrhosis	Death	0.013	Dienstag 2011
Decompensated cirrhosis	Death	0.067	Wright 2006
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.245	Wright 2006
Transplant	Death	0.078	Wright 2006
Post-transplant	Death	0.0151	Wright 2006

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices.
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices.

(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices.

As presented in the above tables, the majority of the transition probabilities originated from the Wright 2006 UK HTA and an economic evaluation on HBV drugs conducted by Dakin et al 2010. For use in the current model those figures where sourced from the Crossan 2015 HTA. The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013, those were adjusted by assuming that 2/3 of patients develop medium to large varices; this adjustment was applied to all subgroups evaluated in the model. Bleeding rates were obtained from a prospective study of 321 patients with cirrhosis and varices and no history of bleeding conducted by the North Italian Endoscopic Club (NIEC 1988). The HCC incidence rate was assumed to be constant across all patients with cirrhosis (compensated/decompensated), an approach also followed by the Crossan 2015 HTA. Bleeding mortality was sourced from Stevenson 2012 and it was based on clinical judgement. The decompensation rates were adjusted for people with and without varices with a ±25% adjustment to the baseline rate that was based on GDG expert opinion. This adjustment was considered appropriate by the GDG and was applied to all the subgroups considered in the model.

N.2.3.3.2 NAFLD

Table 79: NAFLD – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3	Compensated cirrhosis	0.033	Singh 2015
Compensated cirrhosis	Decompensated cirrhosis	0.028 (a)	Hui 2003
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices	Bleeding	0.065	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.154	NIEC 1988
Compensated/Decompensated cirrhosis/Bleeding	HCC	0.013	Ascha 2010
Decompensated cirrhosis/HCC/bleeding	Transplant	0.009	Average from HBV and HCV cohorts
F3	Death	0.003	Younossi 2011
Compensated cirrhosis	Death	0.009	Younossi 2011
Decompensated cirrhosis	Death	0.114	Average from HBV and HCV cohorts
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010 (from HBV cohort)
Transplant	Death	0.094	Average from HBV and HCV cohorts
Post-transplant	Death	0.022	Average from HBV and HCV cohorts

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices.
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices.

As presented in the above table, for the progression of NAFLD patients to cirrhosis a transition probability was obtained from the Singh 2015 meta-analysis of studies with a paired biopsy study design. The decompensation rate was sourced from Hui 2003, a study observing the long-term outcomes of cirrhosis in Non-alcoholic steatohepatitis (NASH) patients. The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013, those were adjusted by assuming that 2/3 of patients develop medium to large varices. Bleeding rates were obtained from a prospective study of 321 patients with cirrhosis and varices and no history of bleeding conducted by the North Italian Endoscopic Club (NIEC 1988). Bleeding mortality was sourced from Stevenson 2012 and it was based on clinical judgement. The incidence of HCC was obtained from Ascha 2010, a study evaluating the incidence and risk factors of HCC in 195 NASH patients. It was assumed that this rate applied to both compensated and decompensated patients. Due to the lack evidence in the remaining transition probabilities, those from the hepatitis cohorts were used after agreement with the GDG.

N.2.3.3.3 ALD

Table 80: ALD – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3	Compensated cirrhosis	0.078	Pares 1986
Compensated cirrhosis	Decompensated cirrhosis	0.036 (a)	Fleming 2010
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices (abstainers)	Bleeding	0.025	Stevenson 2012
Compensated cirrhosis with varices (drinkers)	Bleeding	0.078	Stevenson 2012
Decompensated cirrhosis with varices (abstainers)	Bleeding	0.059	GDG assumption
Decompensated cirrhosis with varices (drinkers)	Bleeding	0.189	GDG assumption
Compensated/Decompensated cirrhosis/Bleeding	HCC	0.042	Average from HBV and HCV cohorts
Decompensated cirrhosis/HCC/bleeding	Transplant	0.009	Average from HBV and HCV cohorts
Compensated cirrhosis	Death	0.019	Average from HBV and HCV cohorts
Decompensated cirrhosis	Death	0.114	Average from HBV and HCV cohorts
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010 (from HBV cohort)
Transplant	Death	0.094	Average from HBV and HCV cohorts
Post-transplant	Death	0.022	Average from HBV and HCV cohorts

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices.
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices.

As presented in the table above, progression to cirrhosis was obtained from Pares 1986, a study on the histological course of alcoholic hepatitis. The decompensation rate was sourced from an epidemiologic analysis of patients from the UK General practice research database conducted by

Fleming 2010. The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013, those were adjusted by assuming that 2/3 of patients develop medium to large varices. Bleeding rates were obtained from Stevenson 2012 where separate rates where reported for drinkers and abstainers (for abstainers this was based on clinical judgement). Those were adjusted for decompensated cirrhosis patients according to the proportional increase reported in NIEC 1988 that was used in the HBV, HCV and NAFLD model cohorts. The HCC incidence rate was assumed to be constant across all people with cirrhosis (compensated/decompensated), an approach also followed by the Crossan 2015 HTA. Bleeding mortality was sourced from Stevenson 2012 and it was based on clinical judgement. Due to the lack evidence in the remaining transition probabilities, the mean between the HBV and HCV cohorts were used after agreement with the GDG.

N.2.3.4 Life expectancy and mortality rates

Life tables for England and Wales, published by the Office of National Statistics (ONS) based on 2011–2013 mortality data were used to establish population mortality rates for men and women for ages 45 to 100 years.[648] ONS 2013 mortality statistics for England and Wales by cause of death[646,647,648] were used to calculate the proportion of deaths for each 5-year age group which were due to liver related or non-liver related causes. These proportions were applied to the mortality rates to give the risk of death due to non-liver related causes for each annual age group for both men and women.

N.2.3.5 Utilities

N.2.3.5.1 Hepatitis B and hepatitis C

Quality of life figures were systematically sought in the literature (details on Appendix G) with a priority to studies in a UK population using EQ-5D with UK weights, in line with the NICE reference case. For both hepatitis B & C cohorts, utilities were sourced from a 2006 NIHR HTA study by Wright et al. on HCV patients. These were obtained through a separate observational study on 355 patients to whom an EQ-5D questionnaire was administered. For the health states of decompensated cirrhosis, HCC and transplant, utilities were sourced from Longworth et al. 2003, a UK transplantation study. Although HBV figures for the later health states were also available for a HBV population in the Longworth study those were not used, as there was a lack of consistency with the utilities reported by Wright 2006 that was highlighted by the GDG.

In addition, our search identified HBV-specific utilities in a non-UK population also used by the NICE Hepatitis B clinical guideline (CG165), those were not used however as they were considered too high for a population with advanced liver disease.

N.2.3.5.2 Alcohol-related liver disease

The systematic literature search identified a lack of quality of life evidence for this population. The GDG noted that this is mainly due to the fact that it is difficult for any quality of life instrument to isolate the effect of liver disease from the other effects of a patient's alcohol dependence.

For this reason the GDG suggested the use of utility values derived from alcohol-dependent patients as a baseline for the QoL of patients with compensated cirrhosis (since this state is asymptomatic). After a comprehensive literature search, a study from Pettinati et al 2009 was identified and used as a source for this value. The objective of the study was to quantify the effectiveness of extended-release naltrexone in alcohol-dependent patients through a randomised control trial. The SF-36 values of the trial's control group were transformed into QoL utilities through the Ara & Brazier mapping algorithm (first regression model).[45]

To acquire utilities for the remaining model health states, using the baseline value from Pettinati et al 2009 for the compensated cirrhosis state, we estimated the utilities for the other health states in this subgroup as the product of the baseline value by the proportional difference in utility in the Hep B

population for the health state compared to the compensated cirrhosis state. For example, in the Hep B subgroup compensated cirrhosis has a utility of 0.55 while decompensated cirrhosis has a utility of 0.49. Therefore in the ALD subgroup the utility of decompensated cirrhosis is calculated as the utility of compensated cirrhosis in the ALD population (0.52) multiplied by the ratio of the 2 states in the Hep B group (0.52 * 0.49/0.55).

N.2.3.5.3 Non-alcoholic fatty liver disease

The systematic literature review identified a variety of evidence on NAFLD patients. In the majority of this evidence authors did not report QoL results per liver disease state (fibrosis, compensated cirrhosis, decompensated cirrhosis). In addition, a range of relevant literature could not be used due to the lack of available mapping algorithms for transformation to EQ-5D utilities. A study conducted by David et al. 2009 reported a QoL estimate specifically on non-NASH NAFLD patients (ADD VALUE), however this was considered too low by the NAFLD GDG and not appropriate to be used in the economic model.

As an alternative, the NAFLD GDG suggested using the utility attributed to patients with obesity as a baseline for QoL of non-NASH NAFLD patients. This value was obtained from recent NICE public health guidance (PH53) that simulated the relation of BMI with quality of life in two-dimensional tables. To acquire utilities for the remaining model health states the same method used for the ALD subgroup was used (ie using the proportional increments/decrements from the hepatitis B subgroup).

N.2.3.6 Resource use and cost

N.2.3.6.1 Diagnostic test costs

The majority of the unit costs were sourced from the two relevant published HTAs.[204,237] The cost of ARFI VTq was built on top of the ultrasound NHS tariff (NHS reference costs 2013-14) assuming an extra kit has to be acquired in order to perform an ARFI examination. The cost of the kit was sourced from the relevant NICE M-Tec assessment.[623] A machine lifespan of 5 years with 500 Ultrasound/ARFI scans per year was assumed after GDG guidance. Point shear wave elastography cost was assumed to be similar to ARFI due to technology similarities and a lack of available evidence around it.

Table 81: Cirrhosis test unit costs

Test	Cost (£)	Source	Comment
Transient elastography	68.00	NHS hospital trust	Provided by GDG member
ARFI-VTq	50.96	Assumption	Built on top of ultrasound NHS tariff – see below
pSWE	50.96	Assumption	Assumed similar to VTq
ELF	111.06	Crossan 2015	
Fibrotest (one threshold)	44.83	Crossan 2015	
Fib4 (one threshold)	4.52	Crossan 2015	
AST/ALT ratio	5.41	Crossan 2015-Donnan 2009	Assumed to equal the cost of an LFT plus the cost of an extra biomarker
APRI	4.16	Crossan 2015	
Platelets	2.71	Donnan 2009	Part of FBC
Liver biopsy	639.61	NICE MTG027	
SAFE algorithm	193.09	Estimation	Based on the proportions of the cohort that received each of the tests included in the algorithm, figures sourced from the original paper
Castera algorithm	248.42	Estimation	Based on the proportions of the cohort that

Test	Cost (£)	Source	Comment
			received each of the tests included in the algorithm, figures sourced from the original paper

(a) All values were inflated to 2013/14 prices

N.2.3.6.2 Surveillance for complications costs

Table 82: Unit costs of surveillance

Test	Cost (£)	Source	Comment
Diagnostic endoscopy	205.66	NHS reference costs 2013/14	FZ60Z, Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over
Ultrasound	49.00	NHS reference costs 2013/14	RA23Z, Ultrasound scan less than 20 minutes
AFP	1.42	Crossan 2015	

(a) All values were inflated to 2013/14 prices

N.2.3.6.3 Drugs

Unit costs were sourced from BNF 69. The dosages were either taken from the relevant NICE technology appraisals or were based on GDG guidance.

Table 83: Unit costs of drugs

Drug	Cost per 28 days (£)	Dose
Pega-2a (Pegasys ®)	497.76	180 mg weekly
Entecavir	339.04	500 mg daily
Tenofovir	190.76	245 mg daily
Sofosbuvir (Sovaldi ®)	11,660.98	400 mg daily
Sofosbuvir/Ledipasvir (Harvoni®)	12,993.33	400 mg daily
Ribavirin (Copegus®)	246.65	400 mg daily

Source: BNF 69

N.2.3.6.4 Health states

Health state costs were constructed with GDG guidance so they represent a reference patient pathway. These include staff, test, procedure and drug costs where relevant. When pegylated interferon was used as a drug treatment a more intensive management is assumed according to current clinical protocols. Staff costs were sourced from the NHS reference cost 2013/14 schedules and PSSRU 2014. A multi-speciality staff mix was also agreed with the GDG so that it better represents current care arrangements. Test costs where sourced from a relevant HTA (Donnan 2009). Complication costs related to cirrhosis were sourced from an HTA on HCV patients (Wright 2006) and were assumed to be relevant to all aetiologies. Liver transplant costs for hepatitis B or C patients were sourced from Brown 2006 and Wright 2006. An average of those figures was used for the NAFLD and ALD aetiologies.

Table 84: Unit costs of staff

Drug	Cost	Details
Hepatologist – first appointment	217.00	Non-Admitted Face to Face Attendance (WF01B)
Hepatologist – follow up	176.00	Non-Admitted Face to Face Attendance (WF01A)
Hospital nurse	19.33	20 min appointment, £58 per hour of face-to-face contact

Drug	Cost	Details
		including qualifications
Hospital pharmacist	32.00	20 min, £96 per hour of direct patient time (including travel and qualifications)

Source: NHS reference costs 2013/14, PSSRU 2014

Table 85: 6-monthly health state costs (based on GDG guidance)

Input	Value	Details
HBV		
Fibrosis F3 during first line treatment (includes drug costs)	4,192	7 appointments (50%hepatologist+25%nurse+25%pharmacist)+ combination of tests[(a)]
Fibrosis F3 during second line treatment (includes drug costs)	1,662	1 appointment (50%hepatologist+25%nurse+25%pharmacist)+ combination of tests[(a)]
Fibrosis F3 (treated)	255	1 appointment (50%hepatologist+25%nurse+25%pharmacist)+ combination of tests [(a)]
Compensated cirrhosis during first line treatment (includes drug costs)	4,192	7 appointments (50%hepatologist+25%nurse+25%pharmacist) + combination of tests [(a)]
Compensated cirrhosis during second line treatment (includes drug costs)	1,662	1 appointment (50%hepatologist+25%nurse+25%pharmacist) + combination of tests[(a)]
Compensated cirrhosis (treated)	255	1 appointment (50%hepatologist+25%nurse+25%pharmacist + combination of tests[(a)]
Decompensated cirrhosis	6,929	4 hepatologist appointments+ combination of tests[(a)] + Complication costs
Bleeding	2,653	1 non elective band ligation + 1.5 follow up band ligations
HCC	6,929	Similar to those of decompensated cirrhosis state
HCV		
Fibrosis F3 – genotype 1 (includes drug costs)	26,380	2 appointments with nurse + 2 with pharmacist + combination of tests [(b)]
Fibrosis F3 – genotype 2/3 (includes drug costs)	5,693	7 appointments (50%hepatologist+25%nurse+25%pharmacist) + combination of tests [(b)]
Fibrosis F3 – genotype 4 (includes drug costs)	11,385	14 appointments (50%hepatologist+25%nurse+25%pharmacist) + combination of tests [(b)]
Fibrosis F3 (treated)	94.57	1 /2 appointment with hepatologist + combination of tests [(c)]
Compensated cirrhosis – genotype 1/4 (includes drug costs)	39,485	3 appointments with nurse + 2 with pharmacist + combination of tests[(b)]
Compensated cirrhosis – genotype 2 (includes drug costs)	36,631	4 appointments with nurse + 2 with pharmacist + combination of tests [(b)]
Compensated cirrhosis - genotype 3 (includes drug costs)	37,823	5 appointments with nurse + 4 with pharmacist + combination of tests [(b)]
Compensated cirrhosis - treated	189	1 appointment with hepatologist + combination of tests [(c)]
Decompensated cirrhosis	6,720	3 hepatologist appointments + combination of tests [(b)] + complication costs
Bleeding	2,653	1 non elective band ligation + 1.5 follow up band ligations
HCC	6,720	Similar to those of decompensated cirrhosis state

Input	Value	Details
ALD		
Fibrosis F3	186	1 appointment with hepatologist + combination of tests [(c)]
Compensated cirrhosis	186	1 appointment with hepatologist + combination of tests [(c)]
Decompensated cirrhosis	9,450	3 hepatologist appointments + combination of tests[(c)] +50% Increased complication costs
Bleeding	2,653	1 non elective band ligation + 1.5 follow up band ligations
HCC	9,450	Similar to those of decompensated cirrhosis state
NAFLD		
Fibrosis F3	186	same as compensated cirrhosis (NAFLD chair suggestion)
Compensated cirrhosis	186	1 appointment with hepatologist + combination of tests [(c)]
Decompensated cirrhosis	6,495	3 hepatologist appointments + combination of tests [(c)] + complication costs
Bleeding	2,653	1 non elective band ligation + 1.5 follow up band ligations
HCC	6,495	Similar to those of decompensated cirrhosis state
Liver transplant – Year 1	29,575	Average of HBV-HCV cohort costs
Liver transplant – Year 2	9,186	Average of HBV-HCV cohort costs
Post-transplant	4,198	Average of HBV-HCV cohort costs

(a) DNA+ full blood count + international normalized ratio + liver blood test
(b) RNA+ full blood count + international normalized ratio + liver blood test + urea & electrolytes
(c) Full blood count + international normalized ratio + liver blood test

N.2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for other cause mortality.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities.

Where not already available, transition probabilities were calculated using an assumption of a fixed rate across each source-study follow up

Rates were converted into transition probabilities for the respective cycle length (6 months) before inputting into the Markov model. The probability of the event over the time horizon specified by the literature was converted into a rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (X months)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (6 months)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in each state of the model (6 months) was weighted by a utility value that is dependent on the

time spent in the model and the treatment effect. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and resource costs accrued by patients in every health state was recorded. These subtotals were summed across all subgroups to ascertain the total number of patients in the population and the total QALYs and resource costs accrued for the population. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

N.2.5 Model validation

The model was developed in consultation with the NAFLD and Cirrhosis GDGs; model structures, inputs and results were presented to and discussed with the GDGs for clinical validation and interpretation.

The models were systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The models were peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations.

N.2.6 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost-effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the

total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = (QALYs(X) \times \lambda) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy. The NMB figure is followed by the test ranking and the 95% confidence intervals of the ranks. An additional figure that represented the percentage of simulations where every test ranked first was also calculated.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown.

N.2.7 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[624] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several diagnostic tests, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained. Where the differences in the NMBs between alternative options were considered small ICERs were calculated to interpret the model results.

N.3 Results

Cost-effectiveness results of the cirrhosis diagnostic tests and the optimal surveillance frequency for HCC and oesophageal varices are presented in separate sections. For ALD, ICERs comparing all strategies to no test – no monitor were also calculated due to the high uncertainty depicted in the confidence intervals. For the HCV cohort, diagnostic test results are only presented for genotypes 1 & 3 as those for remaining genotypes did not differ (top 3 test rankings are instead presented for all genotypes). To define the most cost-effective surveillance frequency for HCC and oesophageal varices, ICERs were calculated across the available options. Base case results below were obtained through the probabilistic analysis to take combined parameter uncertainty into account.

Table 86: Definitions of column categories

Header	Definition
Transplants	Number of transplants per patient
Unexpected HCCs	HCC episodes in patients with a false negative diagnosis
Expected HCCs	HCC episodes in patients with a true positive diagnosis
Bleedings	Number of bleeding events per patient
Liver deaths	Deaths occurred due to liver associated mortality (applied to all health states

Header	Definition
	apart from F3 fibrosis)
Decomp	Time spent in decompensated cirrhosis state
Var+dcVar – Unprotected	Time spent with non-band ligated varices
Var+dcVar – Protected	Time spent with band ligated varices
Life years	Total life years per patient

N.3.1 Diagnostic tests – base cases

N.3.1.1 People with NAFLD

Table 87: Number of events & time spent in health states

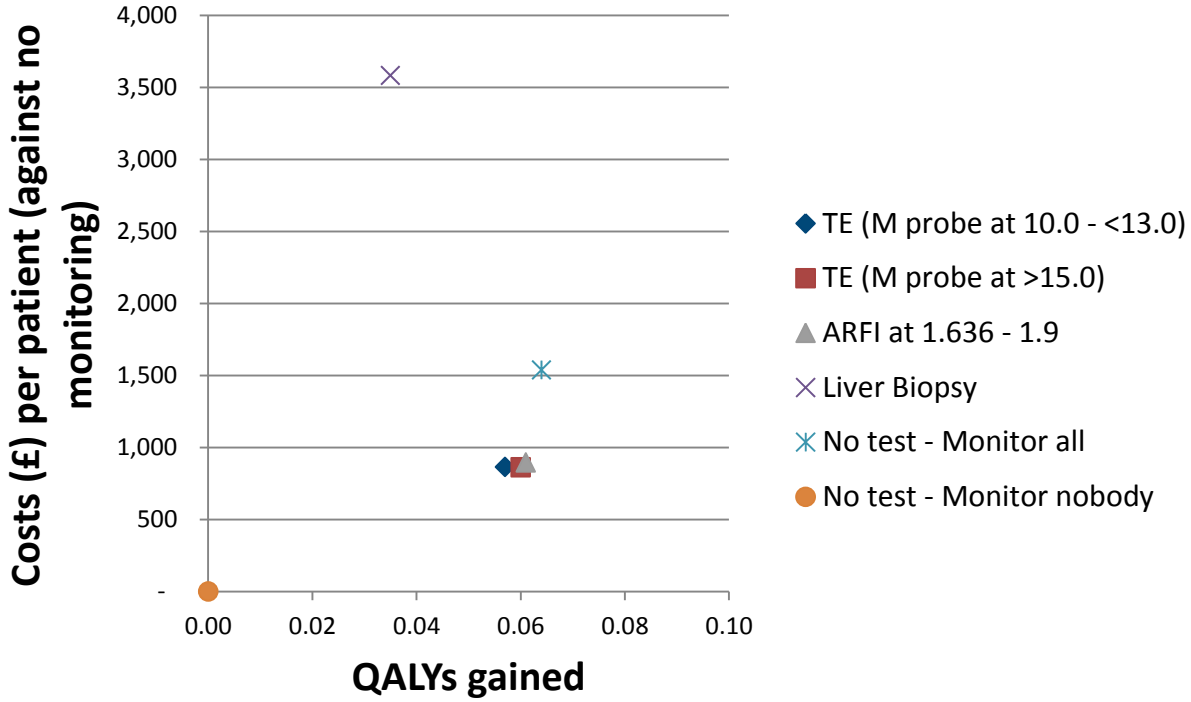
	Events					Time spent (months)		
Test	Transplants	Unexpexted HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
TE at 10.0 - <13.0	0.028	0.025	0.173	0.167	0.670	7.344	2.609	17.511
TE at >15.0	0.028	0.018	0.180	0.166	0.670	7.345	2.736	17.863
ARFI at 1.636 - 1.9	0.028	0.014	0.184	0.165	0.670	7.346	2.799	18.005
Liver Biopsy	0.028	0.012	0.185	0.164	0.667	7.317	2.810	18.274
No test - Monitor all	0.028	0.000	0.198	0.165	0.670	7.348	3.057	18.130
No test - No monitor	0.029	0.159	0.034	0.199	0.677	7.331	0.417	6.994

Table 88: Life years and results

Test	Life years (undiscounted)	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
TE (at 10.0 - <13.0)	19.98	19,328	9.22	165,034	3	1	4	0.1172
TE (at >15.0)	19.99	19,325	9.22	165,107	1	1	4	0.5242
ARFI at 1.636 - 1.9	19.99	19,369	9.22	165,082	2	1	4	0.3462

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20000/QALY	Rank	Rank 95% CIs		Prob (c/e)
Liver Biopsy	19.91	22,173	9.19	161,692	6	6	6	0
No test - Monitor all	20.00	20,022	9.23	164,488	5	4	5	0
No test - No monitor	19.77	18,399	9.15	164,690	4	2	5	0.0124

Figure 214: Cost-effectiveness plot: NAFLD



Across the 6 strategies compared, the non-invasive tests ranked on top with TE at a <15.0 threshold ranking first having a NMB of £165,034. All 3 non-invasive strategies delivered similar QALY figures and slightly differed in the overall mean costs. The confidence intervals in the rankings only excluded liver biopsy and the no test strategies from ranking first, highlighting the uncertainty in the cost-effectiveness of the 3 non-invasive tests. In the probabilistic analysis TE at <15 ranked 1st in 52% of the simulations followed by ARFI and TE at 10.0 < 13.0 (35% and 12% respectively).

N.3.1.2 People with ALD

Table 89: Number of events & time spent in health states

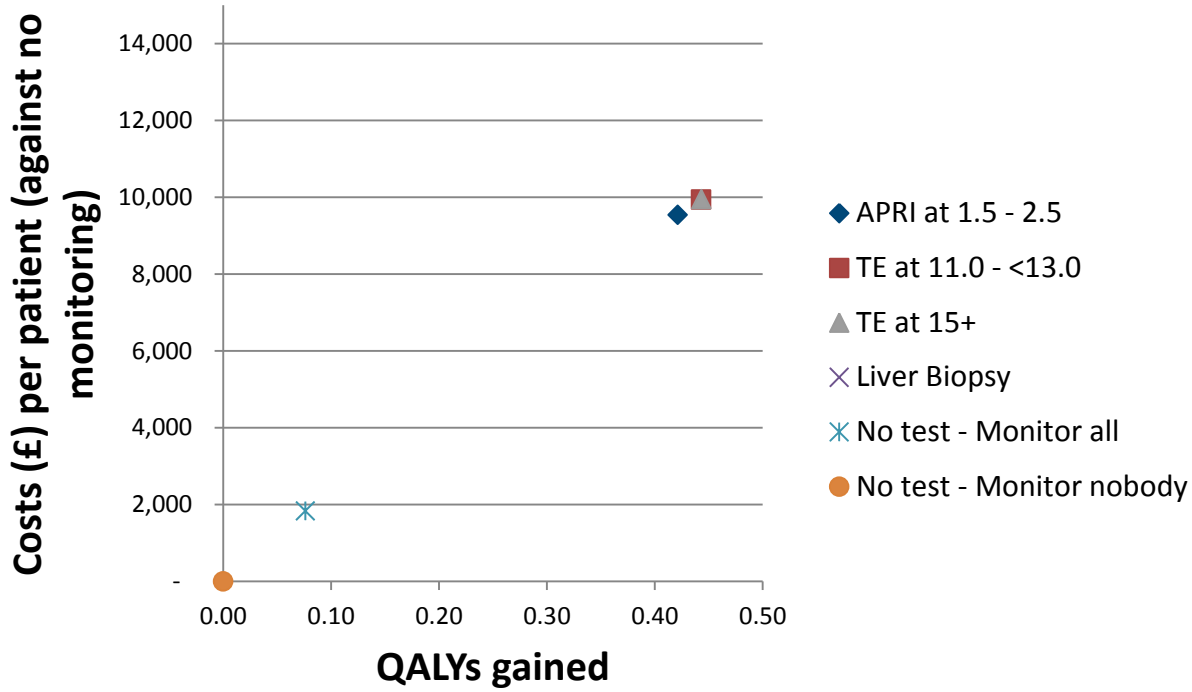
	Events					Time spent (months)		
Test	Transplants	Unexpexted HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
APRI at 1.5 - 2.5	0.044	0.051	0.497	0.132	0.891	8.154	2.342	15.010
TE at 11.0 - <13.0	0.044	0.022	0.529	0.128	0.890	8.173	2.508	16.113
TE at 15+	0.044	0.020	0.531	0.127	0.890	8.175	2.510	16.176
Liver Biopsy	0.047	0.014	0.551	0.127	0.882	8.598	2.624	17.495
No test - Monitor all	0.033	0.000	0.491	0.163	0.910	6.482	2.269	12.741
No test - No monitor	0.032	0.387	0.094	0.196	0.914	6.446	0.342	5.322

Table 90: Life years and results

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20000/QALY	Rank	Rank 95% CIs		Prob (c/e)
APRI at 1.5 - 2.5	12.34	39,096	5.33	67,512	5	1	5	0.0314
TE at 11.0 - <13.0	12.39	39,493	5.35	67,535	3	1	5	0.168

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20000/QALY	Rank	Rank 95% CIs		Prob (c/e)
TE at 15+	12.40	39,509	5.35	67,532	4	1	5	0.046
Liver Biopsy	12.67	44,106	5.44	64,649	6	6	6	0
No test - Monitor all	11.24	31,327	4.98	68,344	2	1	5	0.1284
No test - No monitor	11.02	29,436	4.91	68,720	1	1	5	0.6262

Figure 215: Cost-effectiveness plot: ALD



In the ALD cohort, testing for cirrhosis was not cost-effective at a £20,000 threshold with the 2 no test strategies ranking higher. The no monitor strategy had the highest NMB value of £68,720 and the monitor all followed with £68,344. The diagnostic test that ranked first was TE at 11.0<13.0 with a NMB of £67,535. All diagnostic test strategies delivered considerably higher QALY values compared to no testing (up to 0.5 more QALYs) but at increased mean costs. All strategies apart from liver biopsy had wide confidence intervals of their ranks ranging from 1st to 5th and depicting the high uncertainty in the results. ICERs comparing all strategies against no test – no monitoring ranged from £22,671 to £22,860 for the non-invasive strategies and at £27,682 for liver biopsy.

N.3.1.3 People with HBV: HBV– antigen

Table 91: Number of events & time spent in health states

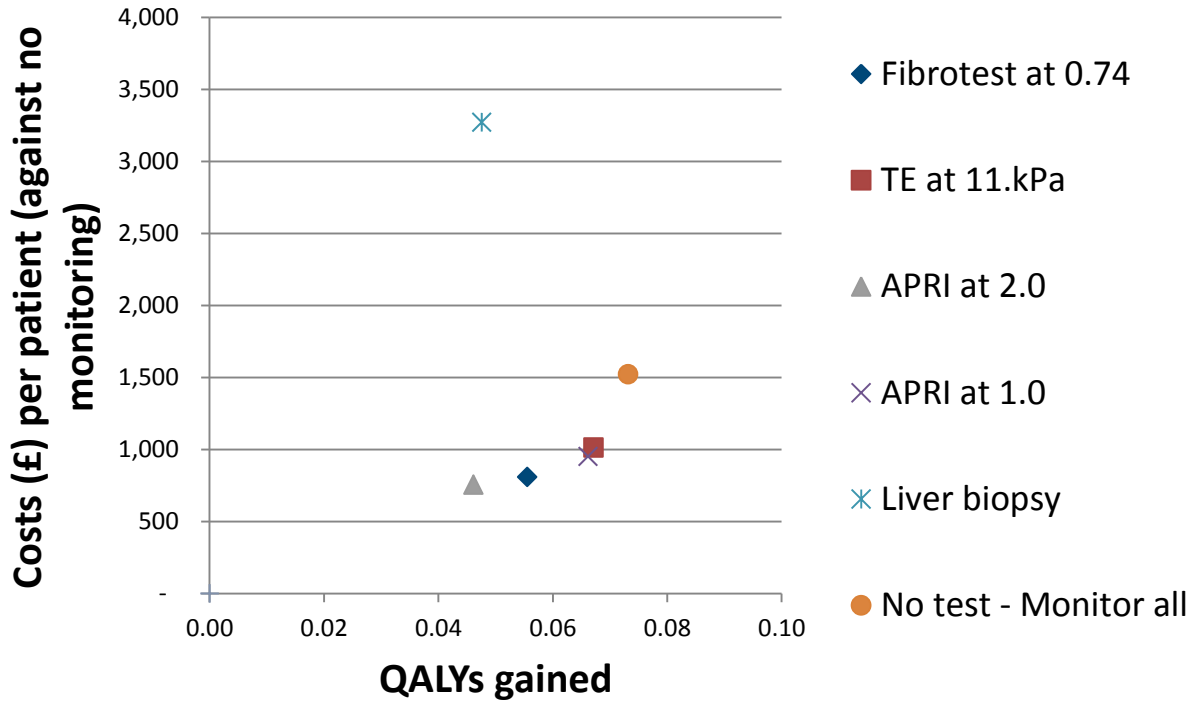
	Events					Time spent (months)		
Test	Transplants	Unexpexted HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
Fibrotest at 0.74	0.039	0.043	0.184	0.237	0.707	9.856	2.900	22.637
TE at 11.kPa	0.039	0.019	0.208	0.232	0.706	9.864	3.333	24.193
APRI at 2.0	0.039	0.054	0.172	0.242	0.707	9.853	2.720	21.140
APRI at 1.0	0.039	0.017	0.210	0.233	0.706	9.864	3.368	23.980
Liver biopsy	0.039	0.014	0.213	0.230	0.703	9.832	3.408	24.692
No test - Monitor all	0.039	0.000	0.228	0.231	0.706	9.871	3.717	24.523
No test - No monitor	0.040	0.171	0.052	0.273	0.714	9.824	0.646	12.251

Table 92: Life years and results

Test	Life years (undiscounted)	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
Fibrotest at 0.74	19.23	63,185	8.33	103,405	3	1	5	0.2194
TE at 11.kPa	19.26	63,388	8.34	103,433	2	1	5	0.1968
APRI at 2.0	19.20	63,132	8.32	103,269	4	2	5	0.0046
APRI at 1.0	19.26	63,327	8.34	103,475	1	1	4	0.4408

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20000/QALY	Rank	Rank 95% CIs		Prob (c/e)
Liver biopsy	19.21	65,646	8.32	100,785	7	7	7	0
No test - Monitor all	19.28	63,899	8.35	103,043	6	3	6	0.0002
No test - No monitor	19.03	62,376	8.27	103,103	5	1	6	0.1382

Figure 216: Cost-effectiveness plot: HBV– antigen



In the HBeAg-negative cohort APRI at 1.0 ranked first with NMB of £103,475. TE at 11kPa and Fibrotest at 0.74 followed with NMBs of £103,433 and £103,405 respectively. TE delivered similar QALYs to APRI at 1.0 but for an incremental cost of £61 per patient. Fibrotest was less costly then TE and APRI at 1.0 but less effective too. Liver biopsy ranked lowest across all strategies particularly due to its high overall mean costs. In the confidence intervals of the ranks TE, Fibrotest, APRI at 1.0 and no test – no monitoring could all rank first with APRI at 1.0 ranking first in 44% of the simulations followed by Fibrotest (22%).

N.3.1.4 People with HBV: HBV+ antigen

Table 93: Number of events & time spent in health states

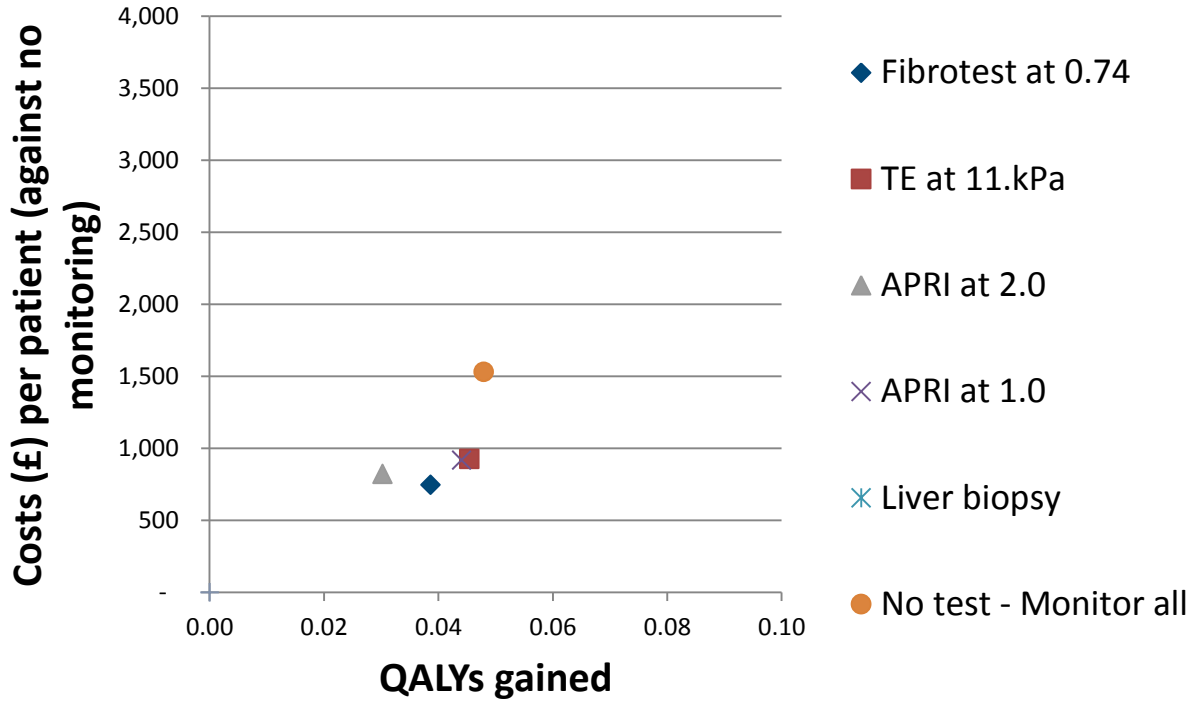
	Events					Time spent (months)		
Test	Transplants	Unexpexted HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
Fibrotest at 0.74	0.034	0.030	0.148	0.203	0.475	8.209	2.294	19.312
TE at 11.kPa	0.034	0.013	0.166	0.198	0.475	8.213	2.612	20.538
APRI at 2.0	0.034	0.036	0.141	0.206	0.476	8.205	2.194	18.134
APRI at 1.0	0.034	0.011	0.167	0.199	0.475	8.213	2.644	20.363
Liver biopsy	0.034	0.010	0.168	0.196	0.473	8.178	2.641	20.953
No test - Monitor all	0.034	0.000	0.179	0.197	0.475	8.216	2.859	20.851
No test - No monitor	0.034	0.129	0.046	0.231	0.481	8.184	0.564	11.331

Table 94: Life years and results

Test	Life years (undiscounted)	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
Fibrotest at 0.74	24.19	42,678	10.07	158,762	1	1	5	0.2316

Test	Life years (undiscounted)	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
TE at 11.kPa	24.21	42,857	10.08	158,720	3	1	5	0.1962
APRI at 2.0	24.17	42,752	10.06	158,521	5	3	5	0.0008
APRI at 1.0	24.21	42,847	10.08	158,702	4	1	5	0.209
Liver biopsy	24.09	45,968	10.04	154,830	7	7	7	0
No test - Monitor all	24.22	43,460	10.08	158,167	6	4	6	0
No test - No monitor	24.05	41,931	10.03	158,738	2	1	6	0.3624

Figure 217: Cost-effectiveness plot: HBV+ antigen



In the HBeAg-positive cohort it was Fibrotest at 0.74 that ranked first. 'No test – Monitor all' and TE at 11kPa followed as second and third options. NMB for Fibrotest was £158,762 and for 'No test – Monitor all' and TE at 11kPa was £158,738 and £158,720 respectively. Liver biopsy ranked lowest across all strategies particularly due to its high mean costs. The top 4 options (TE, Fibrotest, APRI at 1.0 and no test – no monitoring) had NMB sufficiently close that it is impossible to be sure which of these should be preferred in terms of cost-effectiveness. Each could rank first within the confidence intervals. In the probabilistic analysis no test – no monitoring ranked first in 36% of the simulations with TE, Fibrotest, APRI at 1.0 all ranking first in about 20% of the simulations each highlighting the high uncertainty in the results.

N.3.1.5 People with HCV: genotype 1

Table 95: Number of events & time spent in health states

	Events					Time spent (months)		
Test	**Transplants**	**Unexpexted HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
Platelet count	0.002	0.008	0.039	0.004	0.047	0.093	0.034	0.293
Fibrotest at 0.56 - 0.75	0.002	0.010	0.041	0.004	0.052	0.114	0.042	0.331
ELFat 9.3 – 10.44	0.002	0.009	0.039	0.004	0.049	0.101	0.036	0.305
APRI at 0.5 - <1.5	0.002	0.008	0.040	0.004	0.048	0.096	0.037	0.301
APRI at 1.5 – 2.5	0.004	0.042	0.027	0.011	0.077	0.216	0.028	0.442
FIB-4 at 2.3122	0.002	0.011	0.039	0.004	0.050	0.107	0.037	0.316
AST/ALT ratio at 1.0	0.004	0.047	0.026	0.012	0.082	0.234	0.027	0.463
TE at 11.0 - <13.0	0.002	0.010	0.038	0.004	0.047	0.092	0.029	0.283
TE at 13.0 - <15.0	0.002	0.005	0.040	0.003	0.043	0.073	0.028	0.258
TE at 15+	0.002	0.010	0.038	0.004	0.048	0.093	0.029	0.284
ARFI at 1.55 – 2.0	0.002	0.006	0.040	0.003	0.045	0.085	0.033	0.282
pSWE (optimal cut-off)	0.002	0.009	0.039	0.003	0.047	0.090	0.031	0.284
TE+ARFI (12.2kPa and 1.8m/s)	0.002	0.011	0.037	0.004	0.047	0.092	0.027	0.277
TE or ARFI (12.2kPa or 1.8m/s)	0.002	0.003	0.041	0.003	0.043	0.076	0.034	0.273

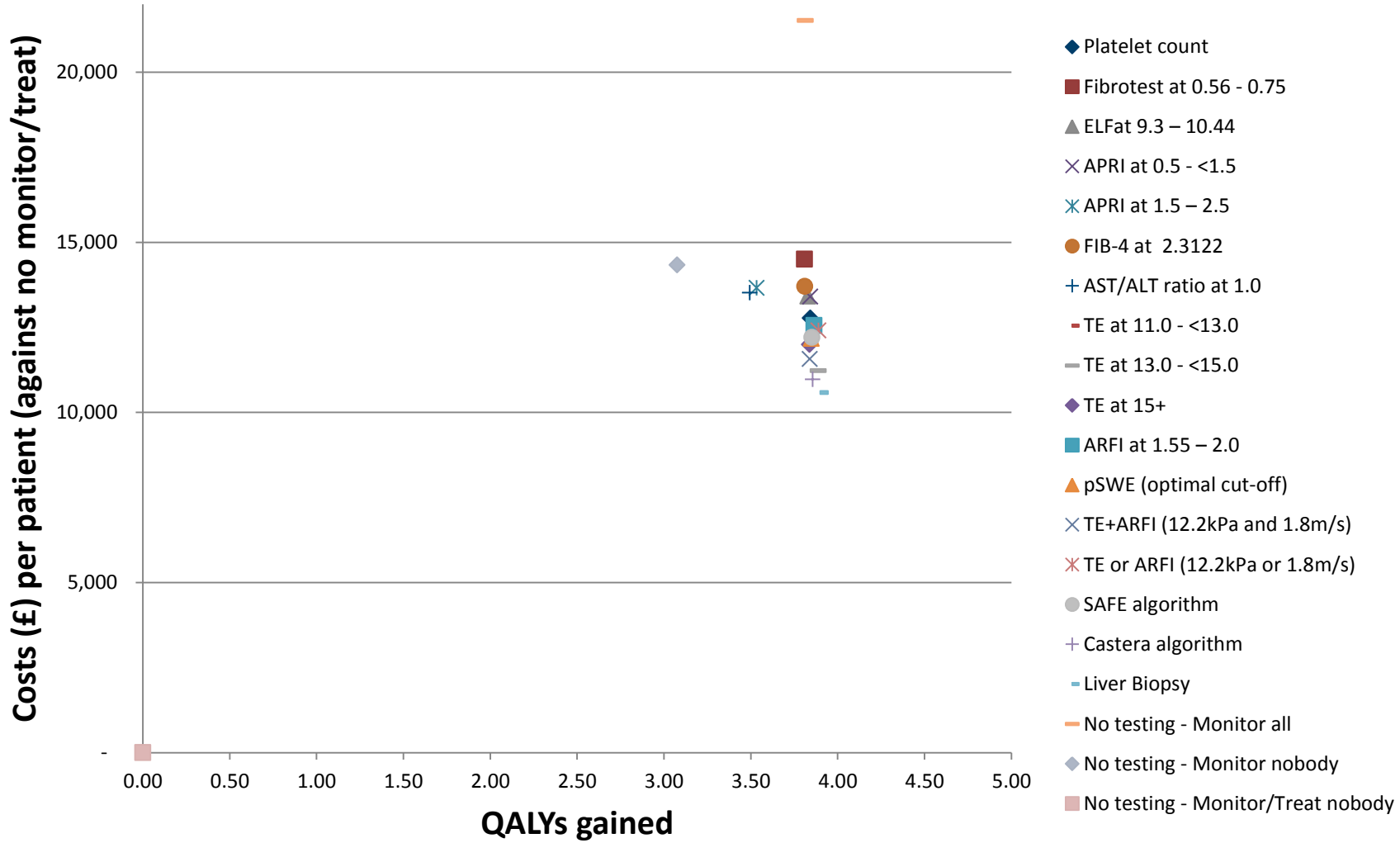
	Events					Time spent (months)		
Test	**Transplants**	**Unexpexted HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
SAFE algorithm	0.002	0.008	0.038	0.003	0.046	0.087	0.030	0.279
Castera algorithm	0.002	0.010	0.038	0.003	0.046	0.086	0.025	0.264
Liver Biopsy	0.002	0.003	0.040	0.002	0.041	0.064	0.024	0.237
No testing - Monitor all	0.003	0.000	0.059	0.004	0.060	0.159	0.086	0.428
No testing - No monitor	0.006	0.091	0.018	0.023	0.130	0.432	0.030	0.749
No testing - Monitor/Treat nobody	0.029	0.441	0.083	0.084	0.626	2.670	0.182	2.743

Table 96: Life years and results

Test	Life years (undiscounted)	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
Platelet count	31.39	30,957	12.20	213,138	11	4	15	0
Fibrotest at 0.56 - 0.75	31.30	32,688	12.17	210,740	15	9	17	0
ELFat 9.3 – 10.44	31.35	31,599	12.19	212,212	13	4	16	0.0022
APRI at 0.5 - <1.5	31.39	31,583	12.20	212,496	12	7	15	0
APRI at 1.5 – 2.5	30.57	31,838	11.90	206,079	16	14	18	0
FIB-4 at 2.3122	31.31	31,887	12.17	211,576	14	8	16	0
AST/ALT ratio at 1.0	30.46	31,700	11.86	205,417	17	13	18	0

Test	Life years (undiscounted)	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
TE at 11.0 - <13.0	31.39	30,256	12.20	213,773	10	4	14	0.0004
TE at 13.0 - <15.0	31.51	29,407	12.25	215,610	2	2	6	0.023
TE at 15+	31.38	30,178	12.20	213,832	8	3	15	0
ARFI at 1.55 – 2.0	31.45	30,737	12.23	213,783	9	3	13	0.0018
pSWE (optimal cut-off)	31.41	30,357	12.21	213,847	7	2	15	0.0006
TE+ARFI (12.2kPa and 1.8m/s)	31.39	29,750	12.20	214,297	5	2	14	0.0002
TE or ARFI (12.2kPa or 1.8m/s)	31.51	30,592	12.25	214,450	4	3	11	0
SAFE algorithm	31.42	30,386	12.21	213,903	6	4	13	0
Castera algorithm	31.43	29,154	12.22	215,212	3	1	14	0.0732
Liver Biopsy	31.54	28,763	12.26	216,479	1	1	2	0.8986
No testing - Monitor all	31.26	39,702	12.18	203,800	18	16	19	0
No testing - No monitor	29.30	32,513	11.44	196,258	19	18	19	0
No testing - Monitor/Treat nobody	19.93	18,183	8.36	149,067	20	20	20	0

Figure 218: Cost-effectiveness plot: HCV genotype 1



In the HCV genotype 1 cohort it was liver biopsy that ranked first with a NMB value of £216,479. TE at 13.0 - <15.0 and the Castera algorithm followed with £215,212 and £215,610 respectively. Liver biopsy dominated all the other strategies apart from no test- no monitor/no treatment by having the highest QALY value and the second lowest mean costs. TE at 13.0 - < 15.0 delivered slightly lower QALYs for an incremental cost of £644. From all strategies it was only liver biopsy and TE at 13.0 - <15.0 that could rank first according to the ranking confidence intervals with liver biopsy ranking first in 90% of the simulations.

N.3.1.6 People with HCV: genotype 3

Table 97: Number of events & time spent in health states

	Events					Time spent (months)		
Test	**Transplants**	**Unexpexted HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
Platelet count	0.005	0.016	0.076	0.009	0.099	0.310	0.128	0.880
Fibrotest at 0.56 - 0.75	0.005	0.017	0.080	0.010	0.105	0.343	0.145	0.940
ELFat 9.3 – 10.44	0.005	0.017	0.077	0.010	0.101	0.322	0.133	0.898
APRI at 0.5 - <1.5	0.005	0.014	0.078	0.009	0.098	0.311	0.136	0.899
APRI at 1.5 – 2.5	0.007	0.075	0.056	0.018	0.150	0.534	0.095	0.948
FIB-4 at 2.3122	0.005	0.018	0.076	0.010	0.101	0.326	0.134	0.904
AST/ALT ratio at 1.0	0.008	0.086	0.054	0.020	0.160	0.577	0.090	0.964
TE at 11.0 - <13.0	0.005	0.021	0.074	0.009	0.101	0.317	0.117	0.858
TE at 13.0 - <15.0	0.005	0.015	0.077	0.008	0.096	0.292	0.117	0.846
TE at 15+	0.005	0.021	0.074	0.009	0.102	0.319	0.116	0.858
ARFI at 1.55 – 2.0	0.005	0.013	0.077	0.009	0.096	0.300	0.128	0.876

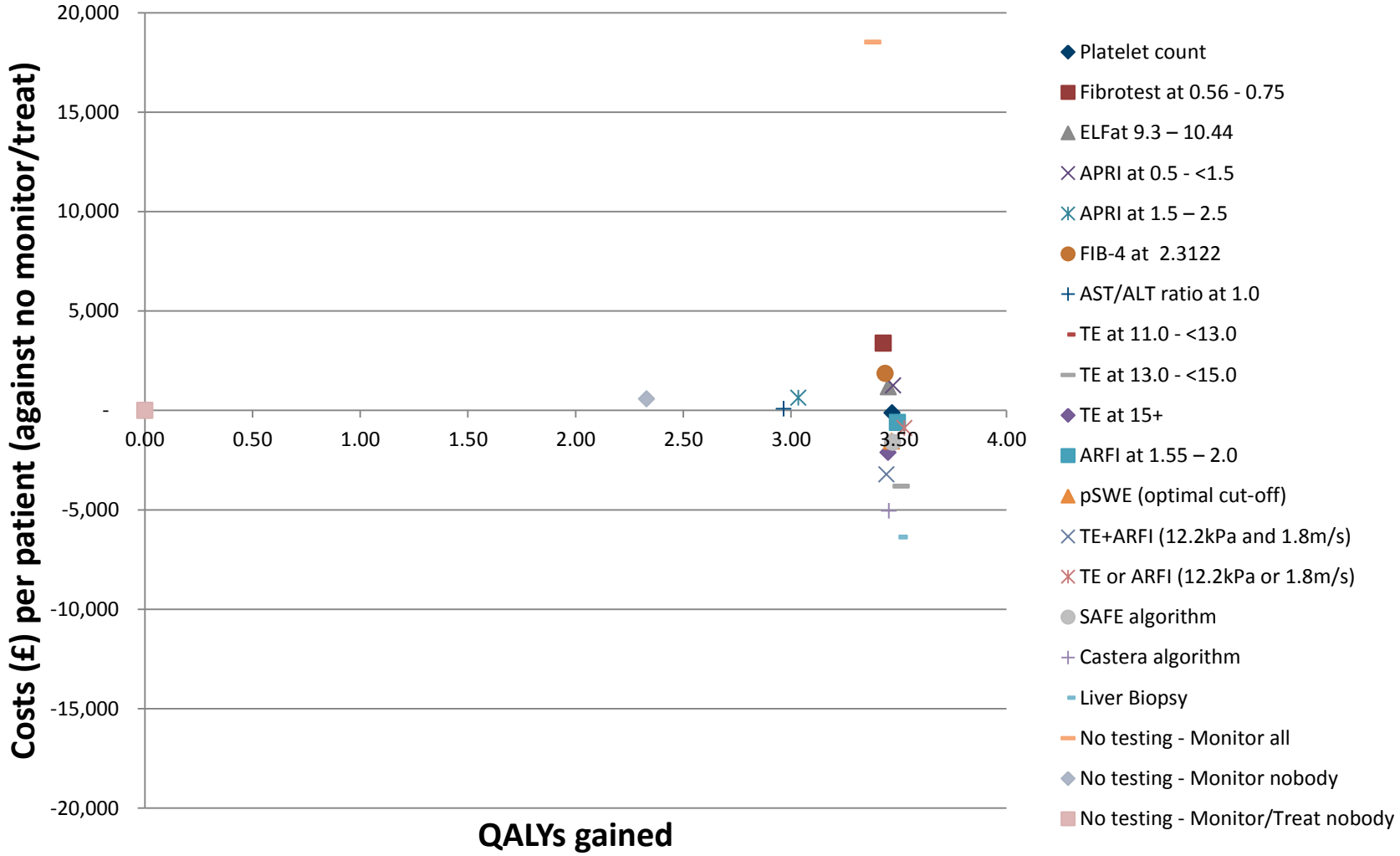
	Events					Time spent (months)		
Test	**Transplants**	**Unexpexted HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
pSWE (optimal cut-off)	0.005	0.018	0.075	0.009	0.099	0.311	0.121	0.867
TE+ARFI (12.2kPa and 1.8m/s)	0.005	0.024	0.073	0.009	0.104	0.325	0.111	0.848
TE or ARFI (12.2kPa or 1.8m/s)	0.005	0.009	0.079	0.008	0.093	0.286	0.131	0.880
SAFE algorithm	0.005	0.018	0.075	0.009	0.099	0.308	0.119	0.859
Castera algorithm	0.005	0.025	0.074	0.009	0.105	0.326	0.107	0.836
Liver Biopsy	0.005	0.016	0.078	0.007	0.098	0.290	0.108	0.823
No testing - Monitor all	0.006	0.000	0.115	0.011	0.124	0.451	0.246	1.223
No testing - No monitor	0.012	0.176	0.034	0.038	0.251	0.970	0.067	1.233
No testing - Monitor/Treat nobody	0.029	0.442	0.083	0.084	0.626	2.655	0.181	2.742

Table 98: Life years and results

Test	**Life years (undiscounted)**	**Mean Costs(£)**	**Mean QALYs**	**NMB (£) at £20000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**
Platelet count	30.31	18,052	11.83	218,565	11	5	15	0
Fibrotest at 0.56 - 0.75	30.19	21,549	11.79	214,248	15	9	17	0
ELF at 9.3 – 10.44	30.26	19,352	11.81	216,922	13	5	17	0.001
APRI at 0.5 - <1.5	30.32	19,423	11.84	217,299	12	8	15	0

Test	Life years (undiscounted)	Mean Costs(£)	Mean QALYs	NMB (£) at £20000/QALY	Rank	Rank 95% CIs		Prob (c/e)
APRI at 1.5 – 2.5	29.10	18,794	11.40	209,134	16	13	18	0
FIB-4 at 2.3122	30.23	20,025	11.80	215,966	14	9	16	0
AST/ALT ratio at 1.0	28.90	18,244	11.33	208,327	17	12	18	0
TE at 11.0 - <13.0	30.26	16,358	11.82	219,945	9	4	13	0
TE at 13.0 - <15.0	30.41	14,354	11.87	223,110	3	2	6	0.006
TE at 15+	30.25	16,056	11.81	220,206	6	3	15	0
ARFI at 1.55 – 2.0	30.37	17,566	11.86	219,550	10	4	14	0
pSWE (optimal cut-off)	30.30	16,615	11.83	219,967	8	3	15	0
TE+ARFI (12.2kPa and 1.8m/s)	30.23	14,946	11.81	221,158	4	2	14	0
TE or ARFI (12.2kPa or 1.8m/s)	30.46	17,282	11.89	220,485	5	4	11	0
SAFE algorithm	30.31	16,562	11.83	220,119	7	4	12	0
Castera algorithm	30.24	13,122	11.82	223,207	2	1	12	0.0256
Liver Biopsy	30.37	11,793	11.86	225,501	1	1	2	0.9674
No testing - Monitor all	29.97	36,688	11.74	198,159	18	17	19	0
No testing - No monitor	27.02	18,746	10.69	195,081	19	18	19	0
No testing - Monitor/Treat nobody	19.93	18,169	8.36	149,084	20	20	20	0

Figure 219: Cost-effectiveness plot: HCV genotype 3



In the HCV genotype 3 cohort it was liver biopsy ranking first with a NMB value of £225,501. TE at 13.0 - <15.0 and the Castera algorithm followed with almost identical NMBs at £223,207 and £223,110 respectively. Liver biopsy dominated the Castera algorithm being more effective and less costly. TE at 13.0 - <15.0 delivered marginally more QALYs but for a considerable incremental cost of £2,561. From all strategies it was only liver biopsy and TE at 13.0 - <15.0 that could rank first according to the ranking confidence intervals with liver biopsy ranking first in 97% of the simulations.

N.3.1.7 People with HCV: all genotypes

Table 99: HCV Diagnostic tests – top 3 ranked in every genotype

	Genotype 1	Genotype 2	Genotype 3 [539]	Genotype 4
1st rank	Liver biopsy	Liver biopsy	Liver biopsy	Liver biopsy
2nd rank	TE at 13.0<15.0	Castera algorithm	Castera algorithm	TE at 13.0<15.0
3rd rank	Castera algorithm	TE at 13.0<15.0	TE at 13.0<15.0	TE or ARFI (12.2kPA or 1.8m/s)

(a) For genotype 3, the Castera algorithm and TE at 13.0<15.0 had almost identical NMBs

N.3.2 Frequency of surveillance

N.3.2.1 Frequency of HCC surveillance

Table 100: ICERs comparing 6-monthly surveillance against annual surveillance

Aetiology	ICER	Cirrhosis test used
NAFLD	£23,136	TE at >15.0
ALD	£28,155	TE at 11.0 - <13.0
HBV -antigen	£28,995	TE at 11.0

Aetiology	ICER	Cirrhosis test used
HBV +antigen	£29,585	TE at 11.0
HCV genotype 1	£24,195	Liver biopsy
HCV genotype 3	£17,216	Liver biopsy

The cirrhosis test used in each case was that recommended by the GDG following its consideration of the results of Section N.3.1. Where more than 1 test were recommended, the most cost-effective of those tests was used.

Across all aetiologies 6-monthly surveillance for HCC was overall more costly and more effective compared to the annual strategy. At a £20,000 threshold, 6-monthly surveillance was cost-effective only in the HCV genotype 3 cohort (ICER at £17,216). The ICERs in the remaining cohorts ranged between £23,136 and £29,585.

N.3.2.2 Frequency of oesophageal varices surveillance

Table 101: ICERs comparing annual and 2-yearly surveillance against 3-yearly surveillance

Aetiology	Frequency	ICER	Cirrhosis test used for the comparison
NAFLD	2 years	£53,949	TE at >15.0
	1 year	£110,096	
ALD	2 years	£19,007	TE at 11.0 - <13.0
	1 year	£254,125	
HBV -antigen	2 years	£48,077	TE at 11.0
	1 year	dominated	
HBV +antigen	2 years	dominated	TE at 11.0
	1 year	£2,507,729	
HCV genotype 1	2 years	£339	Liver biopsy
	1 year	dominated	
HCV genotype 3	2 years	£2,911	Liver biopsy

Aetiology	Frequency	ICER	Cirrhosis test used for the comparison
	1 year	dominated	

The cirrhosis test used in each case was that recommended by the GDG following its consideration of the results of Section N.3.1. Where more than 1 test were recommended, the most cost-effective of those tests was used.

Surveillance for the presence of oesophageal varices every 2 years was more effective but also more costly compared to a 3 year surveillance frequency across all aetiologies apart from HBeAg-positive. The ICERs comparing 2 yearly with 3 yearly surveillance were below the £20,000 for ALD and HCV, but not cost-effective for NAFLD or HBV. Annual surveillance was not cost-effective for any aetiology at a £20,000 threshold.

N.3.3 Sensitivity analyses

N.3.3.1 NAFLD

Table 102: NAFLD model - Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	NAFLD prevalence 50% lower	NAFLD prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	Discount rate 1.5%	Fibroscan unit cost 20% higher	ARFI unit costs 20% lower	ARFI unit costs 20% higher	TE>15 diagnostic accuracy- low CI
TE at 10.0 - <13.0	3	3	3	3	3	3	3	3	2	2
TE at >15.0	1	1	1	1	1	1	2	1	1	3
ARFI at 1.636 - 1.9	2	2	2	2	2	2	1	2	3	1
Liver Biopsy	6	6	6	6	6	6	6	6	6	6
No test - Monitor all	5	5	4	5	5	5	5	5	5	5
No test - No monitor	4	4	5	4	4	4	4	4	4	4

Across all scenarios TE at >15.0 ranked first apart from where its unit cost was increased 20% and where it's diagnostic accuracy was set at the low CI value. ARFI ranked first in both the aforementioned scenarios showing the amount of uncertainty between the two tests. Liver biopsy and the two no test strategies remained last in all scenarios without a change in their rank.

N.3.3.2 ALD

Table 103: ALD model - Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	ALD prevalence 50% lower	ALD prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	No abstinence after diagnosis with NILT	Fibroscan unit cost 20% higher	Fibroscan unit costs 20% lower	TE at 11.0 - <13.0 diagnostic accuracy- low CI	TE at 11.0 - <13.0 diagnostic accuracy- high CI	Cirrhosis retesting 2 Year
APRI at 1.5 - 2.5	5	3	5	5	3	3	4	5	4	5	5
TE at 11.0 - <13.0	3	4	3	3	4	4	3	3	5	3	3
TE at 15+	4	5	4	4	5	5	5	4	3	4	4
Liver Biopsy	6	6	6	6	6	6	6	6	6	6	6
No test - Monitor all	2	2	2	2	2	2	2	2	2	2	2
No test - No monitor	1	1	1	1	1	1	1	1	1	1	1

The no test – no monitor strategy remained first in all scenarios. TE at 11.0 - <13.0 remained the diagnostic test ranking first in five out of the ten tested scenarios. In the remaining scenarios APRI ranked higher when the ALD prevalence or the varices prevalence was set 50% lower and when the abstinence after testing was set to zero or cirrhosis retesting was set at 2 years.

N.3.3.3 HBeAg-negative

Table 104: HBV- model - Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	HBV prevalence 50% lower	HBV prevalence 50% higher	Medium to large varices at diagnosis 50% hieher	Medium to large varices at diagnosis 50% lower	Fibroscan unit cost 20% higher	Fibroscan unit costs 20% lower	TE at 11 diagnostic accuracy- low CI	TE at 11 diagnostic accuracy- high CI	Second line treatment effectiveness – low CI	Second line treatment effectiveness – high CI
Fibrotest at 0.74	2	1	3	3	1	2	3	2	3	3	1
TE at 11.kPa	3	3	2	2	3	3	1	4	1	2	4
APRI at 2.0	4	5	4	4	4	4	4	3	4	4	5
APRI at 1.0	1	2	1	1	2	1	2	1	2	1	2
Liver biopsy	7	7	7	7	7	7	7	7	7	7	7
No test - Monitor all	6	6	6	6	6	6	6	6	6	5	6
No test - No monitor	5	4	5	5	5	5	5	5	5	6	3

APRI at a 1.0 threshold remained first in 6 out of 10 scenarios and came second in the 5 remaining ones. Fibrotest ranked first in 3 scenarios and second or third in the remaining ones. TE ranked first in 2 scenarios (20% lower fibroscan unit costs or TE diagnostic accuracy at its high CI) and ranked from second to fourth in the remaining scenarios. No substantial ranking changes are observed in the other test strategies.

N.3.3.4 HCV genotype 3

Table 105: HCV genotype 3 model - Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	HCV prevalence 50% lower	HCV prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	TE at 13 diagnostic accuracy- high CI	Fibroscan unit costs 20% lower	No HCV treatment	No HCC surveillance in SVR patients	Cirrhosis treatment effectiveness – low CI	Cirrhosis treatment effectiveness – high CI	Fib/cirr treatment effectiveness – low CI	Fib/cirr treatment effectiveness – high CI	Drug treatment cost 50% lower	Drug treatment cost 60% lower
Platelet count	11	11	10	11	11	11	11	6	11	11	11	11	11	11	11
Fibrotest at 0.56 - 0.75	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
ELFat 9.3 – 10.44	13	13	13	13	13	13	13	16	13	13	13	13	13	13	13
APRI at 0.5 - <1.5	12	12	12	12	12	12	12	10	12	12	12	12	12	12	12
APRI at 1.5 – 2.5	16	16	17	16	16	16	16	4	16	16	16	16	16	16	16
FIB-4 at 2.3122	14	14	14	14	14	14	14	11	14	14	14	14	14	14	14
AST/ALT ratio at 1.0	17	17	18	17	17	17	17	3	17	17	17	17	17	17	17
TE at 11.0 - <13.0	9	8	11	10	9	10	9	9	10	10	10	10	10	10	10
TE at 13.0 - <15.0	3	3	2	3	3	1	3	5	3	3	3	3	3	3	3
TE at 15+	6	5	7	7	7	7	7	8	7	7	7	7	7	7	7
ARFI at 1.55 – 2.0	10	10	9	9	10	9	10	12	9	9	9	9	9	9	9
pSWE (optimal cut-off)	5	6	5	6	5	5	6	7	6	5	5	5	5	5	5
TE+ARFI (12.2kPa and 1.8m/s)	4	4	6	4	4	4	4	14	4	4	4	4	4	4	4
TE or ARFI (12.2kPa or 1.8m/s)	7	9	4	5	6	6	5	13	5	6	6	6	6	6	6
SAFE algorithm	8	7	8	8	8	8	8	17	8	8	8	8	8	8	8
Castera algorithm	2	2	3	2	2	3	2	19	2	2	2	2	2	2	2

Tests	Base case (deterministic)	HCV prevalence 50% lower	HCV prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	TE at 13 diagnostic accuracy- high CI	Fibroscan unit costs 20% lower	No HCV treatment	No HCC surveillance in SVR patients	Cirrhosis treatment effectiveness – low CI	Cirrhosis treatment effectiveness – high CI	Fib/cirr treatment effectiveness – low CI	Fib/cirr treatment effectiveness – high CI	Drug treatment cost 50% lower	Drug treatment cost 60% lower
Liver Biopsy	1	1	1	1	1	2	1	20	1	1	1	1	1	1	1
No testing - Monitor all	18	19	16	18	18	18	18	18	18	18	18	18	18	18	18
No testing - No monitor	19	18	19	19	19	19	19	1.5	19	19	19	19	19	19	19
No testing - Monitor/Treat nobody	20	20	20	20	20	20	20	1.5	20	20	20	20	20	20	20

In 12 out of the 14 scenarios liver biopsy remained the first ranked strategy. It came twentieth where HCV treatment was not provided and second where the HCV drug costs were reduced by 60%. The Castera algorithm remained second in 10 out of the 14 scenarios and third, fourth and nineteenth in the remaining 4 ones. TE at 11.0 - <13 ranked third in 10 out of the 14 scenarios and first, second and fifth in the remaining 4 ones. It ranked first in the scenario where HCV drug treatment costs were reduced by 60%. Rankings in the remaining test strategies did not differ substantially across the scenarios tested apart from the no HCV treatment scenario which seemed to favour the no testing - no monitor strategy.

N.3.3.5 HCC surveillance frequencies

Table 106: ICERs comparing 6-monthly against annual surveillance

Aetiology	Base case	Surveillance costs – 20% lower	6-monthly surveillance effectiveness – 20% higher	Cirrhosis test used for the comparison
NAFLD	£22,472	£21,331	£20,254	TE at >15.0
ALD	£28,862	£28,484	£27,655	TE at 11.0 - <13.0
HBV -antigen	£27,290	£26,188	£26,342	TE at 11.0

Aetiology	Base case	Surveillance costs – 20% lower	6-monthly surveillance effectiveness – 20% higher	Cirrhosis test used for the comparison
HBV +antigen	£27,007	£25,377	£26,402	TE at 11.0
HCV genotype 1	£20,166	£18,252	£18,173	Liver biopsy
HCV genotype 3	£20,362	£19,008	£18,782	Liver biopsy

Lowering the HCC surveillance costs had a moderately small effect on the ICERs with only the HCV cohorts being lower than the 20,000 threshold. Increasing the effectiveness of 6-monthly surveillance had a slightly larger effect still making 6-monthly surveillance cost-effective only in the HCV cohorts.

N.3.3.6 Oesophageal varices surveillance frequencies

Table 107: ICERs compared to 3-year surveillance

Aetiology	Frequency	Base case	Surveillance costs – 20% lower	RR on bleeding probability – 20% higher	RR on bleeding probability – 20% lower	Cirrhosis test used for the comparison
NAFLD	2 years	£40,453	£31,999	£30,723	£54,982	TE at >15.0
	1 year	£58,416	£46,397	£44,981	£78,505	
ALD	2 years	£27,177	£20,714	£19,088	£39,266	TE at 11.0 - <13.0
	1 year	£141,631	£111,877	£110,029	£191,808	
HBV -antigen	2 years	£57,539	£45,108	£43,334	£78,777	TE at 11.0
	1 year	£85,246	£67,313	£65,312	£115,085	
HBV +antigen	2 years	£92,335	£71,865	£69,696	£126,221	TE at 11.0
	1 year	£145,652	£114,564	£111,959	£196,134	
HCV genotype 1	2 years	£39,891	£31,362	£29,463	£55,315	Liver biopsy

Aetiology	Frequency	Base case	Surveillance costs – 20% lower	RR on bleeding probability – 20% higher	RR on bleeding probability – 20% lower	Cirrhosis test used for the comparison
	1 year	£68,807	£54,582	£52,872	£92,484	
HCV genotype 3	2 years	£54,103	£42,827	£40,978	£73,566	Liver biopsy
	1 year	£77,311	£61,443	£59,762	£103,407	

Amendments in the surveillance costs and the RR on the bleeding probability had little effect on the overall cost-effectiveness of more frequent surveillance for oesophageal varices. Increasing the frequency to 2 years was only cost-effective for the ALD cohort in 2 out of the 3 tested scenarios.

N.4 Discussion

N.4.1 Summary of results

N.4.1.1 NAFLD

TE at a 15 threshold ranked first mainly due to having the highest diagnostic accuracy among the non-invasive test. ARFI followed second being slightly less accurate but also having lower test unit costs. TE at 10.0 - <13.0 ranked third having similar specificity to the other two tests but lower sensitivity. All three non-invasive tests had similarly wide confidence intervals (1 to 4).

In the deterministic sensitivity analysis, rankings were sensitive to increases in the TE and ARFI unit costs and in the decrease of the TE>15 diagnostic accuracy. Therefore, no safe conclusion can be made over the most cost-effective option among the 3 comparators.

N.4.1.2 ALD

Testing people with alcoholic liver disease for cirrhosis was not considered cost-effective at a £20,000 threshold ('no test – no monitor' and 'no test – monitor all' ranked first and second). However, ICERs for the 3 NILTs were not far beyond the cost-effectiveness threshold (£22,636 - £22,649). All three non-invasive tests had similarly wide confidence intervals (1 to 5).

In none of the deterministic sensitivity analysis scenarios did a test strategy rank higher than third. Ranking among the 3 NILTs slightly varied across the different scenarios with TE at 11.0 - <13.0 remaining third in ranking for 5 out of the 10 tested scenarios.

N.4.1.3 HBV

For the HBeAg negative group, APRI at 1.0 ranked first, most probably due to its low test unit costs and its moderate diagnostic accuracy (second best after TE). TE and Fibrotest ranked second and third. APRI at 2.0 ranked last among the NILT mainly due to its considerably lower sensitivity. All NILTs had similarly wide 95% confidence intervals.

In the HBeAg positive group, Fibrotest ranked first with no test – no monitor and TE ranking second and third. All NILTs had similarly wide 95% confidence intervals. In the probabilistic analysis, the 3 tests also shared similar probabilities ranking first (20%-23%).

Deterministic sensitivity analysis was only conducted for the HBeAg negative group. Rankings between the deterministic and the probabilistic analyses varied particularly for the Fibrotest and TE tests highlighting how incorporating the uncertainty of the input parameters in the model affects the cost-effectiveness results. APRI at 1.0 ranked first or second in all scenarios. Fibrotest and TE followed with alternating 1^{st} to 4^{th} positions. The cost-effectiveness of APRI at 1.0 was sensitive to the decrease of HBV prevalence, the presence of varices at the point of cirrhosis diagnosis and changes to the cost and accuracy of TE.

N.4.1.4 HCV

For all 4 genotypes, it was liver biopsy that ranked first with substantially higher NMB values compared to the second options. This is mainly attributed to the fact that it was assumed it has a perfect sensitivity and specificity and that cirrhosis misdiagnosis is associated with the incorrect administration of the highly costly polymerase inhibitor drugs. This led to the economic model particularly favouring the test with the highest diagnostic accuracy irrespective of its unit cost. In genotypes 1 and 3 were detailed results are presented, liver biopsy ranked first in 90% and 97% of

the simulations respectively. TE at 13.0 - <15.0 and the Castera algorithm ranked second and third in genotypes 1-4 and the 'TE or ARFI' strategy ranked third in genotype 4.

Deterministic sensitivity analysis was only conducted for the genotype 3 group. Liver biopsy remained first in all but two scenarios. These were the 'no HCV treatment' and the '60% lower drug treatment costs' scenarios, highlighting how crucial the drug treatment element is for the HCV diagnostic model.

N.4.1.5 Frequency of HCC surveillance

At a £20,000 threshold, 6-monthly surveillance was cost-effective only for the HCV genotype 3 group. Although this group had the least liver associated deaths, its risk of HCC progression was particularly high compared to other model cohorts making more frequent surveillance cost-effective at the specified threshold. In the deterministic sensitivity analysis, changes in the surveillance costs or the 6-monthly surveillance effectiveness reduced the ICERs by £400 to £3,500 per QALY across the different groups. Such reductions made 6-montly surveillance cost-effective (at the £20,000 threshold) only for the NAFLD and HCV cohorts.

N.4.1.6 Frequency of oesophageal varices surveillance

Annual surveillance was not cost-effective for any of the model cohorts with the ICERs either exceeding £60,000/QALY values or showing it being dominated by the 3 year frequency option. Surveillance 2-yearly was cost-effective at a £20,000 threshold in the HCV and ALD cohorts. In the deterministic sensitivity analysis, changes in the surveillance costs or the RR applied on the bleeding probability had considerable effect on the ICERs of the higher frequencies. However with the base case ICERs of the deterministic analysis being far beyond the £20,000 threshold, any reductions in the ICERs made 2 yearly surveillance cost-effective only for the ALD cohort.

N.4.2 Comparisons with published studies

N.4.2.1 Cirrhosis diagnostic tests

Three relevant studies identified in our literature review attempted to assess the cost-effectiveness of diagnostic tests for cirrhosis. All of them had contradicting results when compared to each other or the present modelling work.

Canavan 2013[133] found TE to have an ICER of £6,557 when compared with liver biopsy in chronic HCV patients. This is in contrast to the result of this model and it may be down to the fact that the Canavan et al evaluation did not include the recently launched HCV treatments which particularly enhance the cost-effectiveness of highly accurate tests (such as liver biopsy) irrespective of their cost.

Steadman 2013[840] concluded that liver biopsy was more costly and more effective compared to TE with a cost per additional correct diagnosis between £1,136 and 3,841 in the HBV, HCV and NAFLD groups. However, no safe conclusions or comparisons can be made based on these figures since important factors such as the follow up costs and the health related quality of life following correct/incorrect diagnoses have not been included in this economic evaluation.

Stevenson 2012[842] compared 6 relevant diagnostic strategies and concluded that only liver biopsy was cost-effective at a £20,000 threshold for people with ALD. This is in contrast with the results of this model which indicated that neither NILTs nor liver biopsy were considered cost-effective at the £20,000 threshold. The two models followed similar perspectives so result differences are mainly attributed to dissimilarities in the model structure and the input parameters (such as the liver biopsy quality criterion for the study selection followed by the present analysis).

N.4.2.2 Frequency of HCC surveillance

Two relevant studies identified in our literature review attempted to assess the cost-effectiveness of HCC surveillance in different frequencies.

Cucchetti 2012[205] compared annual versus semi-annual surveillance and concluded that semi-annual is not cost-effective for either compensated or decompensated groups at the £20,000 threshold (ICERs at £21,230 and £40,540 respectively). These figures are similar to the ones in the present analysis, which produced ICERs ranging between £20,000 -£30,000 across the different groups.

Thompson Coon 2008[870,871] compared 7 relevant strategies (including annual and semi-annual frequencies) and concluded that only the 'no surveillance' strategy was cost-effective at a £20,000 threshold. ICERs for the non-dominated strategies varied from £25,490 to £83,333. When semi-annual strategies were directly compared with the annual ones ICERs were beyond £27,500. The latter results are also in line with those in the present analysis.

N.4.2.3 Frequency of varices surveillance

No relevant studies were identified in the literature.

N.4.3 Conclusions

- An original cost-utility analysis that compared 6 strategies to diagnose cirrhosis in people with NAFLD and advanced fibrosis with a retest frequency of 1 year found that transient elastography ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - ARFI
  - transient elastography (lower threshold)
  - no test – no surveillance
  - no test – surveillance for all
  - liver biopsy.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 6 strategies to diagnose cirrhosis in people with ALD, with a retest frequency of 1 year, found that:
  - The 'no test – no surveillance' strategy ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
    - no test – surveillance for all
    - transient elastography (low threshold)
    - transient elastography (high threshold)
    - APRI
    - liver biopsy.
  - When compared to the 'no test – no monitor' strategy, the 3 non-invasive tests had ICERs between £22,671 and £22,860 per QALY gained.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 7 strategies to diagnose cirrhosis in people with hepatitis B and HBeAg negative with a retest frequency of 2 years found that APRI ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - transient elastography

  - FibroTest
  - APRI (higher threshold)
  - no test – no surveillance
  - no test – surveillance for all
  - liver biopsy.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 7 strategies to diagnose cirrhosis in people with hepatitis B and HBeAg positive with a retest frequency of 2 years found that FibroTest ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - no test – no surveillance
  - transient elastography
  - APRI (low threshold)
  - APRI (high threshold)
  - no test – surveillance for all
  - liver biopsy.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 20 strategies to diagnose cirrhosis in people with hepatitis C with a retest frequency of 2 years found that liver biopsy ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - Castera algorithm
  - transient elastography (medium threshold)
  - transient elastography and ARFI
  - transient elastography or ARFI
  - transient elastography (high threshold)
  - SAFE algorithm
  - point shear wave elastography
  - transient elastography (low threshold)
  - ARFI
  - platelet count
  - APRI
  - ELF
  - FIB-4
  - Fibrotest
  - APRI
  - AST-ALT ratio
  - no testing – surveillance for all, treat HCV using medication for people with cirrhosis
  - no testing – no surveillance, treat HCV using medication for people with fibrosis
  - no testing – no surveillance, no treatment for HCV.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 6-monthly with annual surveillance for HCC in people with cirrhosis found that:
  - 6-monthly surveillance was cost-effective compared to annual surveillance for people with HCV genotype 3 (ICER: £17,216 per QALY gained).

  - 6-monthly surveillance was not cost-effective compared to annual surveillance for people with NAFLD, ALD, HBV or HCV genotype 1 (ICERs: £23,136–28,995).

  This analysis was assessed as directly applicable with minor limitations.

- An original cost-utility analysis that compared annual, 2-yearly and 3-yearly surveillance for the detection of varices in people with cirrhosis found that:
  - Annual surveillance was not cost-effective compared to 3-yearly surveillance (ICERs: £110,096–2,507,729 per QALY gained or dominated).
  - 2-yearly surveillance was cost-effective compared to 3-yearly surveillance in people with ALD, or hepatitis C (ICERs: £339–19,007 per QALY gained).
  - 2-yearly surveillance was not cost-effective compared to 3-yearly surveillance in people with NAFLD and advanced fibrosis, or hepatitis B and HBeAg positive (ICERs: £48,077–53,949 per QALY gained or dominated).

  This analysis was assessed as directly applicable with minor limitations.

Appendix O: Unit costs

O.1 Risk factors and risk assessment tools

None.

O.2 Diagnostic tests

See Table 81 in Appendix N.

O.3 Severity risk tools

Table 108: Unit costs of severity risk tools

Risk tool	Unit cost	Comments
Child-Pugh	£7.42[(a)]	Includes bilirubin, albumin, INR, ascites events, hepatic encephalopathy events
MELD	£10.42[(a)]	Includes creatinine, bilirubin, INR
Transient elastography	£68.00	Imaging technique

Sources: Donnan 2009, NHS hospital trust (GDG source)
(a) MELD and Child-Pugh are inflated to 2013–14 prices

O.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

See Table 82 in Appendix N.

O.5 Surveillance for the detection of varices

See Table 82 in Appendix N.

O.6 Prophylaxis of variceal haemorrhage

Table 109: Unit costs of variceal haemorrhage prophylaxis – band ligation

Treatment	Unit cost	Details
Band ligation	£1,326	£530 per procedure; assuming 2.5 procedures

Source: NHS Hospital trust; GDG assumption

Table 110: Unit costs of variceal haemorrhage prophylaxis – beta blockers

Treatment	Daily dose	Cost per day	Cost per year
Propranolol[(a)]	60–120 mg	£0.08–0.16	£28.37–56.74
Carvedilol[(b)]	6.25–12.5 mg	£0.05, £0.04	£17.86, £16.42

Sources: NHS Drug Tariff July 2015
(a) Starting dose 20 mg 3 times per day, adjusted up to 40 mg 3 times per day, according to drug response
(b) Starting dose 6.25 mg, adjusted up to 12.5 mg according to drug response; Note that 12.5 mg tablets are cheaper than 6.25 mg tablets

O.7 Primary prevention of bacterial infections in cirrhosis and gastrointestinal bleeding

Table 111: Unit costs of antibiotics to treat bacterial infections

Antibiotic	Daily dose	Cost per day	Cost of 5-day course
Ceftriaxone (IV)	1 g	£9.58	£47.90
Ceftriaxone (IV)	2 g	£19.18	£95.90
Ciprofloxacin (oral)	500 mg ×2	£0.15	£0.74
Norfloxacin (oral)[a]	400 mg ×2[b]	£1.71	£8.57
Norfloxacin (oral)[a] + ceftriaxone (IV)	400 mg ×2 + 2 g	£20.89	£104.47
Ofloxacin (oral)	400 mg ×2	£0.92	£4.59

Sources: BNF August 2014
(a) Norfloxacin is currently unavailable in the UK
(b) Note that the Spanish group study used 1x 400 mg dosage

O.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 112: Unit costs of TIPS and LVP procedures

Procedures	Unit cost	Details
TIPS	£2,904	Average procedure costs of 28 patients
LVP	£672	Cost per single procedure, includes 1 elective day case admission, 100 ml of 20% albumin, catheter system use

Sources: TIPS: Parker 2013; LVP: NHS reference costs 2013–14, Parker 2013, GDG

O.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 113: Unit costs of antibiotics used for primary prevention of SBP

Antibiotic	Daily dose	Cost per day	Cost per year
Ciprofloxacin (oral)	500 mg	£0.07	£27
Ciprofloxacin (oral)	750 mg	£0.80[a]	£292[a]
Norfloxacin (oral)[b]	400 mg	£0.86	£313

Sources: BNF August 2014
(a) Or £0.11 per day (£40 per year) if one and a half 500 mg tablets are used instead
(b) Norfloxacin is not currently available in the UK

Table 114: Unit costs of managing SBP related complications

Cost type	Unit cost	Details
7 day hospital stay	£1,561	GB03D (excess days), Intermediate, Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with CC Score 5-7
Tazocin	£237.30	Piperacillin 4 g/tazobactam 500 mg IV every 8 hours for 5 days
Paracentecis	£78	
Ultrasound	£49	

Sources: NHS reference costs 2013–14, NHS Drug Tariff July 2015, Parker 2013, GDG

O.10 Volume replacers in hepatorenal syndrome

Table 115: Unit costs of IV volume replacers

IV fluid type	Unit cost for 100 ml bag	Unit cost for 250 ml bag	Unit cost for 500 ml bag	Unit cost for 1000 ml bag
IV albumin				
Albumin (4.5%)		£17.03		
Albumin (5%)			£30.52	
Albumin (20%)	£35–50			
IV crystalloids				
Ringer's lactate solution			£1.25	
0.9% sodium chloride (saline)			£0.63	£0.70
Hartmann's solution			£0.70	£0.85
Dextrose (5%)			£0.63	£0.70
IV polygels, plasma, colloids				
Plasmalyte 148ph 7.4				£0.92
Haemocel		-	-	-
Gelofusion/gelofusine				£4.80
Dextran 70 (RescueFlow)		£28.50		
Mannitol (10%)			£3.20	
Mannitol (20%)		£3.78	£5.80	
Voluven			£7.50–12.50	
Volulyte			£7.65–18.00	

Sources: BNF July 2015, NICE CG174 Intravenous fluid therapy in adults in hospital, personal communication with NHS hospitals

O.11 Management of an episode of acute hepatic encephalopathy

Table 116: Unit costs of drugs used to manage acute hepatic encephalopathy

Drug	Cost per day[(a)]	Dosage
BCAA	-	No cost information
Flumazenil (IV)	£81.00	One 5 ml ampule, 6x per day
Lactulose (oral solution)	£0.32	10–30 ml, 2–3x per day (average 50 ml)
Lactitol	Not prescribable	
LOLA	£34.4	10 ml ampoules, 4× per day
Metronidazole	£0.22	One 400 mg tablet, 3× per day
MARS	-	No cost information
Neomycin sulphate	£0.50	One 500 mg tablet, 2× per day
Rifaximin	£9.26	One 550 mg tablet, 2× per day

Sources: NHS Drug Tariff July 2015, BNF July 2015, NHS hospital trust (GDG source)

(a) Costs would apply for the duration of acute care (up to 5 days)

Appendix P: Research recommendations

P.1 Risk factors and risk assessment tools

Research question: Development of a risk tool to identify people at risk of cirrhosis

Why this is important:

Liver disease in the UK stands out as a glaring exception to the huge improvements in health and life expectancy for chronic disorders such as strokes, heart disease and many cancers. Since 1970 mortality rates for liver disease have increased 400% and in those under the age of 65 have risen almost five-fold. As a result liver disease now constitutes the third commonest cause of premature death in working age in men and the second in women. The UK has overtaken European countries such as France, Spain and Italy which previously had very high liver mortality.[929] Of those with cirrhosis 5–10% will go on to develop liver cancer, and the incidence is rising.[249] In England and Wales it is estimated that some 600,000 people have some form of liver disease, of whom 60,000 people have cirrhosis, leading to 57,682 hospital admissions and 10,948 deaths in 2012.[6] This represents an increase of 62% in liver disease and 40% in cirrhosis in 10 years. The underlying cause of liver disease is in the main alcohol but there is a rising incidence of obesity, many of whom will have fatty liver disease (1 in 20 in UK). These patients will have ongoing inflammation and fibrosis (scaring) that will progress over 10 to 20 years to cirrhosis. Annual deaths from hepatitis C have quadrupled since 1996. The incidence of hepatitis B is rising with the changing population demographics in the UK. There are also patients with autoimmune liver disease who go unrecognised and undiagnosed in the community. Left untreated these patients will progress to end-stage cirrhosis. The resultant cost to the NHS is staggering with estimates in excess of £9 billion per year for alcohol- and obesity-related health problems alone.[929]

Part of the problem is that for much of the time, until presentation with jaundice or decompensation, the liver disease may remain asymptomatic and silent. The earlier liver disease and even cirrhosis is diagnosed, the better the opportunity to intervene, limiting disease progression but in many cases offering a cure. The prevention of progression to end stage liver disease, avoiding complications, reducing the need for investigation, hospitalisation and intervention would have the potential to save billions to the NHS. The earlier the diagnosis, the greater the potential patient and financial benefit. This is why general practitioners need a guide or 'tool kit' to identify those patients in the community at greatest risk of having or progressing to advanced liver fibrosis or cirrhosis.

One approach would be to identify a retrospective cohort of patients (with cirrhosis) and to look at risk factors for cirrhosis in these patients. One potential source might be the clinical practice research database (CPRD).[7] This is a longitudinal database consisting of anonymous computerised primary care records for over 13 million patients in the UK. For many of the practices it is possible to link the CPRD data with HES data.

Patients with any diagnostic code for cirrhosis, oesophageal varices or portal hypertension would be identified in a fixed time period. It would then be possible to go back into the patient records to see if there was any mention in their CPRD record of alcoholism, alcohol abuse, addiction or dependence, or 'problem drinking'. The alcohol history will be broken down to drinks per week (<1, 1–7, 8–21, 22–35, >35) and alcohol intake (0.1–1.4, 1.5–4.9, 5–14.9, 15–29.9, >30 g/day).

Other demographic and risk factors would be sought including, age, sex, viral hepatitis, race and ethnicity, intravenous drug use or substance misuse. Other factors may include autoimmune disease, thyroid, rheumatoid disease. Metabolic disease including Hypertension, hypercholesterolaemia, BMI

and type 2 diabetes mellitus. Biochemical parameters, electrolytes, LFTs, AST, albumin, total protein, globulin fraction, Ferritin, FBC, platelets and coagulation studies.

The proposed study should use multivariate analysis to find the risk factors associated with the outcome of cirrhosis. By weighting the risk factors according to their association with the outcome, a risk tool should be developed to predict an individual's risk of developing cirrhosis. The ultimate risk prediction tool will require validation in a separate cohort (an external validation study).

P.2 Prophylaxis of variceal haemorrhage

Research question: Do non-selective beta-blockers improve survival and prevent first variceal bleed in patients with liver cirrhosis associated with small oesophageal varices?

Why this is important:

Bleeding from oesophageal varices is a major complication of cirrhosis. Approximately half of patients with cirrhosis have oesophageal varices and one-third of all patients with varices will experience bleeding at some point. Despite improvements in the management of acute haemorrhage in recent decades, the 6-week mortality associated with variceal bleeding remains of the order of 10–20%. Risk of variceal bleeding increases. Whether NSBB are of benefit as primary prophylaxis in persons with cirrhosis and small oesophageal varices has not been adequately studied.

Criterion	Explanation
Population	Adults with cirrhosis and small oesophageal varices with no history of variceal haemorrhage.
Interventions	Oral non-selective beta-blocker (for example propranolol, carvedilol)
Comparison	Placebo
Outcomes	• Acute variceal bleeding • Mortality • Regression of varices • Progression to large varices • Side effects
Importance to patients or the population	Bleeding from oesophageal varices is a major complication of cirrhosis. Approximately 50% of people with cirrhosis have oesophageal varices and one-third of these will develop variceal haemorrhage at some point. Despite improvements in the management of acute bleeding in recent decades, the 6-week mortality associated with variceal bleeding remains in the order of 10–20%. Therefore, measures that might reduce the likelihood of such life-threatening bleeding are clearly important.
Relevance to NICE guidance	The NICE guideline on cirrhosis (which is currently under development) recommends that all patients with cirrhosis be offered surveillance for oesophageal varices and that those with large varices are offered primary prophylaxis. The results of the proposed trial will allow NICE to make a recommendation on the use of NSBB as primary prophylaxis of variceal bleeding in people with small varices.
Relevance to the NHS	Acute variceal bleeding is a frequent cause of emergency hospital admission and one which is usually associated with high financial cost related to prolonged hospital stay (often on an intensive care unit) and use of high cost interventions such as emergency endoscopy and intravenous medical therapies.
National priorities	Tbc
Current evidence base	Data are limited with regard to the appropriate primary prophylactic strategy in the population described above. Recent national societal guidelines also identify this as an area for future study.
Equality	Liver disease represents one of the few diseases nationally where the inequalities gap is

	increasing. This study would recruit adults with cirrhosis regardless of gender, socio-demographic status or aetiology of cirrhosis.
Study design	Double-blind placebo-controlled trial. A crossover trial would be inappropriate because of progressing liver disease.
Feasibility	Many hospitals in the UK already offer surveillance for varices to patients with cirrhosis, often on designated endoscopy lists and patients could be easily identified prospectively via this route. Duration of follow-up would be around 2 years.
Other comments	Care would need to be taken to establish a universal definition of small varices as various definitions exist in the literature and this is a potential area of inter-observer variability.

P.3 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Research question: Assessment of the quality of life of people who have had a transjugular intrahepatic portosystemic shunt (TIPS)

Why this is important:

Prior to TIPS patients may have had several problems due to their portal hypertension including variceal bleeding from veins in the stomach, oesophagus, or intestines; ascites and hydrothorax with consequent detriment to their quality of life. TIPS should alleviate these problems but little is known about the consequential effect on quality of life and any effects that potential problems following TIPS (such as hepatic encephalopathy, shunt blockages, infection or cardiac problems) have on each person's quality of life.

It is therefore important to assess what benefits TIPS has to the quality of life of people with advanced liver disease.

Criterion	Explanation
Population	Adults with portal hypertension due to advanced liver disease.
Interventions	TIPS
Comparison	Adults with portal hypertension who do not have TIPS
Outcomes	• Improvements in quality of life • Benefits of having TIPS
Importance to patients or the population	Portal hypertension is a life-threatening problem of advanced liver disease with physical and psychological quality of life problems for anyone living with it. TIPS offers an effective treatment for portal hypertension but there is little evidence to prove that it has a positive quality of life impact.
Relevance to NICE guidance	The NICE guideline on liver cirrhosis (which is currently under development) recommends TIPS as a treatment for portal hypertension. The answer to this question will allow NICE to make a definitive statement on the quality of life affects this has.
Relevance to the NHS	Whilst procedures like TIPS are thought to be beneficial at reducing the impact of advanced liver disease it is vital to know that this symptom control has a beneficial quality of life impact.
National priorities	PHE Liver Disease Improvement Framework (Autumn 2015) DoH/NHS Living Longer Lives: Reducing Premature Mortality NHS Improving Quality - Patient safety and quality
Current evidence base	Data are limited with regard to the quality of life impact of TIPS. Current JLA/NIHR PSPs for liver disease may also identify this as an area for future study.
Equality	Liver disease represents one of the few diseases nationally where the inequalities gap is increasing. This study would recruit adults with portal hypertension regardless of gender,

	socio-demographic status or aetiology of portal hypertension.
Study design	Qualitative study
Feasibility	All services providing TIPS could include this as part of the preparation and follow-up of patients who had had TIPS with a comparison group that do not.
Other comments	Quality of life evidence is scarce throughout hepatology – this could be an example of why it is so important for all interventions, for example, for symptom control.

P.4 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Research question: How frequently does antibiotic resistance occur and how significant are antibiotic treatment related complications when antibiotics are used for the primary prevention of spontaneous bacterial peritonitis in high-risk patients with cirrhosis?

Why this is important:

Spontaneous bacterial peritonitis (SBP) is the most common serious infection in patients with cirrhosis, occurring in 25% of patients who develop ascites. It is associated with significant morbidity and mortality rates of 20–40%.

It occurs most commonly in patients with advancing liver disease; approximately 70% of cases occur in patients with Child-Pugh class C cirrhosis. Bacterial overgrowth associated with portal hypertension, reduced bowel motility, impairment of the intestinal barrier and reduced host defences result in bacterial translocation from the gut via the mucosa, to the circulation and other extra-intestinal sites. Patients who have ascites with a low ascitic fluid protein concentration, that is, less than 15 g/litre are at particularly high risk of developing a first episode of SBP.

Patients with SBP commonly present with general malaise, pyrexia, abdominal pain, diarrhoea, vomiting, confusion and jaundice although up to 30% of patients may be asymptomatic. Most infections are caused by *E. coli*, *Klebsiella* sp., *Proteus* sp., *Enterococcus faecalis* and *Pseudomonas*. Diagnostic paracentesis and blood cultures should be undertaken to confirm or refute the diagnosis however immediate empirical antibiotic therapy is required to prevent deterioration which may lead to worsening ascites, hepatorenal syndrome, liver failure and death. Hospitalisation, intravenous antibiotic therapy and the supportive care required to manage SBP are associated with significant healthcare costs. Following a primary episode of SBP, recurrence is common and up to 70% of patients relapse within 1 year. Two-year survival is estimated at 20%.

Several oral antibiotics have been investigated for the prophylaxis of SBP which have shown benefits and a significant reduction in the incidence of SBP in high risk patients. They are however associated with the emergence of resistance, adverse reactions and drug interactions which may be important although data are currently lacking.

This group found that primary, oral prophylactic antibiotic therapy with ciprofloxacin or norfloxacin is currently more cost-effective than to diagnose and treat SBP in high-risk patients. Treatment should be offered to patients with severe disease (Childs-Pugh B and C) and an ascitic protein concentration of less than 15 g/litre as an adjunct to the management of ascites.

There was however a paucity of good quality, recent, evidence regarding the prevalence and consequences of antibacterial resistance which may occur during long-term oral antibiotic therapy. Antibiotic therapy with broad-spectrum agents suppresses susceptible host commensal organisms allowing resistant pathogens such as *Clostridium difficile* to proliferate, releasing toxins which may damage the gut wall, exacerbating symptoms of SBP and potentially leading to sepsis and death.

Resistant pathogens emerge in hospital and community treatment settings over time irrespective of the antibiotic prophylaxis used and are a major concern for patients and healthcare providers. Antibiotic therapies currently available may be rendered ineffective and conditions incurable. Presently Hospital Trusts face financial penalties when outbreaks of infection with *C. difficile* occur. Local antimicrobial therapy guidance and epidemiological resistance patterns may need to be considered. Due consideration also needs to be given to antimicrobial stewardship when prophylactic antibiotic therapy is prescribed. Public Health England (2013) and NICE (2015) have published guidance that recommends the prudent prescribing of antimicrobials to prevent the emergence of resistance.

Prospective, randomised trials specifically in this group, adequately powered to determine optimal treatment are required. The incidence and consequences of resistance, depending on the antibiotic used, the dose, treatment schedule (continuous, intermittent or cyclical) and duration of therapy need to be determined.

Criterion	Explanation
Population	Adult patients with cirrhosis and ascites (Child-Pugh B and C) who are at high risk of developing SBP. Including: Patients with an ascitic protein concentration below 15 g/litre. Patients who have not previously had an episode of SBP. Excluding: Patients who have active GI bleeding. Patients on antibiotic therapy at the time of presentation. Patients with other confounding pathologies, for example colitis, perforation.
Interventions	Prophylactic oral antibiotic therapy to prevent a primary episode of SBP, specifying the antibiotic, dose, frequency and duration of therapy in different subgroups.
Comparison	A placebo given for the same duration as the active treatment group or until the first episode of SBP occurs. An alternative suitable antibiotic as a head to head comparator. A crossover or sequential study could be considered.
Outcomes	Frequency of antibiotic-related adverse effects, for example, *Clostridium difficile* diarrhoea, superinfection with other resistant organisms. Time to and the frequency of detection of resistant microbes in stool samples. Time to first episode of SBP or hospitalisation due to breakthrough infection. Quality of life All-cause mortality.
Importance to patients or the population	Patients with cirrhosis and ascites have a poor quality of life and a high risk of developing SBP requiring hospitalisation and IV antibiotics. Optimising prophylactic antibiotic therapy would improve quality of life whilst reducing the associated morbidity, mortality and healthcare costs. Judicious use of appropriate antibiotic regimes should minimise the occurrence of resistance and the ensuing adverse outcomes for individual patients, the population at large and healthcare providers.
Relevance to NICE guidance	This information will allow NICE to make a definitive statement about the overall safety and effectiveness of specific prophylactic antibiotic regimens used to prevent primary episodes of SBP. The results may be used to ensure compliance with NICE recommendations on Antimicrobial Stewardship.
Relevance to the NHS	Ensures optimal use of healthcare resources.
National priorities	Public Health England Expert advisory committee on Antimicrobial Resistance and Healthcare Associated infection: Antimicrobial Prescribing and Stewardship

	Competencies. 2013
Current evidence base	Limited (as reviewed for the NICE Cirrhosis guideline)
Equality	Patients need to be informed about the balance of risks of prophylactic antibiotic therapy versus the likelihood and consequences of developing SBP
Study design	RCT study or sequential (crossover) study. (n≥100)
Feasibility	The study population should be hepatology clinic, out-patient attenders from various centres in England who would be considered suitable for antibiotic prophylaxis.
Other comments	Funding for the study (studies) may be limited for generic antibiotics, long established in use.

P.5 Volume replacement in hepatorenal syndrome

Research question: Which is the most clinically and cost-effective volume replacer for patients with hepatorenal syndrome due to cirrhosis who are also receiving vasoactive drugs?

Why this is important:

Hepatorenal syndrome (HRS) develops in people with cirrhosis with ascites and is characterised by impaired renal function.[758] Terlipressin, a vasoconstrictor most active in the splanchnic circulation, is used to treat HRS but it is given with a plasma volume expander, which serves to maintain the blood volume and increase the blood oncotic pressure, reducing the movement of free fluid into the peritoneum. Human albumin solution is the recommended intravenous volume replacement during large volume paracentesis[82] and in patients with SBP, in combination with antibiotics, when the serum creatinine is >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL.[805] However, in HRS there are no clinical studies examining the benefits and harms associated with albumin compared with other volume replacers.

People with HRS have a low intravascular volume state and there is general agreement that they require volume expansion in combination with vasopressors. Whilst these people have intravascular depletion, the pathophysiology of decompensated cirrhosis is such that they are also fluid overloaded, but that the majority of fluid is outside the vascular compartment. People with decompensated cirrhosis are, therefore, more prone to complications of fluid overload, such as pulmonary oedema if given intravenous fluids. The ideal volume expander to be used in HRS should be able to provide its effect with a minimum of infused fluid (that is, have a high oncotic pressure).

PICO question	Population: • Adults and young people (16 and over) with confirmed cirrhosis and hepatorenal syndrome. Hepatorenal syndrome is defined as reversible renal dysfunction occurring in patients with cirrhosis (with a serum creatinine >133 micromol/litre and an absence of other identifiable causes of renal failure. • People will also receive the vasoconstrictor terlipressin Intervention(s): • IV human albumin solution • IV crystalloid (Ringer's lactate solution, 0.9% sodium chloride (saline), Hartmann's solution, dextrose) • IV colloid expander (gelofusion/gelofusine, dextran, voluven) Comparison: • IV albumin versus IV crystalloids • IV albumin versus colloid expanders Outcome(s): **Critical outcomes**

	• Survival (time-to-event) or mortality at 3 months • Health-related quality of life (continuous) • Reversal of hepatorenal syndrome or improved renal function (dichotomous – as defined by the study) at 3 months (reduction of serum creatinine below 133 micromol/litre, creatinine clearance, renal function returning to functioning kidneys without the requirement for drugs) **Important outcomes** • Time to discharge from hospital (time to event) • Re-admission to hospital (dichotomous) • Adverse events such as infection, heart failure and deterioration of renal function.

P.6 Management of an episode of acute hepatic encephalopathy

Research question: In people with cirrhosis and an acute episode of hepatic encephalopathy secondary to a clearly identified, potentially reversible precipitating factor does management of the precipitating event alone result in amelioration of the hepatic encephalopathy without specific treatment?

Why this is important:

Hepatic encephalopathy is a major complication of cirrhosis. Approximately 50% of people with cirrhosis will develop clinically apparent hepatic encephalopathy at some stage after diagnosis – the risk being of the order of 5–25% within 5 years. Hospital admissions are common and inpatient stays often prolonged. The presence of hepatic encephalopathy is associated with a significant increase in mortality; survival after the first episode is 42% at 1 year and 23% at 3 years.

At present, treatment of the hepatic encephalopathy is directed primarily at reducing the production and absorption of gut-derived neurotoxins, particularly ammonia, mainly through bowel cleansing, and the use of non-absorbable disaccharides such as lactulose, although several other agent such as non-absorbable antibiotics are also used. However, in approximately 50% of people admitted with episodic hepatic encephalopathy there is a clearly defined precipitating factor; management of these patients is often problematic and some may need to be managed in an intensive care setting at least initially. The identification and correction of any precipitating events is of paramount importance as there is evidence this alone may ameliorate hepatic encephalopathy without recourse to specific therapies. However, this has not been rigorously tested in a randomised clinical trial.

Criterion	Explanation
Population	Adults with cirrhosis and an acute episode of hepatic encephalopathy secondary to (a) clearly identifiable, potentially reversible precipitating factor(s)
Interventions	Management of the precipitating event
Comparison	Management of the precipitating event plus oral lactulose
Outcomes	**Primary outcomes** • All-cause mortality • Liver-related mortality • Improvement of hepatic encephalopathy • Time course of resolution in hepatic encephalopathy • Serious adverse events **Secondary outcomes** • Quality of life

	• Non-serious adverse events: • Surrogate outcomes for example psychometric test results, blood ammonia concentrations, electroencephalogram, critical flicker frequency
Importance to patients or the population	Hepatic encephalopathy is the most common complications of cirrhosis. The cumulated incidence of overt hepatic encephalopathy is as high as 40% and its development often results in emergency hospital admission. The survival probability after a first episode is 42% at 1 year and 23% at 3 years. Measures which improve the management of episodic hepatic encephalopathy during the acute admission will be of benefit to patients
Relevance to NICE guidance	The NICE guideline on cirrhosis (which is currently in development) investigated the treatment options for people with cirrhosis with episodic hepatic encephalopathy and did not make a recommendation because of the paucity of relevant studies and the poor quality of the evidence overall. There was some evidence from 1 very old study (Strauss, 1992), supported by clinical experience, that when the development of an episode of hepatic encephalopathy is associated with an obvious precipitating event, treatment of this event results in amelioration of the hepatic encephalopathy without the need for specific anti-encephalopathy treatment. Thus, it is important to determine whether, in the presence of a reversible precipitating event, specific treatment is of benefit. The results of such a trial would allow NICE to determine if head to head treatment trials are required.
Relevance to the NHS	In the UK the presence of hepatic encephalopathy in people with cirrhosis is associated with a significantly increase in mortality (58% compared to 32%) and longer inpatient stays (8 days compared to 6.8 days) and for those who survive more visits to primary care practitioners (18.2 compared to 8.7.contacts per patient years). Studies from elsewhere have identified a substantial burden for caregivers and a significant financial burden on healthcare systems.
National priorities	Tbc
Current evidence base	There are very few good quality studies on which to base recommendations in this field. The evidence base overall is poor and no recommendation about the efficacy and safety of treatment for episodic hepatic encephalopathy was made in the NICE guideline on cirrhosis (which is currently under development)
Equality	The significant disparity in the provision of care for individuals with cirrhosis by region is well documented and the inequality gap appears to be widening. This multicentre study would recruit patients from all sections of society irrespective of age , gender, racial group and the aetiology of their liver disease.
Study design	Multicentre, double-blind randomised controlled study
Feasibility	People with cirrhosis presenting with episodic hepatic encephalopathy are already assessed to identify likely precipitating factors. Only those in whom a clearly defined, potentially reversible precipitant will be recruited. Individuals in whom no such event is identified will be managed as per local guidelines. The study period will be short (around 7 days) so even with stringent inclusion and exclusion criteria recruitment should not be problematic.
Other comments	• It is difficult to estimate the required population size. In the single-site study by Strauss (2004), 102 patients were admitted over a 5-year period of whom 39 (38%) developed hepatic encephalopathy secondary to a precipitating event. This accords with clinical experience. Treatment of the precipitant alone resulted in amelioration of the hepatic encephalopathy in 90%. There was evidence that use of neomycin, a non-absorbable antibiotic was associated with more rapid improvement and this will be an important primary outcome in any proposed study. • A large number of events can precipitate hepatic encephalopathy and it is possible that the degree of its amelioration might vary depending on the precipitating event and its treatment. It is also possible that unless the randomization is stratified the distribution of patients, by precipitating event might be unbalanced between the groups. For this reason it may be advisable to select only 2 or 3 different precipitating events for inclusion. Management regimens for some complications, for example gastrointestinal bleeding, mandate use of antibiotics and this may have an independent beneficial

	effect on hepatic encephalopathy. • People will need to be monitored intensively during the trial and clear rescue criteria and procedures will need to be put in place for those not showing improvement. • The choice of lactulose as the adjuvant treatment was based on recent International guidelines recommending that it be used as first line therapy in patients with hepatic encephalopathy.

Appendix Q: NICE technical team

Name	Role
Sarah Willett	Guideline Lead
Martin Allaby	Clinical Advisor
Steven Barnes	Technical Lead
Ross Maconachie	Health Economist
Caroline Keir	Guideline Commissioning Manager
Margaret Ghlaimi	Guideline Coordinator
Sarah Palombella	Editor

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