National Institute for Health and Care Excellence

Final version

Cirrhosis in over 16s

Assessment and management

NICE guideline NG50

Appendices A–H

July 2016

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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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 non-financial specific	Declare and participate
	At recruitment: Contributor to the APPHG Report on Liver Disease 2014.	Personal non-financial specific	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
14/03/2016	GDG12: 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
14/03/2016	GDG12: Accepted sponsorship from Gilead to attend the EASL International Liver Conference, April 2016: economy class travel, hotel accommodation and meeting registration fee.	Personal financial non-specific	Nil

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 the 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 the European Association for the Study of the Liver conference 2015.	Personal financial non-specific	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
14/03/2016	GDG12: 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
14/03/2016	GDG12: 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 received.	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
14/03/2016	GDG12: No new DOI.	Nil	Nil
15/04/2016	Post-GDG12: Received an educational grant from Gilead to attend a 'HCV and Transplantation' preceptorship (accommodation and travel expenses) in June 2015.	Personal non-financial non-specific	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

Date	Item declared	Classification	Action taken
			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 the International Liver Transplant Society meeting in Chicago from 7 to 11 July 2015.	Personal financial non-specific	Declare and participate
02/09/2015	GDG11: No new DOI.	Nil	Nil
14/03/2016	GDG12: Apologies received.	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
30/04/2015	GDG8: The British Liver Trust was gifted a Fibroscan machine by Norgine.	Non-personal financial specific	Withdraw 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
14/03/2016	GDG12: 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 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: 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	Personal financial	Declare and

Date	Item declared	Classification	Action taken
	hepatitis C 2015 entries, organised by PMGroup with funding from Bristol-Myers Squibb and Gilead.	non-specific	participate
02/09/2015	GDG11: No new DOI.	Nil	Nil
14/03/2016	GDG12: Apologies received.	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
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
14/03/2016	GDG12: 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
14/03/2016	GDG12: Apologies received.	Nil	Nil

John O'Grady (co-optee)

Date	Item declared	Classification	Action taken
22/01/2015	At recruitment: None declared.	Nil	Nil

Date	Item declared	Classification	Action taken
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 2 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.	Nil	Nil

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
	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

Date	Item declared	Classification	Action taken
	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
14/03/2016	GDG12: Apologies received.	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)

NGC team

Date	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
02/09/2015	GDG11: No change to existing declarations.	N/A	N/A
14/03/2016	GDG12: No change to existing declarations.	N/A	N/A

NIHR team

Date	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
14/03/2016	GDG12: 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 predicting the 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)?
Objectives	The first-line approach will be to review RCT test and treat studies. Patients are 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) The second-line approach will be 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 the newer test excludes age as an additional variable). Validated in HCV and some metabolic liver diseases. • APRI (aspartate aminotransferase (AST)/platelet ratio index) • FIB-4 (platelets, ALT, AST) • AST/ALT ratio Only tests that have been validated in an independent validation cohort for the aetiology will be included.
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 15 mm 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 25 mm 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 15 mm and 6 portal tracts
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** • ROC curve or area under curve The GDG set the critical measure for decision making as 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	The first-line approach will be to review RCT test and treat studies. Patients are 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) The second-line approach will be 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 MRI (all forms, including 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 one)	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 15 mm 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 25 mm 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 15 mm and 6 portal tracts.
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** • ROC curve or area under curve

	The GDG set the critical measure for decision making as 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)?
Objectives	The first-line approach will be to review RCT test and treat studies. Patients are 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) The second-line approach will be 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	Individual blood tests: • Albumin • Platelets • Prothrombin Time (INR) • AST • ALT • Bilirubin • γGT (alcohol/ cholestasis)
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 15 mm 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 25 mm 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 15 mm and 6 portal tracts
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** ROC curve or area under curve The GDG set the critical measure for decision making as 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	The first-line approach will be to review RCT test and treat studies. Patients are 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) The second-line approach will be 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 blood fibrosis tests that have been validated in an independent validation cohort for the aetiology will be included. 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	Cirrhosis diagnosed by liver biopsy using one of the following scoring systems:

standard (could be more than one)	• 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 15 mm 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 25 mm 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 15 mm and 6 portal tracts.
Statistical measures	**Critical outcomes:** • Specificity • Sensitivity **Important outcomes:** • ROC curve or area under curve 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? 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. The aims of the review are: • 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 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 discrimination/	• ROC area under the curve (of each risk tool for each outcome)/concordance c-statistic • Sensitivity, specificity, predictive values

Component	Description
calibration)	• 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 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. 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 cholangitis 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 comparators: generic/class; specific/drug (All interventions will be compared with each other)	IV: Penicillin (beta-lactams); Amoxicillin 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: third generation Cephalosporins (beta-lactams); Cefotaxime IV: third generation Cephalosporins (beta-lactams); Ceftazidime IV: third 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: third 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) • Readmission 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 impact on the effectiveness of antibiotics. • Different modes of administration (IV administration; IV, then oral administration; oral; other; IV and oral): must give IV initially 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) • Readmission 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) • Readmission 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 impact on the 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 [1.5 g/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; third 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) Readmission 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. • We will only consider 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 Exclusions: • 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 to 2 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 an 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

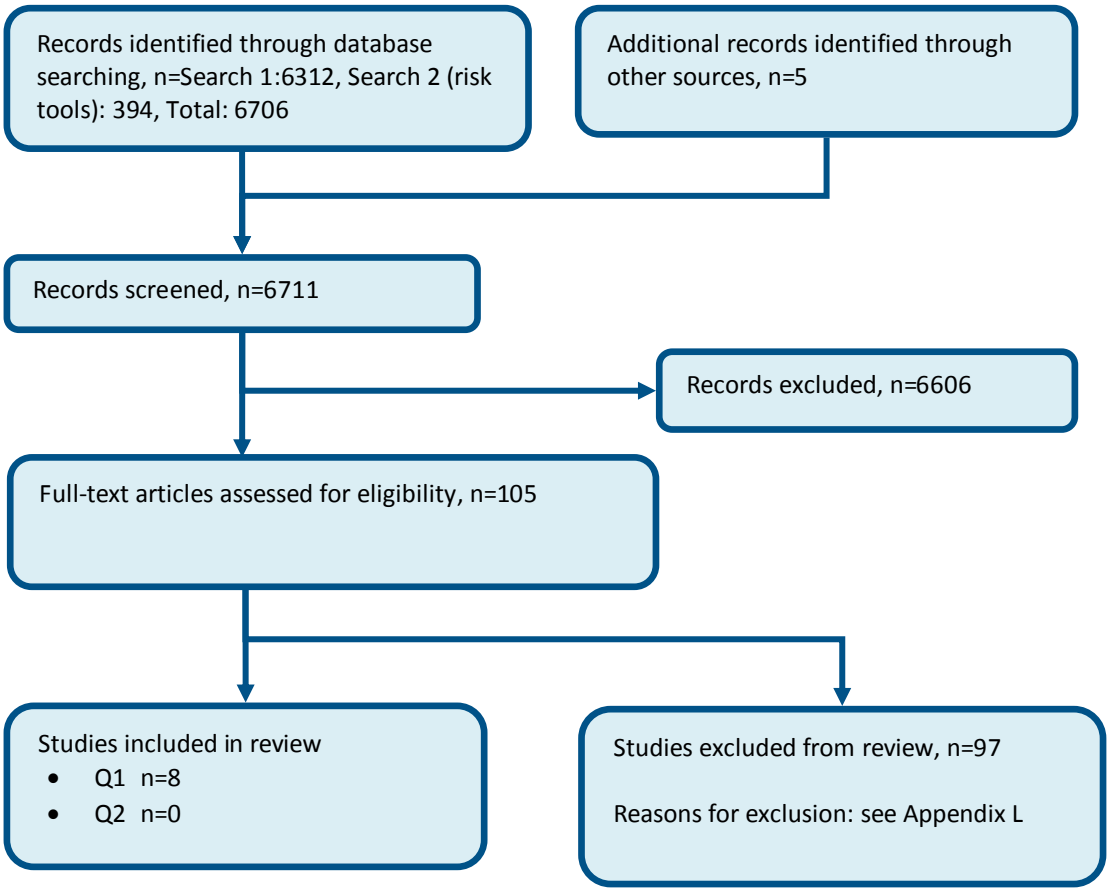
Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic 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).[92] **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

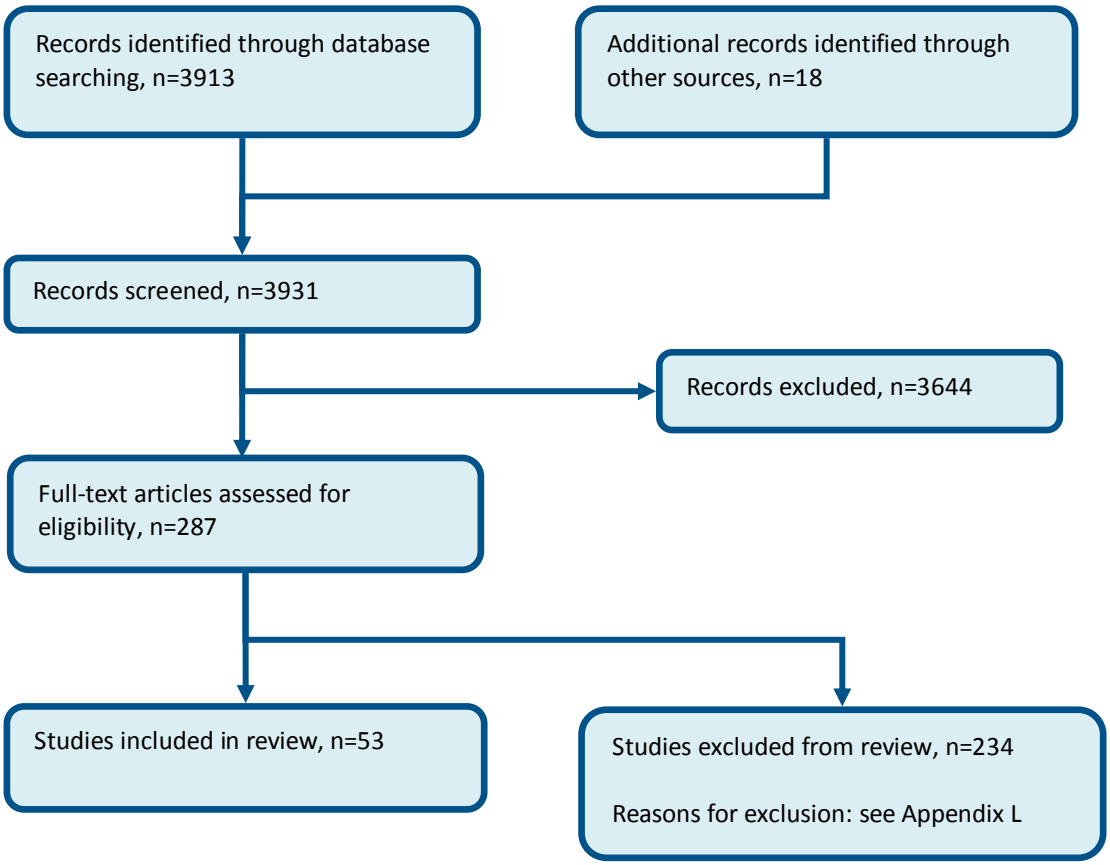
E.1 Risk factors and risk assessment tools

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



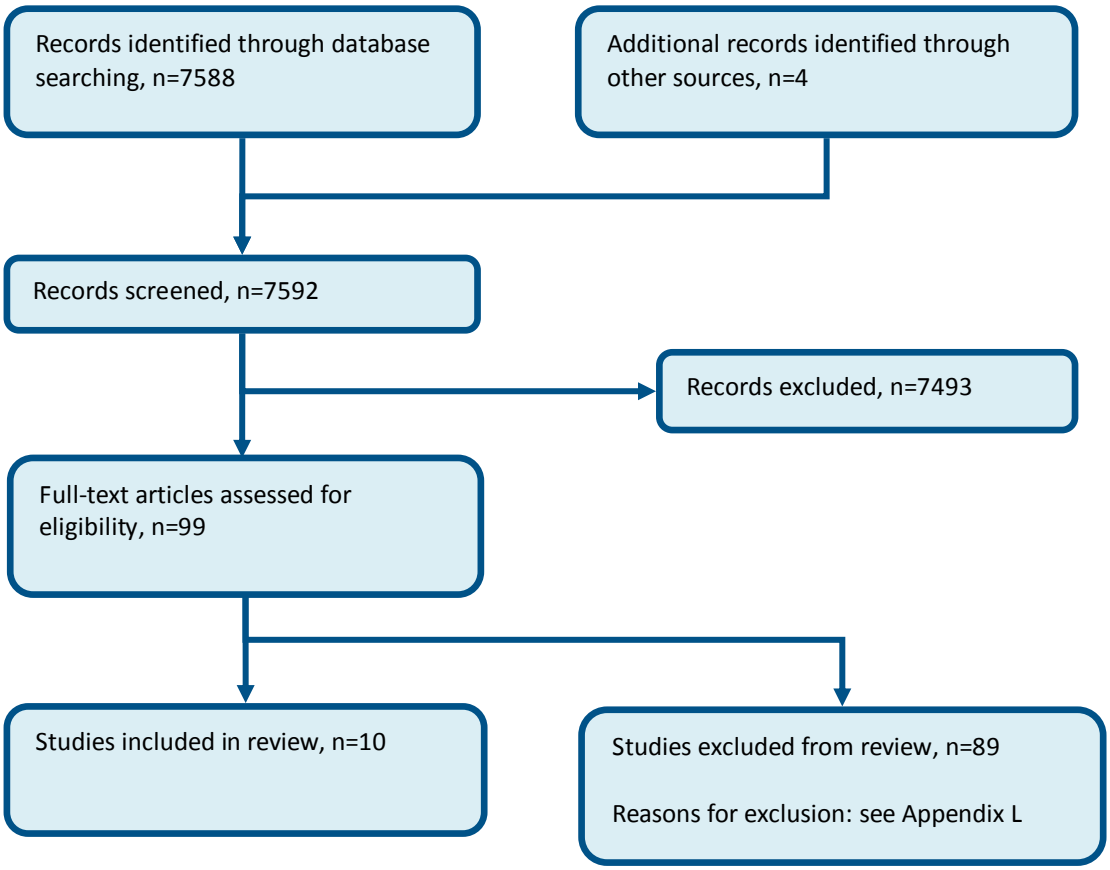
E.2 Diagnostic tests

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



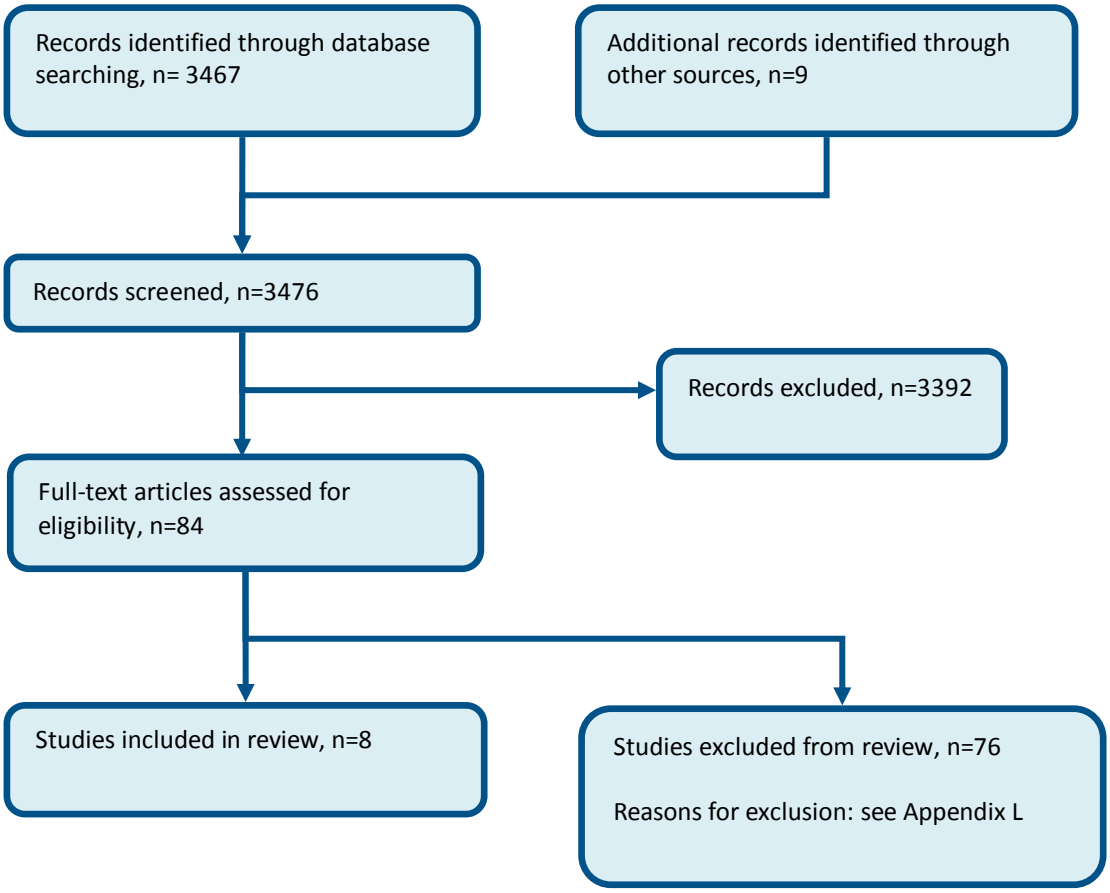
E.3 Severity risk tools

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



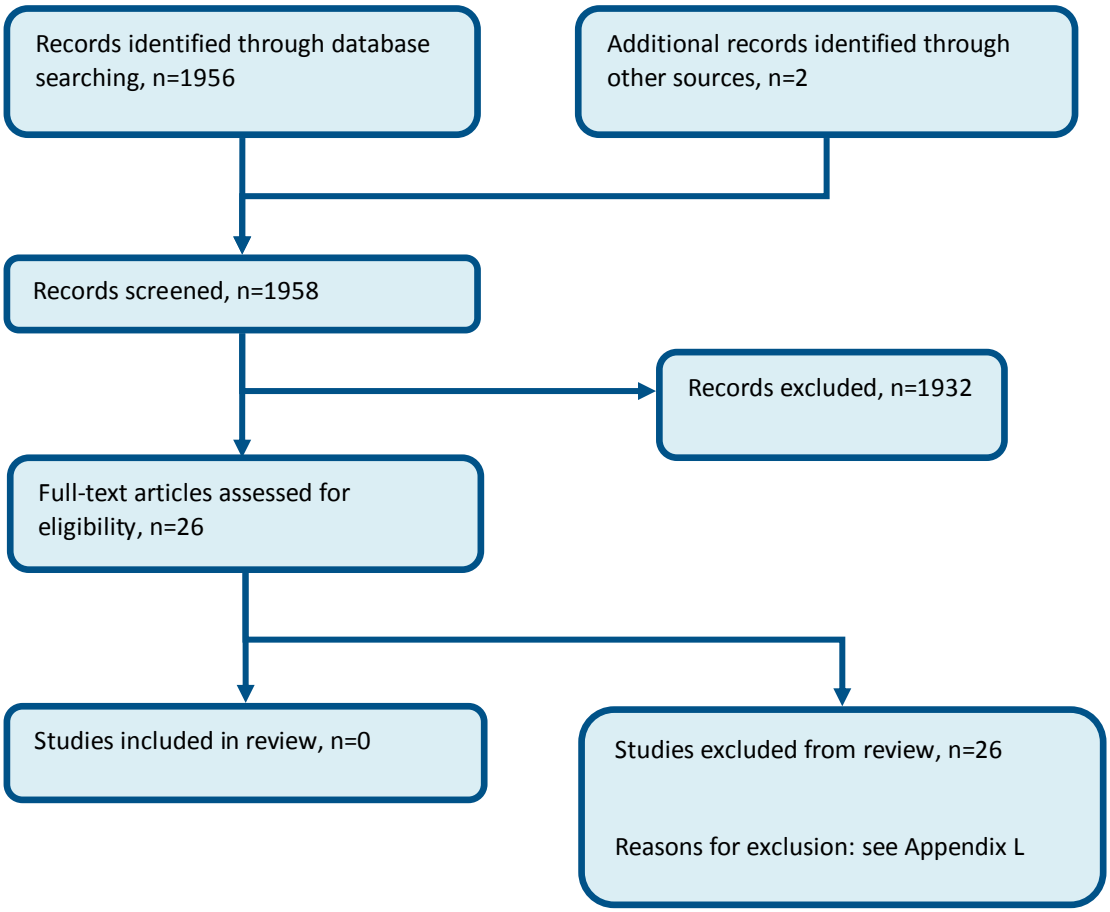
E.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

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



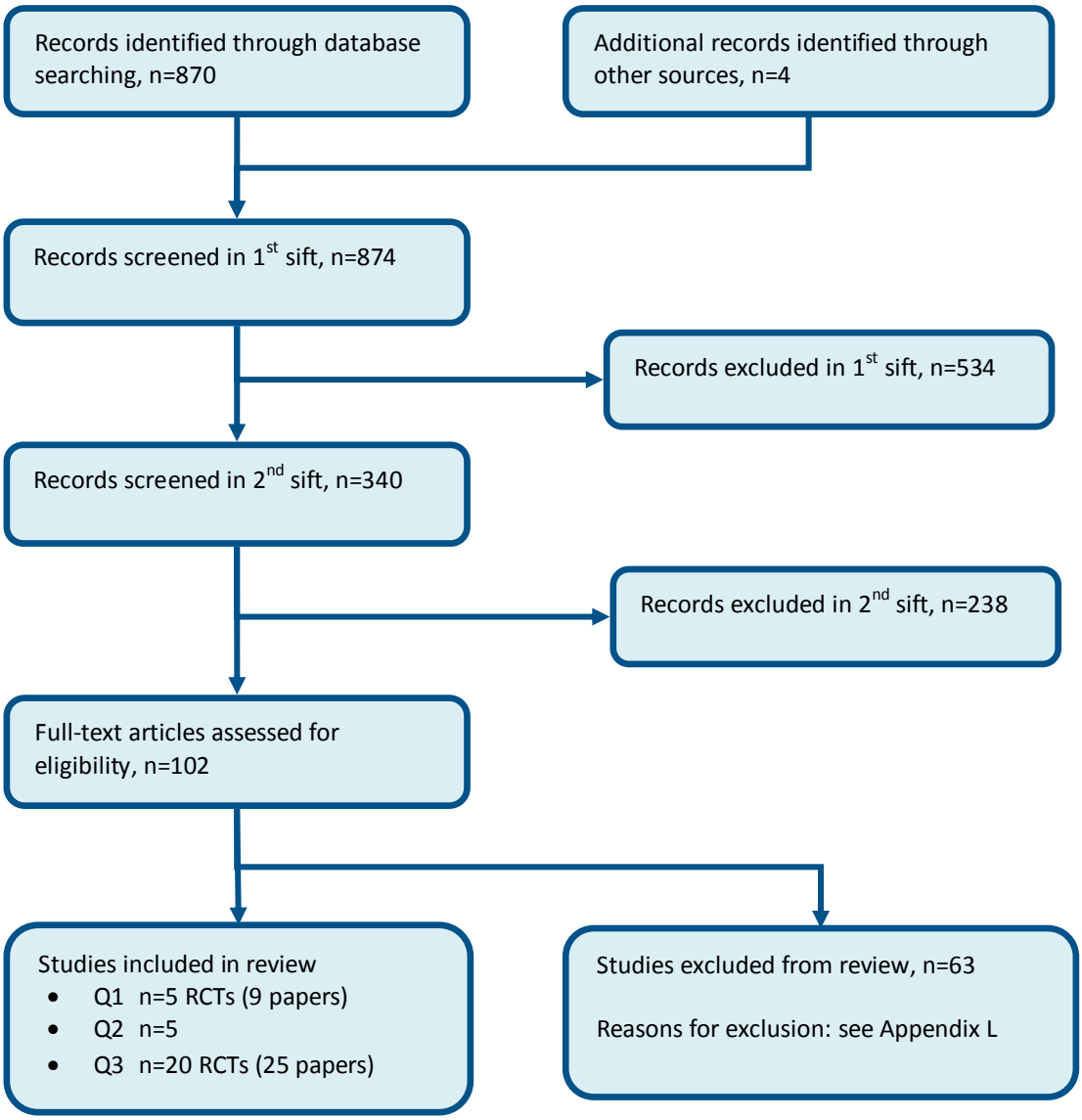
E.5 Surveillance for the detection of varices

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



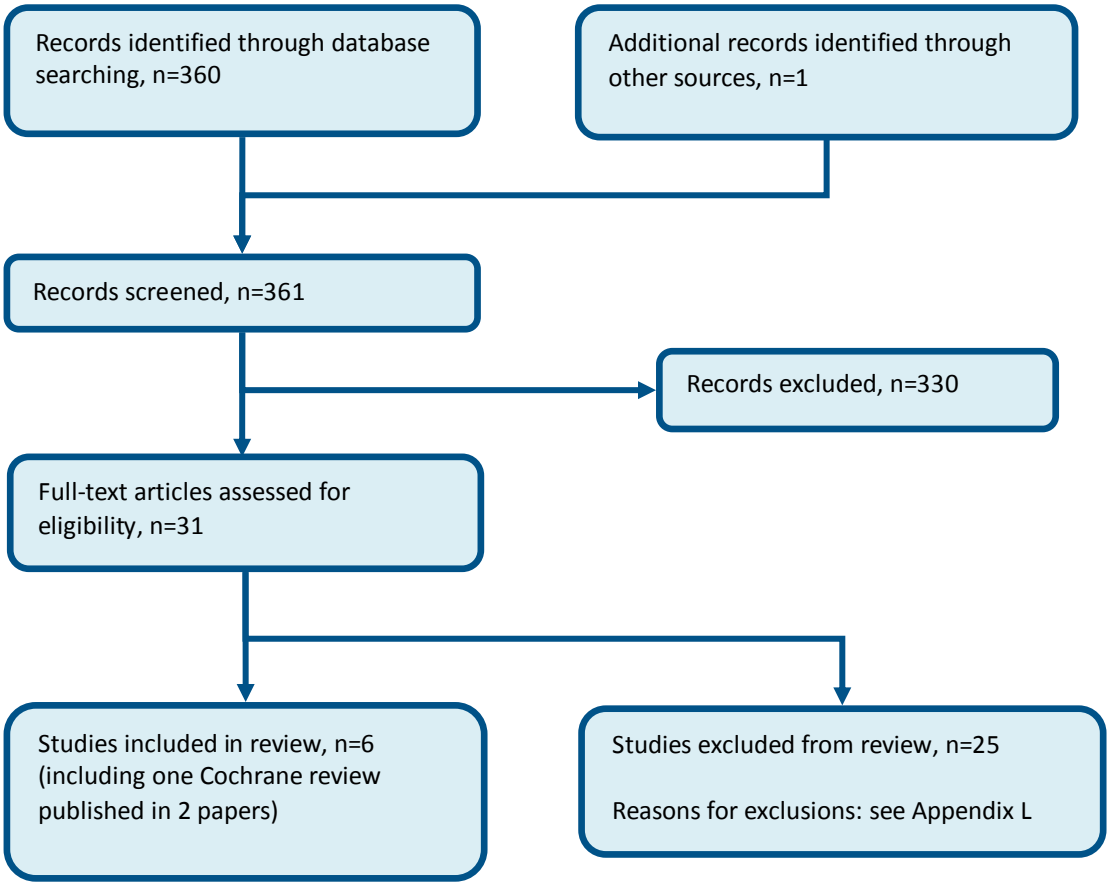
E.6 Prophylaxis of variceal haemorrhage

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



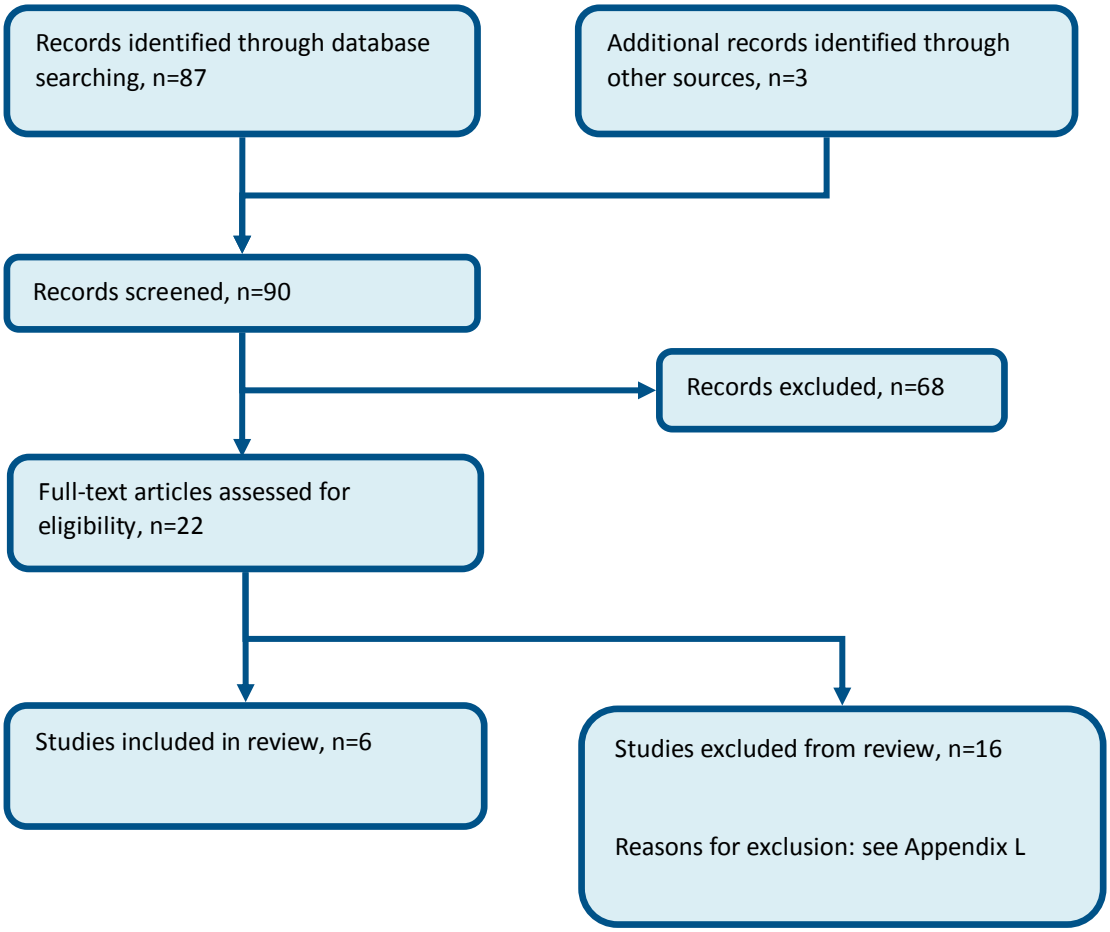
E.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

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



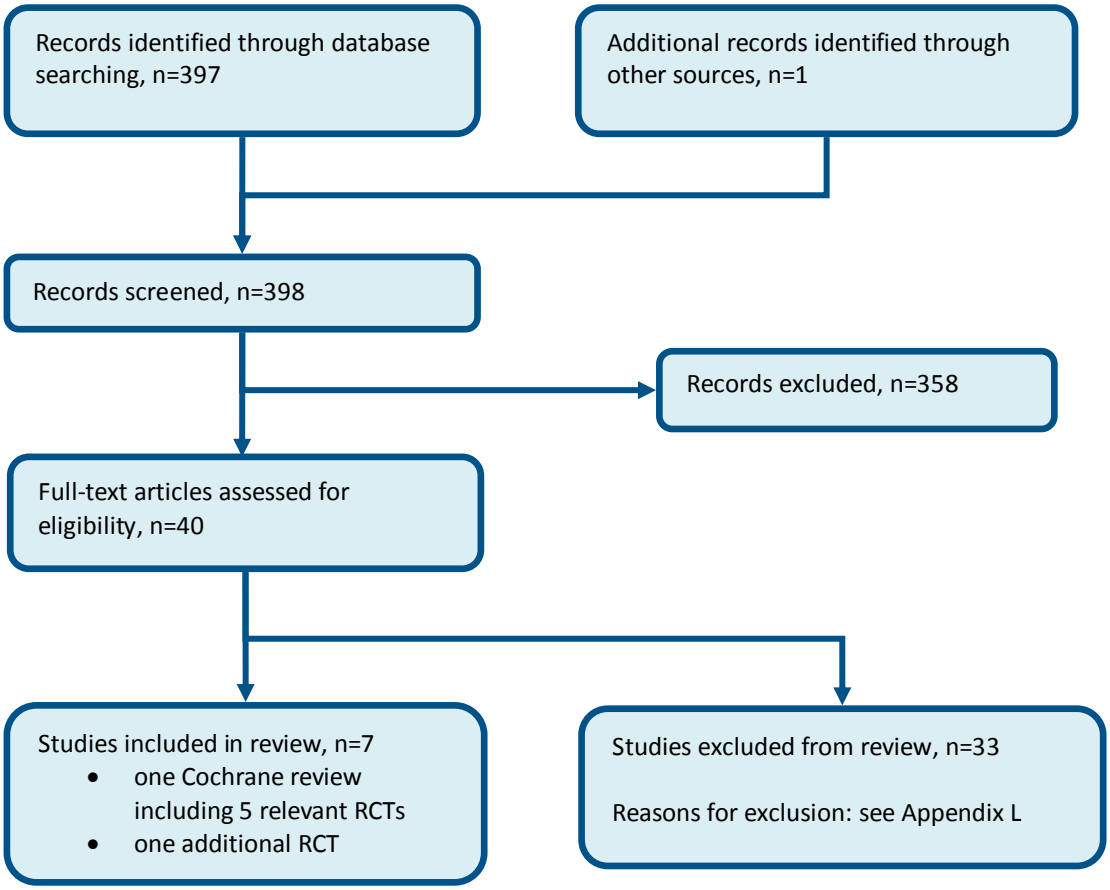
E.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

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



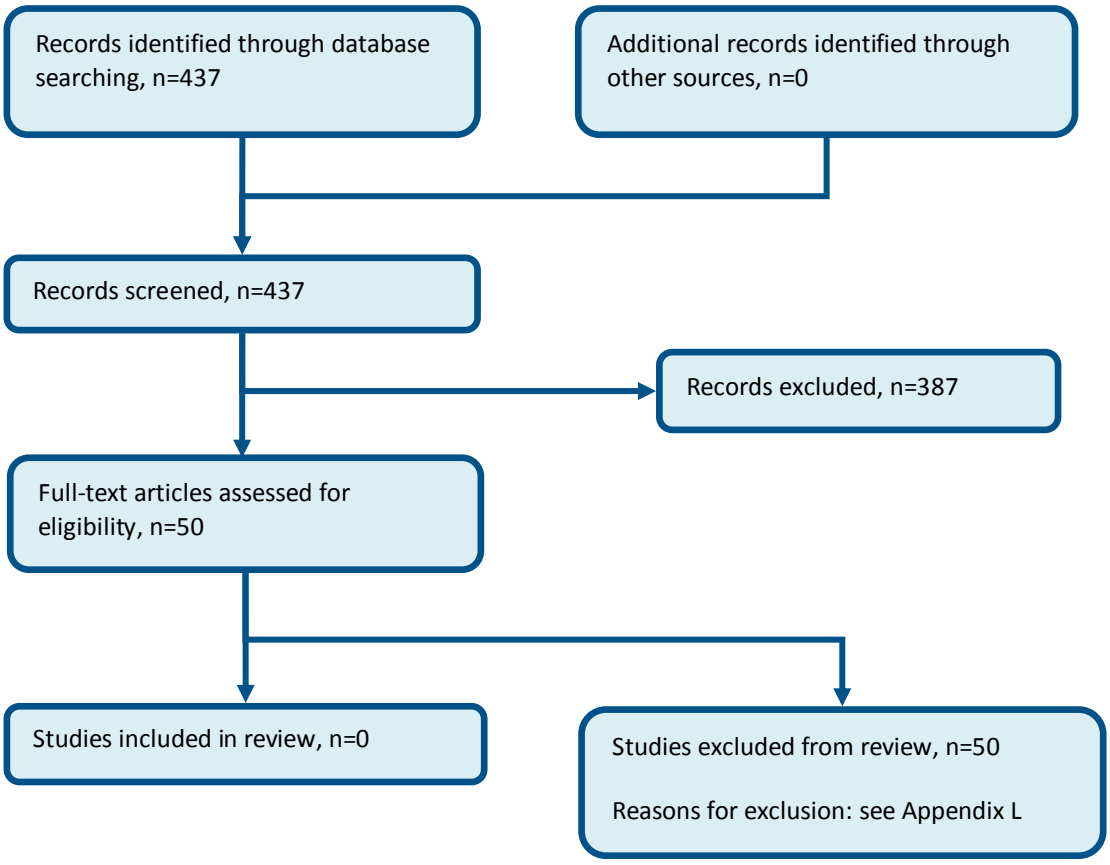
E.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

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



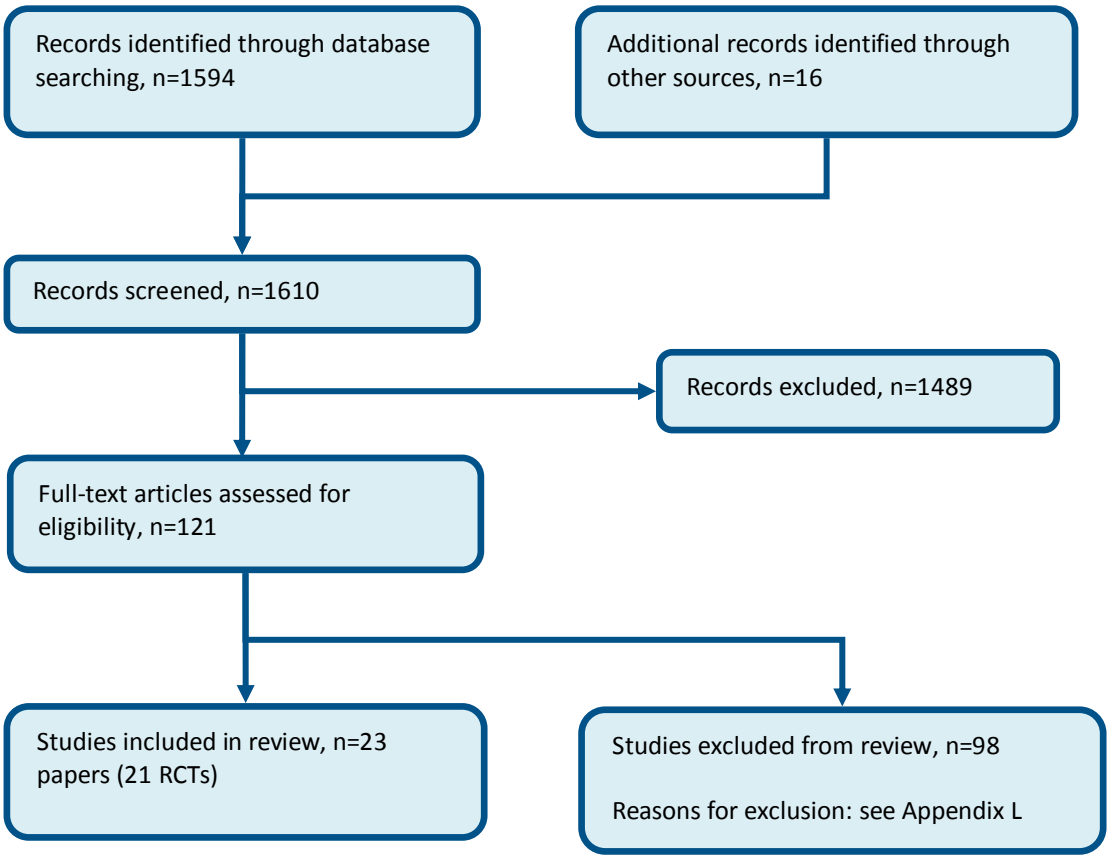
E.10 Volume replacers in hepatorenal syndrome

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



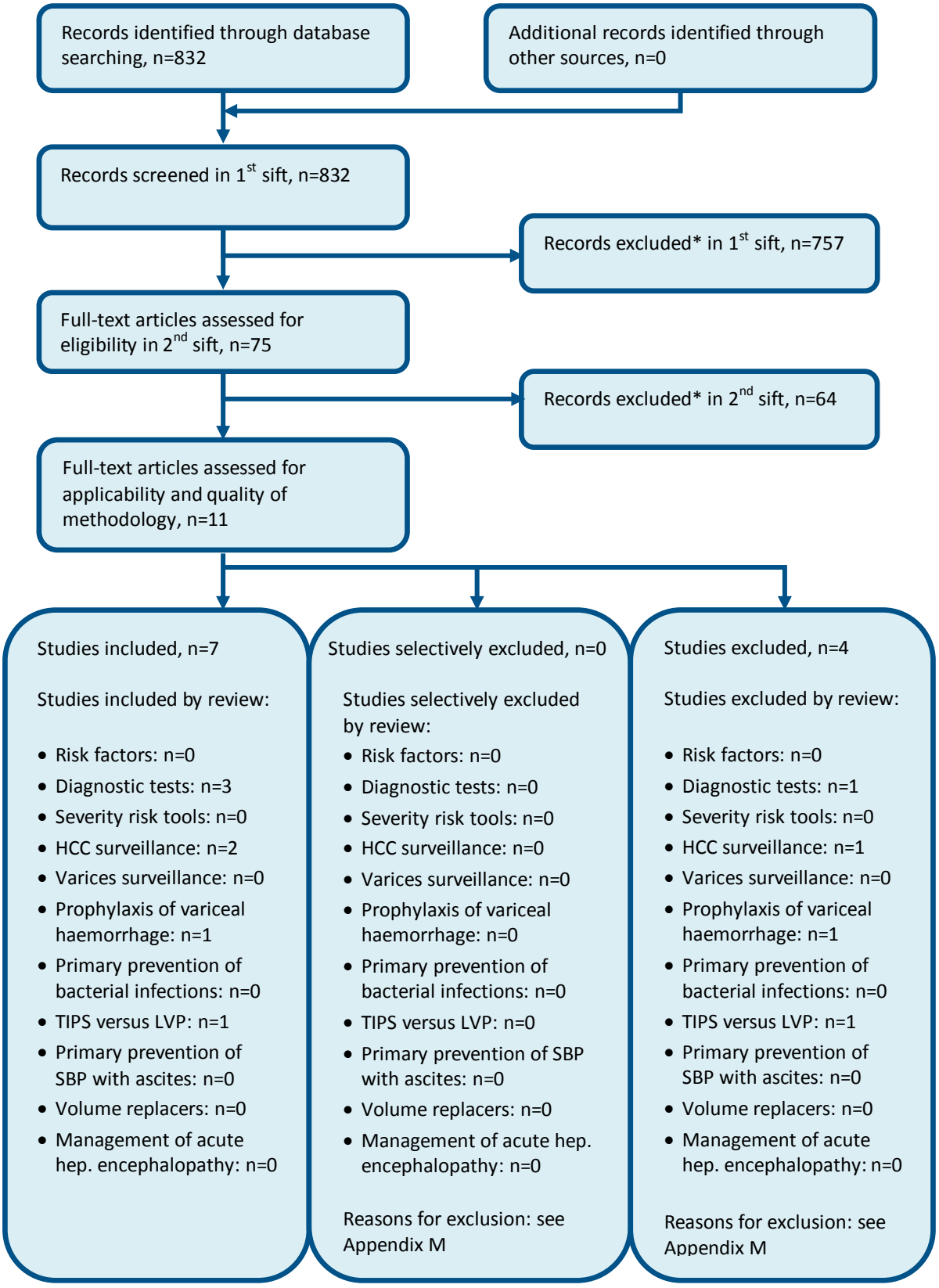
E.11 Management of an episode of acute hepatic encephalopathy

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.[92] 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}nav

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 (G.3.9)
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 (G.3.9)
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

Appendix H: Clinical evidence tables

H.1 Risk factors and risk assessment tools

H.1.1 Risk factors

Reference	ASKGAARD 2015[9]
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[9]
	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[9]
	Drinking alcohol at baseline: Lifetime abstainers n=0; HR 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; HR 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[11]
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[11]
	participants=30,630. Mean age at first examination was 52 years (range 21–93). Male/female: 16,295/14,335 Total alcohol intake (drinks/week) <1: n=6,119; events at follow up (death or discharge with alcohol-induced cirrhosis):26. Total alcohol intake (drinks/week)1–7: n=11,460; events at follow up (death or discharge with alcohol-induced cirrhosis):35. Total alcohol intake (drinks/week) 8–21: n=8,918; events at follow up (death or discharge with alcohol-induced cirrhosis):75 Total alcohol intake (drinks/week) 22–35: n=2,481; events at follow up (death or discharge with alcohol-induced cirrhosis): 58 Total alcohol intake (drinks/week) >35: n=1,652; events at follow up (death or discharge with alcohol-induced cirrhosis): 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 that 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. Twenty-six individuals who developed alcohol-induced cirrhosis were non-drinkers. Data were analysed 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

Reference	BECKER 2002[11]
	relative risk for developing alcohol-induced cirrhosis with increasing alcohol intake was observed among women, and a J-shaped relationship among men. Alcohol results for men: Total alcohol intake (drinks/week) <1: RR=7.76 (3.35–18.0) Total alcohol intake (drinks/week) 1–7: RR=1 (reference) Total alcohol intake (drinks/week) 8–21: RR=2.34 (1.18–4.62) Total alcohol intake (drinks/week) 22–35: RR=10.4 (5.4–19.9) Total alcohol intake (drinks/week) >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) Total alcohol intake (drinks/week)1–7: RR=1.19 (0.54–2.59) Total alcohol intake (drinks/week) 8–21: RR=5.33 (2.63–10.8) Total alcohol intake (drinks/week) 22–35: RR=10.8 (4.28–27.1) Total alcohol intake (drinks/week) >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[12]
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

Reference	BLACKWELDER 1980[12]
	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. 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[49]
Study type and analysis	Prospective cohort. Proportional-hazards model to adjust for multiple risk factors simultaneously.
Number of participants	n=85,709 Average alcohol intake (g/day) 0: n=25,535; events at follow-up (death due to cirrhosis of the liver): 12.

Reference	FUCHS 1995[49]
and characteristics	Average alcohol intake (g/day) 0.1–1.4: n=11,304; events at follow-up (death due to cirrhosis of the liver): 1 Average alcohol intake (g/day) 1.5–4.9: n=18,406; events at follow-up (death due to cirrhosis of the liver): 5 Average alcohol intake (g/day) 5.0–14.9: n=17,783; events at follow-up (death due to cirrhosis of the liver): 10 Average alcohol intake (g/day) 15.0–29.9: n=8106; events at follow-up (death due to cirrhosis of the liver): 9 Average alcohol intake (g/day) ≥30: n=4521; events at follow-up (death due to cirrhosis of the liver): 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)

Reference	FUCHS 1995[49]
	• energy-adjusted intake of dietary fibre and saturated fat (in quintiles). 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[62]
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

Reference	IOANNOU 2003[62]
	(NHEFS). 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	Death or hospitalisation caused by cirrhosis.

Reference	IOANNOU 2003[62]
effect sizes	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 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

Reference	IOANNOU 2003[62]
	serum cholesterol level.

Reference	KLATSKY 1992[71]
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

Reference	KLATSKY 1992[71]
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). 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

Reference	KLATSKY 1992[71]
	3–5: RR 21.6 ≥6: RR 83.4 Death from non-alcoholic cirrhosis n=32 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[78]
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

Reference	LIU 2010A[78]
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, 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. 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: RR 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).

Reference	LIU 2010A[78]					
	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)
	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[126]
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, two 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):

Reference	SCHULT 2011[126]
	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) 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[8]
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	Transient elastography (Fibroscan, Echosens, France), optimal cut-off threshold calculated (14.8 kPa): operator was a staff physician (AU) who had previously performed determinations in patients with chronic liver disease. Considered

Study	Arena 2008[8]
whether threshold pre-specified)	representative measurements of the median value of 10 successful acquisitions with a success rate of at least 60%, and with an IQR over 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 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 (0.950.99) Optimal cut-off threshold (if calculated): 14.8 kPa Threshold: 14.8 kPa (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 likelihood ratios (LRs) and concluded that thresholds of <12 kPa and >18 kPa 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 18 kPa could not reliably predict the presence or absence of cirrhosis at multilevel LRs analysis.	

Study	Arena 2008[8]
<12 kPa: 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 transient elastography (TE).	
General limitations according to QUADAS II: Unclear if reference standard interpreted without knowledge of the index test result.	

Study	Aykut 2014[10]
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; subjects with normal transaminases in presence of hepatomegaly and/or splenomegaly; subjects with normal transaminases but persistently increased gamma-glutamyl transferase. Absent to low alcohol consumption (<30 g/day men and <20 g/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 manufacturer's 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 75 mm 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%.

Study	Aykut 2014[10]
Reference standard	Liver biopsy (NAFLD activity score F4 [reference McPherson 2010 paper which used Kleiner score]): all liver biopsies were at least 20 mm long and/or contained more than 11 complete portal tracts.
Time between index test and reference standard	Not reported
Target condition	Cirrhosis
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.	

Study	Aykut 2014[10]
Liver biopsies could be <25 mm.	

Study	BORRONI 2006[13]
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 (Knodell F4): The biopsies were performed under ultrasound guidance using 16-gauge needles and the lateral transcostal approach. Only samples with a length >20 mm 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	Undergone serum markers during the 3 months preceding liver biopsy.

Study	BORRONI 2006[13]
reference standard	
Prevalence of cirrhosis according to reference standard	30/228 (13.2%)
Target condition	Cirrhosis
Results: APRI 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	

Study	BORRONI 2006[13]
FN: Not reported TN: Not reported Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II: Up to 3 months between index test and reference standard. Retrospective chart analysis. Liver biopsy sample <25 mm and 10 portal tracts.	

Study	BOTA 2011A[14]
Study type	Retrospective cohort
Number of studies (number of participants). Recruitment period.	1 study (n=212 patients). Recruitment between January 2008 and 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 13.3 kPa, not-prespecified, from previous studies): 10 valid TE measurements, included only liver stiffness (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

Study	BOTA 2011A[14]
	studies. FIB-4: 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 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: 13.3 kPa (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)	

Study	BOTA 2011A[14]
Sensitivity: 80.0 Specificity: 74.1 PPV: 33.8 NPV: 95.7 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: FIB-4 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[15]
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)

Study	BOTA 2015[15]
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.
Index test (including threshold and whether threshold pre-specified)	ARFI (pre-published cut-off 1.87 m/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 15.3 kPa): 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: 1.87 m/s (pre-published)	

Study	BOTA 2015[15]
Sensitivity: not reported Specificity: not reported PPV: not reported 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 <25 mm. Reliable LS measurements by means of ARFI elastography were obtained in 117/132 patients (87.9%), patients included in the final analysis.	

Study	CARDOSO2012 [16]
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 chronic hepatitis C [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,

Study	CARDOSO2012 [16]
	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) Inclusion: Presence of anti-HCV antibodies and detectable serum HCV-RNA by PCR (>50IU/ml) Exclusion: Excessive alcohol consumption (>30 g/day for men, >20 g/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 12.5 kPa, 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 ≥15 mm 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	

Study	CARDOSO2012 [16]
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 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 <15 mm or 10 portal tracts.	

Study	CASTERA 2010A[17]
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:

Study	CASTERA 2010A[17]
	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, 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 the calculation of 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 15 mm). 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

Study	CASTERA 2010A[17]
	Results: SAFE algorithm AUC (95% CI): 0.87 (0.84–0.90) Optimal cut-off threshold (if calculated): Not reported Threshold: as above 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

Study	CASTERA 2010A[17]
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: Liver biopsy could be <25 mm or <10 portal tracts	

Study	CATANZARO 2013[18]
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 co-infection 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/day of ethanol), heart failure or pregnancy, and patients with BMI >30 kg/m^2.
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.), which 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]

Study	CATANZARO 2013[18]
	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' 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	

Study	CATANZARO 2013[18]
	Specificity: 87.4 PPV: 68.1 NPV: 90.4 +ve/-ve likelihood ratios: LH+ 5.9 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 <25 mm and <10 portal tracts.

Study	CAVIGLIA 2013[19]
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,

Study	CAVIGLIA 2013[19]
	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 whether threshold pre-specified)	Transient elastography (Fibroscan, Echosens, Paris): (cut-off 13.8 kPa, optimal chosen to maximise sensitivity and specificity) performed on the right lobe of the liver through the intercostal spaces. Measurement depth between 25 and 65 mm 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 20 mm 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): 13.8 kPa Threshold: 13.8 kPa (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	

Study	CAVIGLIA 2013[19]
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	
General limitations according to QUADAS II: Up to 12 months between index test and reference standard Liver biopsy sample < 25 mm	

Study	CHEN 2012[25]
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 [liver stiffness measurement] 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) co-infection, human immunodeficiency virus (HIV) co-infection, liver abscess, acute hepatitis, extrahepatic cholestasis, severe haemolysis, 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.

Study	CHEN 2012[25]
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 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	

Study	CHEN 2012[25]
	TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: ARFI AUC (95% CI): 0.831 (0.723–0.939) Optimal cut-off threshold (if calculated): 1.98 m/s Threshold: 1.98 m/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=0.341. Any complications associated with tests reported: Not reported
	General limitations according to QUADAS II: Liver biopsy sample < 25 mm and <10 portal tracts

Study	CHRYSANTHOS 2006[26]

Study	CHRYSANTHOS 2006[26]
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).
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	

Study	CHRYSANTHOS 2006[26]
	Specificity: 60 PPV: 35 NPV: 88 +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 <25 mm

Study	DE 2006[30]
Study type	Multicentre cross-sectional study
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 <7 mm, 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 11.8 kPa, and for the highest sensitivity with specificity forced no less than 95%, cut=of 14.5 kPa): tip of probe transducer placed on the skin between the ribs at the level of the right lobe of the liver. Measurement depth 25–65 mm 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 22 mm (range 7–48 mm) 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	17/72 (23.6%)

Study	DE 2006[30]
reference standard	
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.97 (0.94–1) Optimal cut-off threshold: 11.8 kPa (highest sensitivity with specificity no less than 90%), 14.5 kPa (highest sensitivity with specificity no less than 95%) Threshold: 11.8 kPa (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: 14.5 kPa (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)	

Study	DE 2006[30]
	Results: AST/ALT ratio (n=46) 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: Area under the receiver operating characteristic curve (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[34]
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

Study	Esmat 2013[34]
	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. 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	

Study	Esmat 2013[34]
FN: 5 TN: 135 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 <25 mm and <10 portal tracts	

Study	Fahmy 2011[35]
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.

Study	Fahmy 2011[35]
Reference standard	Liver biopsy (METAVIR F4): specimens composed of core >15 mm were assessed
Time between index test and reference standard	Within 1 week
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 <25 mm	

Study	Fernandes 2015[37]
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	Two liver units in Brazil
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 co-infection; alcohol daily intake >20 g for women and 40 g 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): 15 ml 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 12.5 kPa, 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 22 mm (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[37]
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) Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II: Liver biopsy sample <25 mm or <10 portal tracts	

Study	FERRAIOLI 2014[40]
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 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)

Study	FERRAIOLI 2014[40]
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 9.3 kPa): 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 7 years and 2 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 one 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) Optimal cut-off threshold (if calculated): N/A Threshold: 9.3 kPa (pre-published)	

Study	FERRAIOLI 2014[40]
	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): 7.2 kPa Threshold: 7.2 kPa (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 Any complications associated with tests reported: Not reported
General limitations according to QUADAS II: Liver biopsy sample <10 portal tracts and <25 mm.	

Study	FIERBINTEANU BRATICEVICI 2013[43]
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 (>20 g 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. Ten 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 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 24 mm).
Time between index test and reference standard	<6 months
Prevalence of cirrhosis according to	12/64 (18.75%)

Study	FIERBINTEANU BRATICEVICI 2013[43]
reference standard	
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[45]
Study type	Cross-sectional study

Study	FLOREANI 2011[45]
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 male/female: 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 through the intercostal 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): combination of TE with each marker.

Study	FLOREANI 2011[45]
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 AUC (95% CI): 0.74 (0.58–0.88)	

Study	FLOREANI 2011[45]
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[47]
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
Funding	None
Age, gender, ethnicity, ALT (U/l):	Not reported for HCV population alone

Study	FRIEDRICH-RUST 2010[47]
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 analysed 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 AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: 0.73 (pre-published)	

Study	FRIEDRICH-RUST 2010[47]
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 Optimal cut-off threshold (if calculated): Not reported Threshold: 12.5 (pre-published) Sensitivity: 78	

Study	FRIEDRICH-RUST 2010[47]
	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)
	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[46]
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.
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 20–43 kg/m^2

Study	FRIEDRICH-RUST 2010A[46]
Patient characteristics	Population: NAFLD or NASH Inclusion: Diagnosis of NAFLD or NASH made histologically by liver biopsy. Exclusion: Men with alcohol consumption more than 30 g/week and women with alcohol consumption more than 20 g/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 an 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 20 mm, range 10–40 mm.
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 Threshold: Not reported Sensitivity: Not reported Specificity: Not reported PPV: Not reported	

Study	FRIEDRICH-RUST 2010A[46]
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: Time between reference standard and index test up to 18 months Size of liver biopsy <6 portal tracts	

Study	FUJII 2009[50]
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 (20 g/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 weeks 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. (>1 cm with >10 portal tracts). Histological diagnosis was performed.
Time between index test and reference standard	Within 4 weeks
Prevalence of cirrhosis according to reference standard	9/50 (18%)
Target condition	Cirrhosis
Results: AAR AUC (95% CI): 0.813 (0.674–0.952) Optimal cut-off threshold (if calculated): Not reported Results: APRI	

Study	FUJII 2009[50]
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[51]
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
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

Study	GAIA 2011[51]
	known cause of liver disease. Exclusion: Patients with alcoholic liver disease (>40 g/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 cut-off values to maximize sensitivity, specificity, and diagnostic accuracy): 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 20 mm 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): 11.5 kPa 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	

Study	GAIA 2011[51]
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): 10.5 kPa Threshold: 10.5 kPa (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 disease-related factors may modify its accuracy.	
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[58]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	n=590 enrolled, consecutive recruitment reported previously Zarski 2012[164] (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, Wilson's disease, hemochromatosis, autoimmune hepatitis, alcohol consumption >30 g/day for men and >20 g/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 (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 was 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

Study	GUECHOT 2012[58]
	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 25 mm 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 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[60]
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 (for example 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) 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)	

Study	Halfon 2007[60]
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) 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 (≥21 mm and <21 mm). Any complications associated with tests reported: Not reported	

Study	Halfon 2007[60]
General limitations according to QUADAS II: Consecutive or random recruitment not reported. Retrospective recruitment. Liver biopsy size <25 mm.	

Study	Janssens 2010[63]
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, 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 ≥9.5 kPa) 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 (70 g 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

Study	Janssens 2010[63]
	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 1.5 mm (Cook, Denmark). All specimens analysed by an experienced liver pathologist blinded to the biological, radiological and clinical data. Liver biopsy specimen of at least 15 mm 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 23.5 kPa Threshold: 19.6 kPa 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: 21.1 kPa Sensitivity: 75 Specificity: 80 PPV: Not reported	

Study	Janssens 2010[63]
NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 23.5 kPa 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 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	

Study	Janssens 2010[63]
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 <25 mm Indirectness: Only patients with severe fibrosis (transient elastography ≥9.5 kPa) underwent liver biopsy.	

Study	KAYADIBI 2014[66]
Study type	Retrospective cohort study
Number of studies (number of participants). Recruitment period.	1 study (n=214; 202 with sufficient data to complete) 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, hepatitis 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

Study	KAYADIBI 2014[66]
	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: 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 AST: AUC (95% CI): 0.752 (0.671–0.832) Optimal cut-off threshold (if calculated): Not reported Threshold:	

Study	KAYADIBI 2014[66]
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: 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 FIB-4: AUC (95% CI): 0.853 (0.784–0.921) Optimal cut-off threshold (if calculated): Not reported Threshold: Not reported Sensitivity: Not reported	

Study	KAYADIBI 2014[66]
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: 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 AST/ALT ratio: AUC (95% CI): 0.610 (0.510–0.709) Optimal cut-off threshold (if calculated): Not reported Threshold: Not reported Sensitivity: Not reported Specificity: Not reported	

Study	KAYADIBI 2014[66]
	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: Random or consecutive recruitment not reported.	

Study	KETTANEH 2007[67]
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

Study	KETTANEH 2007[67]
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 antibodies 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 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 15 mm 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: Not reported Sensitivity: Not reported	

Study	KETTANEH 2007[67]
	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. 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 <25 mm.

Study	LACKNER 2005[74]
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.

Study	LACKNER 2005[74]
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- naïve 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).
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 the 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 were 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	

Study	LACKNER 2005[74]
+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 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	

Study	LACKNER 2005[74]
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) 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:

Study	LACKNER 2005[74]
Unclear if reference standard result interpreted without knowledge of clinical data or the index test results. Liver biopsy <10 portal tracts	

Study	LEROY 2014[77]
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 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 30 g/day, hepatocellular carcinoma, Gilbert's disease, chronic haemolysis, 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

Study	LEROY 2014[77]
Prevalence of cirrhosis according to reference standard	Not reported 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 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:	

Study	LEROY 2014[77]
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[83]
Study type	Cross-sectional study
Number of studies (number of participants). Recruitment period.	n=1202 consecutive CHC patients. Between May 2007 and December 2012.
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-Napoc.
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.

Study	LUPSORPLANTON 2013[83]
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): 13.2 kPa Threshold: 13.2 kPa (optimal) Sensitivity: 93.75 (90.8–96.0) Specificity: 93.31 (91.4–94.9) 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 LSMs 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[85]
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. Exclusion: Hepatitis B, other causes of liver disease (autoimmune, tumoural, 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 (Knodell F4). A minimum liver biopsy length of 10 mm was required but only biopsies above 15 mm were included in the 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)	

Study	MACIAS 2006[85]
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) 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	

Study	MACIAS 2006[85]
	+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 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 co-infected patients than in the validation studies performed in HCV mono-infected 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 <25 mm

Study	MARTINEZ 2011A[86]
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± 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	

Study	MARTINEZ 2011A[86]
AUC (95% CI): 0.86 (0.82–0.90) standard threshold Optimal cut-off threshold (if calculated): Not reported Threshold: 1 Sensitivity: 82 Specificity: 74 PPV: 64 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): Not reported Threshold: 0.06	

Study	MARTINEZ 2011A[86]
Sensitivity: 90 Specificity: 53 PPV: 52 NPV: 90 +ve/-ve likelihood ratios: 1.9/0.2 Diagnostic odds ratio: 9.5 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: FIB-4 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	

Study	MARTINEZ 2011A[86]
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: 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[89]
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): not reported
Patient characteristics	Population: Alcohol-related liver disease (ALD)

Study	MUELLER 2010[89]
	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 tumours.
Index test (including threshold and whether threshold pre-specified)	Transient elastography (FibroScan, using the M probe; cut-off of 12.5 kPa 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 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): 11.5 kPa (to give 100% sensitivity) Threshold: 11.5 kPa (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	

Study	MUELLER 2010[89]
	Threshold: 12.5 kPa (pre-published) Sensitivity: 96 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 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 <25 mm	

Study	MYERS 2012B[90]
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

Study	MYERS 2012B[90]
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, ascites, implantable cardiac devices, previous liver transplant, terminal disease.
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 22.3 kPa, XL probe 16 kPa]): 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 15–53 mm, 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): 22.3 kPa Threshold: 22.3 kPa Sensitivity: 80 (28–99) Specificity: 91 (82–97) PPV: 40 (12–74)	

Study	MYERS 2012B[90]
NPV: 98 (92–100) +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 (0.89–1.00) Optimal cut-off threshold (if calculated): 16.0 kPa Threshold: 16.0 kPa 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 hepatitis 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 cut-offs 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:	

Study	MYERS 2012B[90]
Random or consecutive recruitment not reported Up to 6 months between index test and reference standard Liver biopsy sample <25 mm and 10 portal tracts	

Study	RIZZO 2011[106]
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 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 co-infection, 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 11 kPa, determined as optimal cut-off by Kolmogorov – Smirnov index]: Performed 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 2 m/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 segment (V, VI, VII, and VIII) within the right lobe. A median of the 20 results has been calculated.

Study	RIZZO 2011[106]
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%)
Target condition	Cirrhosis
Results: Fibroscan AUC (95% CI): 0.80 (0.72–0.86) Optimal cut-off threshold (if calculated): 11 kPa Threshold: 11 kPa (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): 2 m/s Threshold: 2 m/s (optimal) Sensitivity: 83 Specificity: 86 PPV: 63	

Study	RIZZO 2011[106]
	NPV: 95 +ve/-ve likelihood ratios: 6.1/0.2 TP: Not reported FP: Not reported FN: Not reported TN: Not reported 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 <25 mm

Study	SANCHEZ-CONDE 2010[117]
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 the 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.

Study	SANCHEZ-CONDE 2010[117]
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 '25 mm in length in most cases'. Formalin-fixed, paraffin-embedded liver tissue was stained by haematoxylin-eosin, Mason's trichrome and Perl's iron.
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: 14 kPa (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 co-infected patients. Any complications associated with tests reported: Not reported	

Study	SANCHEZ-CONDE 2010[117]
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 <25 mm (unclear how many)	

Study	Shehab 2014[129]
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. However, 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 hepatitis C (HCV) Inclusion: Positive HCV RNA, compensated liver disease and availability of serum biomarker results done within 1 month prior to liver biopsy. Exclusion: Co-infection with HBV or HIV; other causes of liver disease; alcohol consumption higher than 20 g/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; FIB-4: 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 FIB-4 (pre-published cut-off of 3.25): [age (years) x AST (IU/l)] / platelet count 109/l x ALT (IU/l)1/2

Study	Shehab 2014[129]
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.
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	

Study	Shehab 2014[129]
TP: Not reported FP: Not reported FN: Not reported TN: Not reported Results: FIB-4 AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported 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 Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II: Liver biopsies <25 mm 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[130]
Study type	Cross-sectional study

Study	SILVIA JUNIOR 2014[130]
Number of studies (number of participants). Recruitment period.	1 study (n=51 consecutive patients). Recruitment from January 2012-March 2013
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 1.95 m/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 109/l FIB-4: [age (years) x AST (IU/l)] / platelet count 109/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 20.6 mm (range 15–28 mm), 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. Specimens 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 reference standard	9/51 (17.6%)

Study	SILVIA JUNIOR 2014[130]
Target condition	Cirrhosis
Results: ARFI AUC (95% CI): 0.98 (CI not reported) Optimal cut-off threshold (if calculated): 1.95 m/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 FN: Not reported TN: Not reported	

Study	SILVIA JUNIOR 2014[130]
Results: FIB-4 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 <25 mm	

Study	SIRLI 2010[132]
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

Study	SIRLI 2010[132]
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 13.3 kPa chosen to maximise the sum of the sensitivity and specificity]): Performed by 3 experienced physicians by standard method. Ten 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 109/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 109/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). Echo-assisted using Menghini-type modified needles, 1.4 and 1.6 mm in diameter. Only biopsies of at least 20 mm 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
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): 13.3 kPa Threshold 13.3 kPa (optimal):	

Study	SIRLI 2010[132]
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 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	

Study	SIRLI 2010[132]
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): 155000 mm^3 Threshold 155000 mm^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 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:

Study	SIRLI 2010[132]
Consecutive or random selection not reported. Unknown if the reference standard results were interpreted without knowledge of the index test results Liver biopsies <25 mm and <10 portal tracts	

Study	SPOREA2011A[138]
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, 2 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, non-alcoholic steatohepatitis, autoimmune chronic hepatitis, haemochromatosis, Wilson's disease)
Index test (including threshold and whether threshold pre-specified)	Transient elastography (optimal cut-off value 12.2 kPa 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 1.8 m/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. Ten 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.

Study	SPOREA2011A[138]
	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): Echo-guided TruCut technique, with a 1.8 mm (14 G) diameter automatic needle device-Biopty Gun (Bard GMBh), or echo-assisted, 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 centre) 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): 12.2 kPa Threshold: 12.2 kPa (optimal) 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 Results: ARFI AUC (95% CI): 0.91 Optimal cut-off threshold (if calculated): 1.8 m/s	

Study	SPOREA2011A[138]
Threshold: 1.8 m/s (optimal) 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 Results: Combination of Fibroscan and ARFI AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported Threshold: Values both for TE and ARFI above the cut-offs12.2 kPa and 1.8 m/s (optimal) Sensitivity: 84.9 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 1.8 m/s (optimal)	

Study	SPOREA2011A[138]
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	
General limitations according to QUADAS II: Consecutive or random selection not reported. Liver biopsy sample <10 portal tracts.	

Study	SPOREA 2012A [137] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[33,42,84,103,136] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[48,145] (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

Study	**SPOREA 2012A [137] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[33,42,84,103,136] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[48,145] (presumed authors were contacted for further information).**
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, ascites
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 intercostal approach, in the right liver lobe, segment V-VIII, 1–2 cm (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, 5 mm wide) in the desired 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 – 14 G needle and Hyogo – 16 G needle) percutaneous biopsy using semi-automatic instruments in 2 centres (Saga – 16 G 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	

Study	SPOREA 2012A [137] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[33,42,84,103,136] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[48,145] (presumed authors were contacted for further information).
AUC (95% CI): 0.842 Optimal cut-off threshold (if calculated): 1.55 m/s (or 1.69 m/s reported for n=400 subgroup who also had TE) Threshold: 1.55 m/s (optimal) Sensitivity: 84.3 Specificity: 76.3 PPV: 53.1 NPV: 93.7 +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Accuracy: 77.9% Results: TE (n=400) 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. Lupsor 2009[84] (n=112); cirrhosis F4: 42/112 (37.5%): Threshold: >13.1 (optimal) Sensitivity: 95.12 Specificity: 89.17 PPV: 84.8	

Study	SPOREA 2012A [137] Also included data from the following studies: 5 studies which were included and additional information extracted from the individual study[33,42,84,103,136] and 2 studies which were excluded from our review due to data only being available for mixed aetiologies[48,145] (presumed authors were contacted for further information).
NPV: 96.8 +ve/-ve likelihood ratios: 9.24/0.05 TP: Not reported FP: Not reported FN: Not reported TN: Not reported Fierbinteanu-braticeuici 2009[42] (n=74) TE not assessed by study, APRI assessed by study but accuracy values not reported Ebinuma 2011[33]; cirrhosis F4: Diagnostic accuracy of TE not reported separately for HCV aetiology (only splits into viral and non-viral aetiologies) Piscaglia 2011[103]; cirrhosis F4: Diagnostic accuracy of TE for cirrhosis not reported Sporea 2011D[136]; 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 <25 mm.	

Study	STIBBE 2011[139]
Study type	Cross-sectional study
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: Mono-infected HCV patients referred for liver biopsy to the outpatient clinic. Exclusion: Alcohol intake >20 g/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 an interquartile range (IQR) <30% of the median.
Reference standard	Liver biopsy (METAVIR F4): Two 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 14 G true-cut needle and required a length ≥20 mm. 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
Results: FibroTest (n=40) AUC (95% CI): Not reported Optimal cut-off threshold (if calculated): Not reported	

Study	STIBBE 2011[139]
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: 14 kPa (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 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 for HCV separately. Hyaluronic acid, APRI, FibroTest, Fib-4 and TE reliably distinguish non-cirrhotic and cirrhotic patients.	
General limitations according to QUADAS II:	

Study	STIBBE 2011[139]
Consecutive or random recruitment not reported. Blinding unclear during interpretation of reference standard test results. Liver biopsy size <25 mm.	

Study	Wong 2010B[160]
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. Two 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, INR>1.3, platelet count <150x109/L, ascites, varices, splenomegaly).
Index test (including threshold and whether threshold pre-specified)	Transient elastography (Fibroscan), optimal cut-off threshold calculated (10.3 kPa) according to highest Youden's index. Accuracy also given at cut-off of 11.5 kPa (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).

Study	Wong 2010B[160]
	APRI, AST/ALT and FIB-4
Reference standard	Liver biopsy (NAFLD specific scoring system, Kleiner et al 2005, F4): Percutaneous liver biopsy was performed using the 16 G 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): 10.3 kPa Threshold: 10.3 kPa (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 FN: Not reported TN: Not reported Threshold: 11.5 kPa (not pre-specified: cut-off giving specificity >90%) Sensitivity: 76.0 Specificity: 91.0 PPV: 48.7 NPV: 97.1	

Study	Wong 2010B[160]
+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: FIB-4 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	
General limitations according to QUADAS: Patients with unreliable TE excluded from the analysis Liver biopsy sample <25 mm and 10 portal tracts.	

Study	WONG 2012[159]
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

Study	WONG 2012[159]
	incorrect classifications, study also reports accuracies not including those without valid TE measurements).
Countries and Settings	France and Hong Kong. Two 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. 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, cut-offs with sensitivity and specificity over 90% were also determined. Measurements 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 16 G 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

Study	WONG 2012[159]
Results: Fibroscan M probe AUC (95% CI): 0.53 (0.36–0.70) Optimal cut-off threshold (if calculated): 10.3 kPa (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 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): 7.9 kPa (Youden's) Threshold: 7.9 kPa (Youden's) Sensitivity: 84 (70–98)	

Study	WONG 2012[159]
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: 7.2 kPa (best sensitivity) Sensitivity: 88 (75–100) Specificity: 67 (60–74) PPV: 28 (18–38) NPV: 97 (95–100) +ve/-ve likelihood ratios: Not reported TP: Not reported FP: Not reported FN: Not reported TN: Not reported Threshold: 11.0 kPa (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	

Study	WONG 2012[159]
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 <25 mm	

Study	Yamanda 2006[161]
Study type	Pilot study
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). 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 (approximately 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	Not reported for HCV population

Study	Yamanda 2006[161]
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: The fibrosis extraction method has great potential for diagnosing liver fibrosis using ultrasound.	
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[162]
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 20 g alcohol daily.

Study	Yoneda 2008[162]
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 the dorsal decubitus position. Success rate of at least 60% or IQR <30% considered reliable. Presumed to have used appropriate probe for patients' 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: 17.5 kPa (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. Any complications associated with tests reported: Not reported	
General limitations according to QUADAS II:	

Study	Yoneda 2008[162]
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[163]
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. 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

Study	Yoneda 2010[163]
	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 patients' 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	
Results: ARFI AUC (95% CI): 0.976 Optimal cut-off threshold (if calculated): 1.90 m/s Threshold: 1.90 m/s (optimal) Sensitivity: 100 Specificity: 96 PPV: 75 NPV: 100 +ve/-ve likelihood ratios: Not reported TP: 6 FP: Not reported FN: Not reported	

Study	Yoneda 2010[163]
	TN: 46 Results: Fibroscan AUC (95% CI): 0.998 Optimal cut-off threshold (if calculated): 16 kPa Threshold: 16 kPa (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 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 <25 mm.

Study	Zarski 2012[164]
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

Study	Zarski 2012[164]
	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 included and those with failed Fibroscan). Recruitment November 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: Not stated Not stated ALT (U/l): 87.9±65.4 88.0±64.9
Patient characteristics	Population: Untreated chronic hepatitis C Inclusion: Time between liver biopsy and other diagnostic tests <3 months. No hepatitis 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, hepatitis 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 <15 mm).
Time between index test and reference standard	<3 months (median 5 days, range 0–65 days)
Prevalence of cirrhosis according to	56/382 (14.7%)

Study	Zarski 2012[164]
reference standard	
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% +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	

Study	Zarski 2012[164]
TN: Not reported FIB-4 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: 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 (n=382) AUC (95% CI): 0.93 (0.89, 0.96) Optimal cut-off threshold (if calculated): Not reported Threshold: 12.9 kPa (published) 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	

Study	Zarski 2012[164]
Other measures reported and conclusions: 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 one or a combination of two 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. Any complications associated with tests reported: Not reported
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 <25 mm.

H.3 Severity risk tools

Study	Aravinthan 2013[7]
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

Study	Aravinthan 2013[7]
	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, 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): Not reported 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[36]
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

Study	Ferlitsch 2012[36]
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 interferon. Patients with alcoholic liver disease needed to be abstinent from alcohol for at least 3 months.
Severity risk tool (for example 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): Not reported Threshold: Not reported Sensitivity: 20.3 Specificity: 88.2 PPV: 56.8 NPV: 28.3 +ve/-ve likelihood ratios: 98.4/2.0	

Study	Ferlitsch 2012[36]
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 intention to diagnose (ITD) approach.	

Study	Finkenstedt 2012[44]
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 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

Study	Finkenstedt 2012[44]
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): Not reported Threshold: ≥16 Sensitivity: 85 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[69]
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

Study	Kim 2012H[69]
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, co-infection 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).
Severity risk tool (for example 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: Not reported Sensitivity: Not reported Specificity: Not reported PPV: Not reported NPV: Not reported +ve/-ve likelihood ratios: Not reported TP: Not reported	

Study	Kim 2012H[69]
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 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[70]
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

Study	Kim 2014D[70]
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), co-infection 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.
Severity risk tool (for example 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)	

Study	Kim 2014D[70]
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[72]
Study type	Prospective, longitudinal study
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; ethnicity: 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 (for example	Transient elastography: At entry into the study. Transient elastography was considered successful only if a minimum of 8

Study	Klibansky 2012[72]
transient elastography, Child-Pugh, MELD)	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): Not reported Threshold: 10.5 kPa Sensitivity: 0.975 Specificity: 0.1 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	

Study	Klibansky 2012[72]
+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 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	

Study	Klibansky 2012[72]
	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 slightly indirect.

Study	Perez-Latorre 2014[102]
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

Study	Perez-Latorre 2014[102]
	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 (for example 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. Ten 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 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)	

Study	Perez-Latorre 2014[102]
+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 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[107]
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 (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: Ten 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)	

Study	Robic 2011[107]
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 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[115]
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

Study	Said 2004[115]
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.
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[158]
Study type	Prospective study
Number of studies (number of	271 consecutive patients were enrolled from January 2008 to October 2011. 51 were excluded (12 patients had failed liver

Study	Wang 2014B[158]
participants	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 scoring system. Exclusion: Presence of ascites or HCC.
Severity risk tool (for example 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).	

Study	Wang 2014B[158]
	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) 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)

Study	Wang 2014B[158]
	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) +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[53]
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
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

Study	Giannini 2000[53]
	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 tumoural 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 cancer staging (according to BCLC system); liver transplant

Study	Miquel 2012[88]
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

Study	Miquel 2012[88]
	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 tumour 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). (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 tumour 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, tumour size, and curative versus palliative. In this analysis, screening was not statistically significant (not an independent predictor

Study	Miquel 2012[88]
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[100]
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
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

Study	Pascual 2008[100]
	the cases, HCC diagnosis was confirmed by histology. Duration: minimum 6 months after HCC diagnosis. Concurrent medication/care: treatment according to tumour characteristics and protocol of care: i) liver transplantation for patients younger than 65 years, with a solitary tumour ≤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 tumours (<3.5–4 cm); iii) transarterial chemoembolisation considered for patients with large/multinodular tumours 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 tumour characteristics and protocol of care: i) liver transplantation for patients younger than 65 years, with a solitary tumour ≤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 tumours (<3.5–4 cm); iii) transarterial chemoembolisation considered for patients with large/multinodular tumours 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, tumour 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[118]
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 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

Study	Santi 2010[118]
	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 tumour (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) tumour 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 tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour 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 tumour not treatable with PEI or a multifocal tumour 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 tumour (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) tumour 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 tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there

Study	Santi 2010[118]
	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 tumour not treatable with PEI or a multifocal tumour 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 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 oesophageal 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 tumour 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 tumour 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[142]
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)

Study	Stroffolini 2011[142]
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.
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 tumours 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 tumours 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).

Study	Stroffolini 2011[142]
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, 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[149]
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.

Study	Trevisani 2004[149]
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.
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) tumour 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 tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour 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 tumour not treatable with PEI or a multifocal tumour 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.

Study	Trevisani 2004[149]
	(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) tumour 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 tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour 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 tumour not treatable with PEI or a multifocal tumour 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) tumour 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	Trevisani 2004[149]
	surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour 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 tumour not treatable with PEI or a multifocal tumour 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
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[150]
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 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

Study	Trevisani 2007[150]
	according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour 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 tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour 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 tumour not treatable with PEI or a multifocal tumour 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) tumour 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 tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour 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 tumour not treatable with PEI or a multifocal tumour 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)

Study	Trevisani 2007[150]
	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 - 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[152]
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 centres 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

Study	Trinchet 2011[152]
	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) co-infection 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 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 oesophageal varices and other portal hypertension-related lesions. In cases of oesophageal 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:

Study	Trinchet 2011[152]
	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 oesophageal varices and other portal hypertension-related lesions. In cases of oesophageal 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 tumour at median follow-up 47 months; Group 1: 31/640, Group 2: 41/638; risk of bias: high; indirectness of outcome: no indirectness

Study	Trinchet 2011[152]
	- 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 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[6]
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	First 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

Study	Andreani 1990[6]
	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, 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 (10 mg) 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

Study	Andreani 1990[6]
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 - 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[28] (Groszmann 1990[57])
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	First 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: 1–3 mm with Valsalva, grade 2: 1–3 mm without Valsalva, grade

Study (subsidiary papers)	Conn 1991[28] (Groszmann 1990[57])
	3: 3–3 mm; grade 4: >6 mm). 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.
Recruitment/selection of patients	Admitted to one 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	

Study (subsidiary papers)	Conn 1991[28] (Groszmann 1990[57])
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 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[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])
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.

Study (subsidiary papers)	**Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])**
Line of therapy	First 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 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 pseudotumourous varices (also known as F2 or F3 varices). Other trials classified as high risk if they had a diameter of at least 5 mm or at least 3 mm plus at least one 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.

Study (subsidiary papers)	**Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])**
	(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 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[32] 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[79] 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[101] 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[82] 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[104] 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[125] 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[153] 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

Study (subsidiary papers)	Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])
	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[32] 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; indirectness of outcome: no indirectness - Actual outcome for Lo 2004[79] 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 - Actual outcome for Lui 2002[82] 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[104] 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[123] 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[125] 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[153] 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[123] 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

Study (subsidiary papers)	Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])
- 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[76]
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	First 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 oesophagitis). Therefore, all patients had blue varices of F2 or F3 size with at least one 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

Study	Lay 1997[76]
	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 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 haematemesis, 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

Study	Lay 1997[76]
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[80]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=133)
Countries and setting	Conducted in Taiwan; setting: general hospital
Line of therapy	First 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): not reported. Ethnicity: not reported.
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/hepatitis B/hepatitis 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.

Study	Lo 1999[80]
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 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:

Study	Lo 1999[80]
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[94] (Pagliaro 1988,[95] Pagliaro 1989[96])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=174)
Countries and setting	Conducted in Italy; setting: multicentre (4 hospitals)
Line of therapy	First 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

Study (subsidiary papers)	Pagliaro 1989[94] (Pagliaro 1988,[95] Pagliaro 1989[96])
	the resting heart rate by 25%. Dose ranged from 10–480 mg. 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 (10 mg) 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 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[99] (Pascal 1987[98])
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	First 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
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 20 mg of conventional formulation twice daily. Titrated up to 160 mg or 320 mg of long-acting once daily to achieve a 20–25% reduction in resting heart rate or until maximum dose permitted (320 mg of long acting once daily). Patients evaluated every 2 months. Duration: mean 1.2 years. Concurrent medication/care: not reported.

Study (subsidiary papers)	Pascal 1989[99] (Pascal 1987[98])
	(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 - 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[120]
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	First 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

Study	Sarin 1996[120]
Stratum	Size of varices (medium/large): patients had blue varices of F2 or F3 size with at least one 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 one or 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 >5 mm 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 one of the red colour signs.
Exclusion criteria	Hepatorenal syndrome or hepatic encephalopathy
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-alcohol related 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 1–2 cm above the gastro-oesophageal junction. One or two bands applied at each variceal column between the lower 4–5 cm 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

Study	Sarin 1996[120]
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 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[122]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in India; setting: single-centre, hospital liver clinic
Line of therapy	First 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).

Study	Sarin 2013[122]
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 <90 mmHg, 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.
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 20 mg twice daily. Incremental dosing used to achieve target heart rate (dose increased every alternate day to achieve a target heart rate of 55/minute or to the maximum dose of 360 mg/day if the medication was well tolerated and the systolic BP remained above 90 mmHg). Dose decreased stepwise on occurrence of intolerable adverse effects, systolic BP <90 mmHg or pulse rate <55/minute). 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

Study	Sarin 2013[122]
	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 - 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[127]
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	First 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

Study	Shah 2014[127]
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): not reported. 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. 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 6.25 mg 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

Study	Shah 2014[127]
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 2 g/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 - 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 2 g/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[131]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in India
Line of therapy	First 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

Study	Singh 2012[131]
	mm). The risk of bleeding in large varices (>5 mm) was assessed by looking for the presence of at least one "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.
Extra comments	Aetiology (alcohol-related/hepatitis B/hepatitis 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 5–7 cm 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 40 mg oral propranolol. Dose increased by increments of 20–40 mg/day until a 25% decrease in the resting heart rate was achieved. Treatment stopped if systolic BP below 90 mmHg, HR less than 55 bpm 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

Study	Singh 2012[131]
- 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[144]
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	First 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	Patients aged 15-70 who had no previous history of upper gastrointestinal bleeding, oesophargeal varices of grade III and IV; oesophageal varices of grade II with signs of high risk; no previous endoscopic treatment of oesophageal varices; liver cirrhosis with no other serious disease; fully informed consent.
Exclusion criteria	Not reported
Recruitment/selection of patients	Referral of all suitable patients between August 1994 and September 1994
Age, gender and ethnicity	Age – mean (SD): intervention: 48 (12); control: 47 (11). Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (intervention: 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]).

Study	Svoboda 1999[144]
Extra comments	Aetiology (alcohol/infection): intervention 35/17; control 34/16. Child-Pugh (A/B/C): intervention 32/14/6; control 28/16/6. Varices (II/III/IV): intervention: 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. (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:

Study	Svoboda 1999[144]
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[151]
Study type	RCT (patient randomised; parallel)
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	First 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: <5 mm 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 >5 mm – measured with open forceps and not disappearing on oesophageal insufflation; small varices: <5 mm 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

Study	Triantos 2005[151]
	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. (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

Study	Triantos 2005[151]
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[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
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	First 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.

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
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: Third 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 (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: Third 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: Third 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).

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
	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 (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 7 DAYS) (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[39]: 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	

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
- Actual outcome for Fernandez 2006[39]: 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 3 DAYS) (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[114]: 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[114]: mortality at up to 3 weeks; group 1: 1/24, group 2: 2/22; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 3: Length of hospital stay at end of study - Actual outcome for Sabat 1998[114]: 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[135]: 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; readmission rate at end of study, antibiotic complications at end of study

Study	Kim 2011[68]
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	First line
Duration of study	Intervention time: 7 days

Study	Kim 2011[68]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis diagnosis based on clinical, laboratory and ultrasonographic 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 degrees 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 sediment, or data compatible with pneumonia on the 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 one 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 be 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; proton pump inhibitors (PPI) if form peptic ulcer; blood transfusions to maintain haematocrit levels 25–30%.

Study	Kim 2011[68]
	Further details: 1. Different modes of administration: not applicable/not stated/unclear (no details given). (n=66) Intervention 2: IV: Third 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)
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; readmission 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[91]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Japan; setting: enrolled from author's department
Line of therapy	Second 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

Study	Narahara 2011[91]
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 hours, 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
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
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

Study	Narahara 2011[91]
	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 - 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; readmission rate at end of study

Study (subsidiary papers)	Saab 2006[113] (Gines 2002[54], Rossle 2000[112], Salerno 2004[116], Sanyal 2003[119])
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	Second 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; 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[119]: 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[119]: 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[112]: 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[119]: 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[54]: 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[116]: 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[54]: 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[119]: 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; readmission 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[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
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	First 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 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 – active bleeding in previous 30 days, pregnancy, active GI bleeding, encephalopathy >grade 2, HCC, quinolone allergy, creatinine >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

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
	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 creatinine 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., 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. One 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

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
	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 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 were also 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 were also 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/day 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

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
	(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 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 (400 MG/DAY) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Fernandez 2007[38]: 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[38]: 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[38]: 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[38]: 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[38]: 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[38]: 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/DAY) versus PLACEBO

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Grange 1998[56]: occurrence of SBP at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) 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[56]: mortality (dichotomous) at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) days for placebo; group 1: 8/53, group 2: 10/54; risk of bias: very high; indirectness of outcome: serious indirectness

Protocol outcome 3: incidence of resistant organisms at end of study
- Actual outcome for Grange 1998[56]: incidence of resistant organisms not present at baseline at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) 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[56]: liver failure leading to death at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) 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 (500 MG/DAY) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Terg 2008[147]: 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[147]: 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[147]: 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[147]: 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[147]: 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/WEEK) versus PLACEBO

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Rolachon 1995[108]: 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[108]: 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
- Actual outcome for Rolachon 1995[108]: 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[108]: 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[108]: length of hospital stay; 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/DAY) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Soriano 1991[134]: 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[134]: 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[134]: length of hospital stay; 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

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
Protocol outcomes not reported by the study	Quality of life at end of study; readmission rate at end of study

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[146]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Mexico
Line of therapy	First line
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): not reported. Ethnicity: unknown (presumed 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

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[146]
	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. 500 mg/day of an equally appearing placebo. 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: 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; readmission 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[3]
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	First 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 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 20 g (4 ampoules of 10 ml each) mixed in 250 ml 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 20 g (4 ampoules of 10 ml distilled water) mixed in 250 ml of 5% dextrose, appearance indistinguishable from LOLA, daily over 4 hours for 3 consecutive days. Duration: 3 days.

Study	Abid 2011[3]
	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
- Actual outcome: Mortality (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm) 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

Study	Abid 2011[3]
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); 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 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[5]
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	First 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 (for example heart/respiratory/renal failure); presence of infections other than spontaneous bacterial

Study	Ahmad 2008[5]
	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
Interventions	(n=40) Intervention 1: l-Ornithine-l-aspartate (LOLA). IV of 20 g (4 ampoules of 10 ml each) in 250 ml 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 20 g (4 ampoules of 10 ml distilled water) in 250 ml 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[21]
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	First line
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: 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	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: Approximately 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 4 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 6 days of the study or until encephalopathy cleared. (n=10) Intervention 2: Oral non-absorbable antibiotics – neomycin. Four grams per day given orally or by nasogastric tube in 4 divided doses daily. Duration 4–14 days with a follow-up period of at least 7 days after the study or until

Study	Cerra 1983[21]
	death or discharge. To complete the study, a patient had to finish the first 4 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 6 days of the study or until encephalopathy cleared.
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 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[20]
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 5 centres.
Line of therapy	First 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

Study	Cerra 1985[20]
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, patients requiring severe fluid restriction
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (SD): intervention: 53 (2), control: 53 (2). Gender (M:F): intervention: 80% male, control: 93% male. 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	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: Approximately 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 4 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. Four grams of enteral neomycin daily along with 25% dextrose by central venous catheter in 4 divided doses. Duration: up to 14 days. To complete the study, the patient had to finish the first 4 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.

Study	Cerra 1985[20]
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 during treatment; Group 1: 14/40, Group 2: 22/35; risk of bias: high; indirectness of outcome: no indirectness	
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[41]
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	First 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.

Study	Fiaccadori 1984[41]
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 300 mg per day. Duration: 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35 ml/minute for 24 hours. (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/body weight/day. Duration: 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35 ml/minute 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/body weight/day + lactulose administered via a nasogastric tube or enema, at 150 to 300 mg per day. Duration: 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35ml/minute 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 by the seventh 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

Study	Fiaccadori 1984[41]
- Actual outcome: The number of participants that came out of coma by the seventh 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[59]
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	First 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.

Study	Gyr 1996[59]
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 1 mg) at one-minute intervals. [2] IV infusions of flumazenil at 1 mg/hour for 3 hours. Duration: 3 hours. Concurrent medication/care: saline, glucose, 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 1 mg) at one-minute intervals. [2] IV infusions of placebo at 1 mg/hour for 3 hours. Duration: 3 hours. Concurrent medication/care: saline, glucose, lactulose, potassium and vitamin K were allowed as additional treatments.
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 3 hour treatment period + 5 hour 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 3 hour treatment period + 5 hour 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 3 hour treatment period + 5 hour 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[61]
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	First line
Duration of study	Intervention + follow up: Maximum of 5 days of treatment (study period); patients followed up to 180 days after the 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 sulphate. Duration: 5 days. Concurrent medication/care: Most patients received systemic antibiotics.

Study	Hassanein 2007[61]
	(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 sulphate. Duration: 5 days. Concurrent medication/care: Most patients received systemic antibiotics
Funding	Study funded by industry (Grants from Teraklin AG; Rostock & Gambro Renal Products)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MARS + SMT versus STANDARD MEDICAL THERAPY 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[105]
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	First line
Duration of study	Intervention + follow up: Until discharge from hospital or death

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[105]
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.
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 January 2011 and June 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. Four 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 30 g administered orally or by nasogastric tube (3 or more doses within 24 hours) or 200 g 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

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[105]
	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 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 one or more in hepatic encephalopathy grade at 24 hours (hepatic encephalopathy scoring algorithm 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 one grade); 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 encephalopathy scoring algorithm grade 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; 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[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=54)

Study	Laccetti 2000[73]
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
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	

Study	Laccetti 2000[73]
- 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 - 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[81]
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.

Study	Loguercio 1987[81]
	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
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[87]
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	First line

Study	Mas 2003[87]
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 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 200 mg rifaximin tablets taken orally or via nasogastric tube, every 8 hours. Duration: maximum of 10 days. Concurrent medication/care: 20 g placebo sachet dissolved in 100 ml of water, given orally or via nasogastric tube, every 8 hours. (n=53) Intervention 2: Non-absorbable disaccharides – oral lactitol. One 20 g lactitol sachet dissolved in 100 ml of water given orally or via nasogastric tube, every 8 hours. Duration: maximum of 10 days. Concurrent medication/care: two 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 within 28 days of the last dose; Group 1: 1/50, Group 2: 2/53; risk of bias: low; indirectness of

Study	Mas 2003[87]
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 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[97]
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	First 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-hour period before study commencement; on antibiotics during preceding 7 days; previously treated with encephalopathy-causing agents
Recruitment/selection of patients	Unclear

Study	Paik 2005[97]
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 first to third 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
Interventions	(n=32) Intervention 1: Oral non-absorbable antibiotics – rifaximin. 1200 mg 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, 90 ml 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, number connection test [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[111] (Rossi fanelli 1986[109], Rossi 1984[110])
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	First 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
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 2 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): 60 ml/hour for the first 24 hours, and 80 ml/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: 30–40 g 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: 200–300 g/day intermittent enemas. Duration: Until 48 hours (following this, patients who did not recover underwent a combination treatment). Concurrent medication/care:

Study (subsidiary papers)	Rossi-fanelli 1982[111] (Rossi fanelli 1986[109], Rossi 1984[110])
	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 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 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; 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) ; 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) ; 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[128]
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	First line
Duration of study	Intervention + follow up: Treatment was given until complete recovery of hepatic encephalopathy or a maximum of 10 days. Patients were followed till they were discharged or died during their hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis was based on laboratory tests, endoscopic

Study	Sharma 2013[128]
	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 >1.5 mg/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. 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 400 mg 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 60 ml, 3 times a day. (n=57) Intervention 2: Non-absorbable disaccharides – oral lactulose. Lactulose via nasogastric tube, 30 to 60 ml, 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; 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

Study	Sharma 2013[128]
- 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; 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; 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[140]
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	First line
Duration of study	Intervention: Neomycin group received intervention until 2 days after complete recovery of consciousness, the enriched branched chain amino acid group received the intervention until complete recovery of consciousness.
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 (neomycin, lactulose or L-dopa) had already been started.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – range: 28–67. Gender (M:F): 26 men, 3 women. Ethnicity: Not reported.
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.

Study	Strauss 1986[140]
	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 (1–4 g 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 60 g of protein equivalent in 24 hours. A hypertonic glucose solution was given simultaneously, according to the needs of the patient. Duration: Until recovery. Concurrent medication/care: Grades I and II were allowed to eat, receiving initially a diet of 10 g 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. (n=16) Intervention 2: Oral non-absorbable antibiotics – neomycin. 1 g of neomycin sulphate orally every four hours. Intestinal cleansing was performed every 12 hours, with a litre of water and 2 g of neomycin. As patients improved, dietary protein was increased (20 g every second day) while the dosage of neomycin was decreased (2 g 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 10 g 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 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

Study	Strauss 1986[140]
- Actual outcome: Time to recovery 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[141]
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	First line
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: not reported.
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 sulphate 1 g every 4 hours (6 g/day; oral for grades I and II, by nasogastric tube for grades II and IV) and 2 g in 500 ml of tepid water every 12 hours for

Study	Strauss 1992[141]
	intestinal cleansing. Patients in grades III and IV also received 60 g/day of an enriched solution of BCAAs (Portamin) with IV hypertonic glucose. When improvement to grade 0 hepatic encephalopathy observed, neomycin decreased to 2 g each second day (and if BCAAs given, decreased by 20 g every other day). Duration: unclear. Concurrent medication/care: Grade I and II hepatic encephalopathy: oral diet continued but protein restricted to 10 g/day; Grade III and IV hepatic encephalopathy: IV administration of necessary calories. When improvement to grade 0 hepatic encephalopathy observed, dietary protein increased to 20 g/day. (n=19) Intervention 2: Placebo. Patients in grades III and IV also received 60 g/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 20 g every other day. Duration: Unclear. Concurrent medication/care: Grade I and II hepatic encephalopathy: Oral diet continued but protein restricted to 10 g/day; Grade III and IV hepatic encephalopathy: IV administration of necessary calories. When improvement to grade 0 hepatic encephalopathy observed, dietary protein increased to 20 g/day.
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 fifth 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; 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[143]
Study type	RCT (patient randomised; parallel)

Study	Sushma 1992[143]
Number of studies (number of participants)	N/A (n=74)
Countries and setting	Conducted in India; setting: secondary care
Line of therapy	First 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
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), 5 mg twice daily (each dose dissolved in 30 ml 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 20 mg/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 30 ml 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 20 mg/day in whom oral intake was possible.

Study	Sushma 1992[143]
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; 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); Group 1: 30/38, Group 2: 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[154]
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	First 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

Study	Uribe 1981[154]
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 an NCT at least double the normal range (>60 s, normal is >30 s) 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
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 0.5 g 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 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

Study	Uribe 1981[154]
- Actual outcome: Clinical-biochemical improvement (improvement of 1 grade in mental state [Conn's grading 0–4], a reduction of 30 s in time taken to perform the number connection test [NCT] and ammonia reduction of 50ug%); 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; 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[155]
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])
Countries and setting	Conducted in Switzerland; setting: not reported
Line of therapy	First 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 hour 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 s) 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 hepatic encephalopathy: Not applicable/not stated/unclear (at least grade 2+). 2. Severity of the

Study	Uribe 1987[155]
	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 three times daily. 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 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[156]
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	First line
Duration of study	Intervention time: Until recovery or death

Study	Vilstrup 1990[156]
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 – M=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.
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 12.5 ml/kg/day throughout day and night. Duration: Up to recovery or death (maximum of 16 days treatment). Concurrent medication/care: Glucose (50%) 12.5 ml/kg/day + Lactulose syrup 60 ml/day + Cimetidine 200 to 400mg/day + Minerals + Vitamins + other medications according to needs. (n=39) Intervention 2: Placebo. Glucose (8%) 12.5 ml/kg/day in bottles that look identical to those for BCAA. Duration: Up to recovery or death (maximum of 16 days treatment). Concurrent medication/care: Glucose (50%) 12.5 ml/kg/day + Lactulose syrup 60 ml/day + Cimetidine 200 to 400 mg/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	Vilstrup 1990[156]
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[157]
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	First 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: Not reported.
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 5 days. Concurrent medication/care: Five 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 5 days. Concurrent medication/care: Three 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

References

1 202 Endoscopic variceal band ligation in comparison with propranolol in prophylaxis of first variceal bleeding in patients with liver cirrhosis. Journal of Hepatology. 2005; 42(Suppl.1):79

2 Abdelfattah MH, Rashed MA, Elfakhry AA, Soliman MA, Shiha GE. 201 Endoscopic variceal ligation versus pharmacologic treatment for primary prophylaxis of variceal bleeding: a randomised study. Journal of Hepatology. 2006; 44(Suppl.1):S83

3 Abid S, Jafri W, Mumtaz K, Islam M, Abbas Z, Shah HA et al. Efficacy of L-ornithine-L-aspartate as an adjuvant therapy in cirrhotic patients with hepatic encephalopathy. Journal of the College of Physicians and Surgeons--Pakistan. 2011; 21(11):666-671

4 Abulfutuh AR, Morsy M, Solyman AEG, Hendawy SE, Desouky ME, Hadad SE et al. Study of variceal band ligation, propranolol and isosorbide mononitrate in the prevention of the first variceal bleeding. Gastroenterology. 2003; 124(4):A780

5 Ahmad I, Khan AA, Alam A, Dilshad A, Butt AK, Shafqat F et al. L-ornithine-L-aspartate infusion efficacy in hepatic encephalopathy. Journal of the College of Physicians and Surgeons--Pakistan. 2008; 18(11):684-687

6 Andreani T, Poupon R, Balkau BJ, Trinchet JC, Grange JD, Peigney N et al. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. Hepatology. 1990; 12(6):1413-1419

7 Aravinthan A, Pietrosi G, Hoare M, Jupp J, Marshall A, Verrill C et al. Hepatocyte expression of the senescence marker p21 is linked to fibrosis and an adverse liver-related outcome in alcohol-related liver disease. PloS One. 2013; 8(9):e72904

8 Arena U, Vizzutti F, Abraldes JG, Corti G, Stasi C, Moscarella S et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut. 2008; 57(9):1288-1293

9 Askgaard G, Gronbaek M, Kjaer MS, Tjonneland A, Tolstrup JS. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. Journal of Hepatology. 2015; 62(5):1061-1067

10 Aykut UE, Akyuz U, Yesil A, Eren F, Gerin F, Ergelen R et al. A comparison of FibroMeter NAFLD Score, NAFLD fibrosis score, and transient elastography as noninvasive diagnostic tools for hepatic fibrosis in patients with biopsy-proven non-alcoholic fatty liver disease. Scandinavian Journal of Gastroenterology. 2014; 49(11):1343-1348

11 Becker U, Gronbaek M, Johansen D, Sorensen TIA. Lower risk for alcohol-induced cirrhosis in wine drinkers. Hepatology. 2002; 35(4):868-875

12 Blackwelder WC, Yano K, Rhoads GG, Kagan A, Gordon T, Palesch Y. Alcohol and mortality: the Honolulu Heart Study. American Journal of Medicine. 1980; 68(2):164-169

13 Borroni G, Ceriani R, Cazzaniga M, Tommasini M, Roncalli M, Maltempo C et al. Comparison of simple tests for the non-invasive diagnosis of clinically silent cirrhosis in chronic hepatitis C. Alimentary Pharmacology and Therapeutics. 2006; 24(5):797-804

14 Bota S, Sirli R, Sporea I, Focsa M, Popescu A, Danila M et al. A new scoring system for prediction of fibrosis in chronic hepatitis C. Hepatitis Monthly. 2011; 11(7):548-555

15 Bota S, Sporea I, Sirli R, Popescu A, Gradinaru-Tascau O. How useful are ARFI elastography cut-off values proposed by meta-analysis for predicting the significant fibrosis and compensated liver cirrhosis? Medical Ultrasonography. 2015; 17(2):200-205

16 Cardoso AC, Carvalho-Filho RJ, Stern C, Dipumpo A, Giuily N, Ripault MP et al. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. Liver International. 2012; 32(4):612-621

17 Castera L, Sebastiani G, Le Bail B, de Ledinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. Journal of Hepatology. 2010; 52(2):191-198

18 Catanzaro R, Milazzo M, Arona S, Sapienza C, Vasta D, Arcoria D et al. Diagnostic accuracy of enhanced liver fibrosis test to assess liver fibrosis in patients with chronic hepatitis C. Hepatobiliary and Pancreatic Diseases International. 2013; 12(5):500-507

19 Caviglia GP, Ciancio A, Rosso C, Abate ML, Olivero A, Pellicano R et al. Non-invasive methods for the assessment of hepatic fibrosis: transient elastography, hyaluronic acid, 13C-aminopyrine breath test and cytokeratin 18 fragment. Annals of Hepatology. 2013; 13(1):91-97

20 Cerra FB, Cheung NK, Fischer JE, Kaplowitz N, Schiff ER, Dienstag JL et al. Disease-specific amino acid infusion (F080) in hepatic encephalopathy: a prospective, randomized, double-blind, controlled trial. Journal of Parenteral and Enteral Nutrition. 1985; 9(3):288-295

21 Cerra FB, McMillen M, Angelico R, Cline B, Lyons J, Faulkenbach L et al. Cirrhosis, encephalopathy, and improved results with metabolic support. Surgery. 1983; 94(4):612-619

22 Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C et al. Meta-analysis: Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - An updated Cochrane review. Alimentary Pharmacology and Therapeutics. 2011; 34(5):509-518

23 Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, I, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews. 2010;(9):CD002907. DOI:10.1002/14651858.CD002907.pub2

24 Chen CY, Sheu MZ, Su SY. Prophylactic endoscopic variceal ligation (EVL) with multiple band ligator for esophageal varices. Gastroenterology. 1998; 114(Suppl.1):A1224

25 Chen SH, Li YF, Lai HC, Kao JT, Peng CY, Chuang PH et al. Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C. BMC Gastroenterology. 2012; 12:105

26 Chrysanthos NV, Papatheodoridis GV, Savvas S, Kafiri G, Petraki K, Manesis EK et al. Aspartate aminotransferase to platelet ratio index for fibrosis evaluation in chronic viral hepatitis. European Journal of Gastroenterology and Hepatology. 2006; 18(4):389-396

27 Cohen MJ, Sahar T, Benenson S, Elinav E, Brezis M, Soares-Weiser K. Antibiotic prophylaxis for spontaneous bacterial peritonitis in cirrhotic patients with ascites, without gastro-intestinal bleeding. Cochrane Database of Systematic Reviews. 2009;(2):CD004791. DOI:10.1002/14651858.CD004791.pub2.

28 Conn HO, Grace N, Bosch J, Groszmann R, Rodes J, Wright SC et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: A multicenter, randomized clinical trial. Hepatology. 1991; 13(5):902-912

29 de la Mora JG, Farca-Belsaguy AA, Uribe M, de Hoyos-Garza A. Ligation VS propranolol for primary prophilaxis of variceal bleeding using a multiple band liga-tor and objective measurements of treatment adequacy: Preliminary results. Gastroenterology. 2000; 118(4):A1434-A1435

30 de Ledinghen V, Douvin C, Kettaneh A, Ziol M, Roulot D, Marcellin P et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. Journal of Acquired Immune Deficiency Syndromes. 2006; 41(2):175-179

31 De BK, Ghoshal UC, Das T, Santra A, Biswas PK. Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomized controlled trial. Journal of Gastroenterology and Hepatology. 1999; 14(3):220-224

32 Drastich P, Lata J, Petrtyl J, Bruha R, Prochazka V, Vanasek T et al. Endoscopic variceal band ligation compared with propranolol for prophylaxis of first variceal bleeding. Annals of Hepatology. 2011; 10(2):142-149

33 Ebinuma H, Saito H, Komuta M, Ojiro K, Wakabayashi K, Usui S et al. Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan(®). Journal of Gastroenterology. 2011; 46(10):1238-1248

34 Esmat G, Elsharkawy A, El Akel W, Fouad A, Helal K, Mohamed MK et al. Fibroscan of chronic HCV patients coinfected with schistosomiasis. Arab Journal of Gastroenterology. 2013; 14(3):109-112

35 Fahmy MI, Badran HM. Comparison of transient elastography to Doppler indices in prediction of hepatitis C induced liver fibrosis and cirrhosis. Egyptian Journal of Radiology and Nuclear Medicine. 2011; 42(2):111-117

36 Ferlitsch M, Reiberger T, Hoke M, Salzl P, Schwengerer B, Ulbrich G et al. Von Willebrand factor as new noninvasive predictor of portal hypertension, decompensation and mortality in patients with liver cirrhosis. Hepatology. 2012; 56(4):1439-1447

37 Fernandes FF, Ferraz ML, Andrade LE, Dellavance A, Terra C, Pereira G et al. Enhanced liver fibrosis panel as a predictor of liver fibrosis in chronic hepatitis C patients. Journal of Clinical Gastroenterology. 2015; 49(3):235-241

38 Fernandez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. 2007; 133(3):818-824

39 Fernandez J, Ruiz del Arbol L, Gomez C, Durandez R, Serradilla R, Guarner C. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology. 2006; 131(4):1049-1056

40 Ferraioli G, Tinelli C, Lissandrin R, Zicchetti M, Dal Bello B, Filice G et al. Point shear wave elastography method for assessing liver stiffness. World Journal of Gastroenterology. 2014; 20(16):4787-4796

41 Fiaccadori F, Ghinelli F, Pedretti G, Pelosi G, Sacchini D, Zeneroli ML. Branched chain amino acid enriched solutions in the treatment of hepatic encephalopathy: a controlled trial. In: Capocaccia

L, Fischer JE, Rossi-Fanelli F (eds), Hepatic encephalopathy in chronic liver failure, New York: Plenum Press, 1984: 323-333

42 Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G. Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. World Journal of Gastroenterology. 2009; 15(44):5525-5532

43 Fierbinteanu-Braticevici C, Sporea I, Panaitescu E, Tribus L. Value of acoustic radiation force impulse imaging elastography for non-invasive evaluation of patients with nonalcoholic fatty liver disease. Ultrasound in Medicine and Biology. 2013; 39(11):1942-1950

44 Finkenstedt A, Dorn L, Edlinger M, Prokop W, Risch L, Griesmacher A et al. Cystatin C is a strong predictor of survival in patients with cirrhosis: Is a cystatin C-based MELD better? Liver International. 2012; 32(8):1211-1216

45 Floreani A, Cazzagon N, Martines D, Cavalletto L, Baldo V, Chemello L. Performance and utility of transient elastography and noninvasive markers of liver fibrosis in primary biliary cirrhosis. Digestive and Liver Disease. 2011; 43(11):887-892

46 Friedrich-Rust M, Hadji-Hosseini H, Kriener S, Herrmann E, Sircar I, Kau A et al. Transient elastography with a new probe for obese patients for non-invasive staging of non-alcoholic steatohepatitis. European Radiology. 2010; 20(10):2390-2396

47 Friedrich-Rust M, Rosenberg W, Parkes J, Herrmann E, Zeuzem S, Sarrazin C. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. BMC Gastroenterology. 2010; 10:103

48 Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology. 2009; 252(2):595-604

49 Fuchs CS, Stampfer MJ, Colditz GA, Giovannucci EL, Manson JE, Kawachi I et al. Alcohol consumption and mortality among women. New England Journal of Medicine. 1995; 332(19):1245-1250

50 Fujii H, Enomoto M, Fukushima W, Ohfuji S, Mori M, Kobayashi S et al. Noninvasive laboratory tests proposed for predicting cirrhosis in patients with chronic hepatitis C are also useful in patients with non-alcoholic steatohepatitis. Journal of Gastroenterology. 2009; 44(6):608-614

51 Gaia S, Carenzi S, Barilli AL, Bugianesi E, Smedile A, Brunello F et al. Reliability of transient elastography for the detection of fibrosis in Non-Alcoholic Fatty Liver Disease and chronic viral hepatitis. Journal of Hepatology. 2011; 54(1):64-71

52 Gheorghe C, Gheorghe L, Vadan R, Hrehoret D, Popescu I. Prophylactic banding ligation of high risk esophageal varices inpatients on the waiting list for liver transplantation: an interim report. Journal of Hepatology. 2002; 36(Suppl.1):38

53 Giannini E, Arzani L, Borro P, Botta F, Fasoli A, Risso D et al. Does surveillance for hepatocellular carcinoma in HCV cirrhotic patients improve treatment outcome mainly due to better clinical status at diagnosis? Hepato-Gastroenterology. 2000; 47(35):1395-1398

54 Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology. 2002; 123(6):1839-1847

55 Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. Cochrane Database of Systematic Reviews. 2012;(8):CD004544. DOI:10.1002/14651858.CD004544.pub2

56 Grange JD, Roulot D, Pelletier G, Pariente EA, Denis J, Ink O et al. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. Journal of Hepatology. 1998; 29(3):430-436

57 Groszmann R, Bosch J, Grace N, Conn HO, Garcia-Tsao G, Navasa M et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology. 1990; 99(5):1401-1407

58 Guechot J, Trocme C, Renversez JC, Sturm N, Zarski JP, ANRS HC EP 23 Fibrostar Study Group. Independent validation of the Enhanced Liver Fibrosis (ELF) score in the ANRS HC EP 23 Fibrostar cohort of patients with chronic hepatitis C. Clinical Chemistry and Laboratory Medicine. 2012; 50(4):693-699

59 Gyr K, Meier R, Haussler J, Bouletreau P, Fleig WE, Gatta A et al. Evaluation of the efficacy and safety of flumazenil in the treatment of portal systemic encephalopathy: a double blind, randomised, placebo controlled multicentre study. Gut. 1996; 39(2):319-324

60 Halfon P, Bacq Y, de Muret A, Penaranda G, Bourliere M, Ouzan D et al. Comparison of test performance profile for blood tests of liver fibrosis in chronic hepatitis C. Journal of Hepatology. 2007; 46(3):395-402

61 Hassanein T, Tofteng F, Brown RS, Jr., McGuire B, Lynch P, Mehta R et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007; 46(6):1853-1862

62 Ioannou GN, Weiss NS, Kowdley K, Dominitz JA. Is obesity a risk factor for cirrhosis-related death or hospitalization? A population-based cohort study. Gastroenterology. 2003; 125(4):1053-1059

63 Janssens F, de Suray N, Piessevaux H, Horsmans Y, de Timary P, Starkel P. Can transient elastography replace liver histology for determination of advanced fibrosis in alcoholic patients: a real-life study. Journal of Clinical Gastroenterology. 2010; 44(8):575-582

64 Jutabha R, Jensen DM, Martin P, Savides T, Han S, Gornbein J. Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. Gastroenterology. 2005; 128(4):870-881

65 Jutabha R, Jensen DM, Martin P, Savides TJ, Lam F, Jensen ME et al. Initial report of a randomized, prospective study of prophylactic propranolol compared to rubber band ligation for prevention of first variceal hemorrhage in cirrhotics with large esophageal varices. Gastroenterology. 2000; 118(4):A212-A213

66 Kayadibi H, Yasar B, Ozkara S, Serdar MA, Kurdas OO, Gonen C. The diagnostic accuracy of the Forns index, platelet count and AST to Platelet Ratio Index derived fibrosis index for the prediction of Hepatitis C virus-related significant liver fibrosis and cirrhosis. Scandinavian Journal of Clinical and Laboratory Investigation. 2014; 74(3):240-247

67 Kettaneh A, Marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M et al. Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. Journal of Hepatology. 2007; 46(4):628-634

68 Kim BI, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI et al. Increased intestinal permeability as a predictor of bacterial infections in patients with decompensated liver cirrhosis and hemorrhage. Journal of Gastroenterology and Hepatology. 2011; 26(3):550-557

69 Kim BK, Park YN, Kim DY, Park JY, Chon CY, Han KH et al. Risk assessment of development of hepatic decompensation in histologically proven hepatitis B viral cirrhosis using liver stiffness measurement. Digestion. 2012; 85(3):219-227

70 Kim MN, Kim SU, Park JY, Kim DY, Han KH, Chon CY et al. Risk assessment of liver-related events using transient elastography in patients with chronic hepatitis B receiving entecavir. Journal of Clinical Gastroenterology. 2014; 48(3):272-278

71 Klatsky AL, Armstrong MA. Alcohol, smoking, coffee, and cirrhosis. American Journal of Epidemiology. 1992; 136(10):1248-1257

72 Klibansky DA, Mehta SH, Curry M, Nasser I, Challies T, Afdhal N. Transient elastography for predicting clinical outcomes in patients with chronic liver disease. Journal of Viral Hepatitis. 2012; 19(2):e184-e193

73 Laccetti M, Manes G, Uomo G, Lioniello M, Rabitti PG, Balzano A. Flumazenil in the treatment of acute hepatic encephalopathy in cirrhotic patients: a double blind randomized placebo controlled study. Digestive and Liver Disease. 2000; 32(4):335-338

74 Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology. 2005; 41(6):1376-1382

75 Lay CS, Tsai YT, Lee FY, Lai YL, Yu CJ, Chen CB et al. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. Journal of Gastroenterology and Hepatology. 2006; 21(2):413-419

76 Lay CS, Tsai YT, Teg CY, Shyu WS, Guo WS, Wu KL et al. Endoscopic variceal ligation in prophylaxis of first variceal bleeding in cirrhotic patients with high-risk esophageal varices. Hepatology. 1997; 25(6):1346-1350

77 Leroy V, Sturm N, Faure P, Trocme C, Marlu A, Hilleret MN et al. Prospective evaluation of FibroTest, FibroMeter, and HepaScore for staging liver fibrosis in chronic hepatitis B: comparison with hepatitis C. Journal of Hepatology. 2014; 61(1):28-34

78 Liu B, Balkwill A, Reeves G, Beral V, Million Women Study Collaborators. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. BMJ. 2010; 340:c912

79 Lo GH, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI et al. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. Gastrointestinal Endoscopy. 2004; 59(3):333-338

80 Lo GH, Lai KH, Cheng JS, Lin CK, Hsu PI, Chiang HT. Prophylactic banding ligation of high-risk esophageal varices in patients with cirrhosis: a prospective, randomized trial. Journal of Hepatology. 1999; 31(3):451-456

81 Loguercio C, Del Vecchio BC, Coltorti M. Enterococcus lactic acid bacteria strain SF68 and lactulose in hepatic encephalopathy: a controlled study. Journal of International Medical Research. 1987; 15(6):335-343

82 Lui HF, Stanley AJ, Forrest E, Jalan R, Hislop WS, Mills PR et al. Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. Gastroenterology. 2002; 123(3):735-744

83 Lupsor M, Stefanescu H, Feier D, Maniu A, Badea R. Performance of unidimensional transient elastography in staging chronic hepatitis C. Results from a cohort of 1,202 biopsied patients from one single center. Journal of Gastrointestinal and Liver Diseases. 2013; 22(2):157-166

84 Lupsor M, Badea R, Stefanescu H, Sparchez Z, Branda H, Serban A et al. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. Journal of Gastrointestinal and Liver Diseases. 2009; 18(3):303-310

85 Macias J, Giron-Gonzalez JA, Gonzalez-Serrano M, Merino D, Cano P, Mira JA et al. Prediction of liver fibrosis in human immunodeficiency virus/hepatitis C virus coinfected patients by simple non-invasive indexes. Gut. 2006; 55(3):409-414

86 Martinez SM, Fernandez-Varo G, Gonzalez P, Sampson E, Bruguera M, Navasa M et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. Alimentary Pharmacology and Therapeutics. 2011; 33(1):138-148

87 Mas A, Rodes J, Sunyer L, Rodrigo L, Planas R, Vargas V et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. Journal of Hepatology. 2003; 38(1):51-58

88 Miquel M, Sopena J, Vergara M, Gil M, Casas M, Sanchez-Delgado J et al. Factors related to survival in hepatocellular carcinoma in the geographic area of Sabadell (Catalonia, Spain). Revista Espanola De Enfermedades Digestivas. 2012; 104(5):242-247

89 Mueller S, Millonig G, Sarovska L, Friedrich S, Reimann FM, Pritsch M et al. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. World Journal of Gastroenterology. 2010; 16(8):966-972

90 Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology. 2012; 55(1):199-208

91 Narahara Y, Kanazawa H, Fukuda T, Matsushita Y, Harimoto H, Kidokoro H et al. Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin in patients with refractory ascites who have good hepatic and renal function: a prospective randomized trial. Journal of Gastroenterology. 2011; 46(1):78-85

92 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: http://publications.nice.org.uk/the-guidelines-manual-pmg6/

93 Norberto L, Polese L, Cillo U, Grigoletto F, Burroughs A, Neri D et al. A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation. Liver Transplantation. 2007; 13(9):1272-1278

94 Pagliaro L, D'Amico G, Pasta L, Filippazzo G, Manenti F, Dobrilla G et al. Propranolol prevents first gastrointestinal bleeding in non-ascitic cirrhotic patients. Final report of a multicenter randomized trial. Journal of Hepatology. 1989; 9(1):75-83

95 Pagliaro L, D'Amico G, Pasta L, Filippazzo MG, Manenti F, Dobrilla G et al. Propranolol for prophylaxis of bleeding in cirrhotic patients with large varices: A multicenter, randomized clinical trial. Hepatology. 1988; 8(1):1-5

96 Pagliaro L, Pasta L, D'Amico G. A randomised controlled trial of propranolol for the prevention of initial bleeding in cirrhotic patients with portal hypertension. Preliminary results. Drugs. 1989; 37(Suppl.2):48-51 74-76

97 Paik YH, Lee KS, Han KH, Song KH, Kim MH, Moon BS et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. Yonsei Medical Journal. 2005; 46(3):399-407

98 Pascal JP, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. New England Journal of Medicine. 1987; 317(14):856-861

99 Pascal JP, Cales P. Propranolol in the primary prevention of upper gastrointestinal tract haemorrhage in patients with cirrhosis of the liver and oesophageal varices. Drugs. 1989; 37(Suppl.2):52-56

100 Pascual S, Irurzun J, Zapater P, Such J, Sempere L, Carnicer F et al. Usefulness of surveillance programmes for early diagnosis of hepatocellular carcinoma in clinical practice. Liver International. 2008; 28(5):682-689

101 Perez-Ayuso RM, Valderrama S, Espinoza M, Rollan A, Sanchez R, Otarola F et al. Endoscopic band ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices. Annals of Hepatology. 2010; 9(1):15-22

102 Perez-Latorre L, Sanchez-Conde M, Rincon D, Miralles P, Aldamiz-Echevarria T, Carrero A et al. Prediction of liver complications in patients with hepatitis C virus-related cirrhosis with and without HIV coinfection: comparison of hepatic venous pressure gradient and transient elastography. Clinical Infectious Diseases. 2014; 58(5):713-718

103 Piscaglia F, Salvatore V, Di Donato R, D'Onofrio M, Gualandi S, Gallotti A et al. Accuracy of VirtualTouch Acoustic Radiation Force Impulse (ARFI) imaging for the diagnosis of cirrhosis during liver ultrasonography. Ultraschall in Der Medizin. 2011; 32(2):167-175

104 Psilopoulos D, Galanis P, Goulas S, Papanikolaou IS, Elefsiniotis I, Liatsos C et al. Endoscopic variceal ligation vs. propranolol for prevention of first variceal bleeding: a randomized controlled trial. European Journal of Gastroenterology and Hepatology. 2005; 17(10):1111-1117

105 Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350--electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA Internal Medicine. 2014; 174(11):1727-1733

106 Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S et al. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. American Journal of Gastroenterology. 2011; 106(12):2112-2120

107 Robic MA, Procopet B, Metivier S, Peron JM, Selves J, Vinel JP et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. Journal of Hepatology. 2011; 55(5):1017-1024

108 Rolachon A, Cordier L, Bacq Y, Nousbaum JB, Franza A, Paris JC et al. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. Hepatology. 1995; 22(4 Pt.1):1171-1174

109 Rossi-Fanelli F, Cangiano C, Capocaccia L, Cascino A, Ceci F, Muscaritoli M et al. Use of branched chain amino acids for treating hepatic encephalopathy: clinical experiences. Gut. 1986; 27(Suppl.1):111-115

110 Rossi-Fanelli F, Cangiano C, Cascino A, Merli M, Riggio O, Stortoni M. Branched-chain amino acids in the treatment of severe hepatic encephalopathy. In: Capocaccia L, Fischer JE, Rossi-Fanelli F (eds), Hepatic encephalopathy in chronic liver failure, New York: Plenum Press, 1984: 335-344

111 Rossi-Fanelli F, Riggio O, Cangiano C, Cascino A, De Conciliis D, Merli M et al. Branched-chain amino acids vs lactulose in the treatment of hepatic coma: a controlled study. Digestive Diseases and Sciences. 1982; 27(10):929-935

112 Rossle M, Ochs A, Gulberg V, Siegerstetter V, Holl J, Deibert P et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. New England Journal of Medicine. 2000; 342(23):1701-1707

113 Saab S, Nieto J, Lewis SK, Runyon BA. TIPS versus paracentesis for cirrhotic patients with refractory ascites. Cochrane Database of Systematic Reviews. 2006;(4):CD004889. DOI:10.1002/14651858.CD004889.pub2

114 Sabat M, Kolle L, Soriano G, Ortiz J, Pamplona J, Novella M et al. Parenteral antibiotic prophylaxis of bacterial infections does not improve cost-efficacy of oral norfloxacin in cirrhotic patients with gastrointestinal bleeding. American Journal of Gastroenterology. 1998; 93(12):2457-2462

115 Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. Journal of Hepatology. 2004; 40(6):897-903

116 Salerno F, Merli M, Riggio O, Cazzaniga M, Valeriano V, Pozzi M et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. Hepatology. 2004; 40(3):629-635

117 Sanchez-Conde M, Montes-Ramirez ML, Miralles P, Alvarez JMC, Bellon JM, Ramirez M et al. Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers. Journal of Viral Hepatitis. 2010; 17(4):280-286

118 Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. Journal of Hepatology. 2010; 53(2):291-297

119 Sanyal AJ, Gennings C, Reddy KR, Wong F, Kowdley K, Benner K et al. The North American study for the treatment of refractory ascites. Gastroenterology. 2003; 124(3):634-641

120 Sarin SK, Guptan RK, Jain AK, Sundaram KR. A randomized controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. European Journal of Gastroenterology and Hepatology. 1996; 8(4):337-342

121 Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. New England Journal of Medicine. 1999; 340(13):988-993

122 Sarin SK, Mishra SR, Sharma P, Sharma BC, Kumar A. Early primary prophylaxis with beta-blockers does not prevent the growth of small esophageal varices in cirrhosis: A randomized controlled trial. Hepatology International. 2013; 7(1):248-256

123 Sarin S, Lamba G, Kumar M, Misra A, Murthy N. Randomized trial of propranolol vs endoscopic variceal ligation in the primary prophylaxis of bleeding from high risk varices in cirrhosis: an interim analysis. Hepatology. 1997; 26(4 Pt.2):360A

124 Schepke M, Goebel C, Nuernberg D, Willert J, Koch L, Sauerbruch T. Endoscopic banding ligation versus propranolol for the primary prevention of variceal bleeding in cirrhosis: a randomized controlled multicenter trial. Hepatology. 2003; 38(Suppl.4):218

125 Schepke M, Kleber G, Nuernberg D, Willert J, Koch L, Veltzke-Schlieker W et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology. 2004; 40(1):65-72

126 Schult A, Eriksson H, Wallerstedt S, Kaczynski J. Overweight and hypertriglyceridemia are risk factors for liver cirrhosis in middle-aged Swedish men. Scandinavian Journal of Gastroenterology. 2011; 46(6):738-744

127 Shah HA, Azam Z, Rauf J, Abid S, Hamid S, Jafri W et al. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. Journal of Hepatology. 2014; 60(4):757-764

128 Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. American Journal of Gastroenterology. 2013; 108(9):1458-1463

129 Shehab H, Elattar I, Elbaz T, Mohey M, Esmat G. CUFA algorithm: assessment of liver fibrosis using routine laboratory data. Journal of Viral Hepatitis. 2014; 21(12):956-964

130 Silva Junior RG, Schmillevitch J, Nascimento MdFA, Miranda ML, Brant PEAC, Schulz PO et al. Acoustic radiation force impulse elastography and serum fibrosis markers in chronic hepatitis C. Scandinavian Journal of Gastroenterology. 2014; 49(8):986-992

131 Singh B, Saxena PD, Rohtagi V, Kumar V. Comparison of endoscopic variceal ligation and propranolol for the primary prevention of variceal bleeding. Journal, Indian Academy of Clinical Medicine. 2012; 13(3):214-217

132 Sirli R, Sporea I, Bota S, Popescu A, Cornianu M. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. Hepatitis Monthly. 2010; 10(2):88-94

133 Song IH, Shin JW, Kim IH, Choi J, Lim CY, Kim JW et al. A prospective randomized trial between the prophylactic endoscopicvariceal ligation and propranolol administration for prevention offirst bleeding in cirrhotic patients with high-risk esophageal varices. Journal of Hepatology. 2000; 32(Suppl.2):41

134 Soriano G, Guarner C, Teixido M, Such J, Barrios J, Enriquez J et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology. 1991; 100(2):477-481

135 Spanish Group for the Study of Bacterial Infections in Cirrhosis. Norfloxacin versus ofloxacin in the prophylaxis of infection in cirrhotic patients with gastrointestinal hemorrhage. Journal of Hepatology. 1998; 28(Suppl.1):80

136 Sporea I, Sirli RL, Deleanu A, Popescu A, Focsa M, Danila M et al. Acoustic radiation force impulse elastography as compared to transient elastography and liver biopsy in patients with chronic hepatopathies. Ultraschall in Der Medizin. 2011; 32(Suppl.1):S46-S52

137 Sporea I, Bota S, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H et al. Acoustic Radiation Force Impulse elastography for fibrosis evaluation in patients with chronic hepatitis C: an international multicenter study. European Journal of Radiology. 2012; 81(12):4112-4118

138 Sporea I, Sirli R, Popescu A, Bota S, Badea R, Lupsor M et al. Is it better to use two elastographic methods for liver fibrosis assessment? World Journal of Gastroenterology. 2011; 17(33):3824-3829

139 Stibbe KJM, Verveer C, Francke J, Hansen BE, Zondervan PE, Kuipers EJ et al. Comparison of non-invasive assessment to diagnose liver fibrosis in chronic hepatitis B and C patients. Scandinavian Journal of Gastroenterology. 2011; 46(7-8):962-972

140 Strauss E, dos Santos WR, Silva EC, Lacet CM, Capacci MLL, Bernardini AP. Treatment of hepatic encephalopathy: A randomizes clinical trial comparing a branched chain enriched amino acid solution to oral neomycin. Nutritional Support Services. 1986; 6(7):18-21

141 Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepato-Gastroenterology. 1992; 39(6):542-545

142 Stroffolini T, Trevisani F, Pinzello G, Brunello F, Tommasini MA, Iavarone M et al. Changing aetiological factors of hepatocellular carcinoma and their potential impact on the effectiveness of surveillance. Digestive and Liver Disease. 2011; 43(11):875-880

143 Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S, Bhist MS. Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial. Hepatology. 1992; 16(1):138-144

144 Svoboda P, Kantorova I, Ochmann J, Kozumplik L, Marsova J. A prospective randomized controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high-risk esophageal varices. Surgical Endoscopy. 1999; 13(6):580-584

145 Takahashi H, Ono N, Eguchi Y, Eguchi T, Kitajima Y, Kawaguchi Y et al. Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: a pilot study. Liver International. 2010; 30(4):538-545

146 Tellez-Avila F, Sifuentes-Osornio J, Barbero-Becerra V, Franco-Guzman A, Ruiz-Cordero R, Alfaro-Lara R et al. Primary prophylaxis with ciprofloxacin in cirrhotic patients with ascites: a randomized, double blind study. Annals of Hepatology. 2013; 13(1):65-74

147 Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. Journal of Hepatology. 2008; 48(5):774-779

148 Thuluvath PJ, Maheshwari A, Jagannath S, Arepally A. A randomized controlled trial of beta-blockers versus endoscopic band ligation for primary prophylaxis: a large sample size is required to show a difference in bleeding rates. Digestive Diseases and Sciences. 2005; 50(2):407-410

149 Trevisani F, Cantarini MC, Labate AM, De Notariis S, Rapaccini G, Farinati F et al. Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis: effects on cancer staging and patient survival. American Journal of Gastroenterology. 2004; 99(8):1470-1476

150 Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, Benvegnu L et al. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? American Journal of Gastroenterology. 2007; 102(11):2448-2457

151 Triantos C, Vlachogiannakos J, Armonis A, Saveriadis A, Kougioumtzian A, Leandro G et al. Primary prophylaxis of variceal bleeding in cirrhotics unable to take beta-blockers: a randomized trial of ligation. Alimentary Pharmacology and Therapeutics. 2005; 21(12):1435-1443

152 Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology. 2011; 54(6):1987-1997

153 Tripathi D, Ferguson J, Kochar N, Leithead JA, Therapondos G, McAvoy NC et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology. 2009; 50(3):825-833

154 Uribe M, Berthier JM, Lewis H, Mata JM, Sierra JG, Garcia-Ramos G et al. Lactose enemas plus placebo tablets vs. neomycin tablets plus starch enemas in acute portal systemic encephalopathy. A double-blind randomized controlled study. Gastroenterology. 1981; 81(1):101-106

155 Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L et al. Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. Hepatology. 1987; 7(4):639-643

156 Vilstrup H, Gluud C, Hardt F, Kristensen M, Kohler O, Melgaard B et al. Branched chain enriched amino acid versus glucose treatment of hepatic encephalopathy. A double-blind study of 65 patients with cirrhosis. Journal of Hepatology. 1990; 10(3):291-296

157 Wahren J, Denis J, Desurmont P, Eriksson LS, Escoffier JM, Gauthier AP et al. Is intravenous administration of branched chain amino acids effective in the treatment of hepatic encephalopathy? A multicenter study. Hepatology. 1983; 3(4):475-480

158 Wang JH, Chuah SK, Lu SN, Hung CH, Kuo CM, Tai WC et al. Baseline and serial liver stiffness measurement in prediction of portal hypertension progression for patients with compensated cirrhosis. Liver International. 2014; 34(9):1340-1348

159 Wong VW-S, Vergniol J, Wong GL-H, Foucher J, Chan AWH, Chermak F et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. American Journal of Gastroenterology. 2012; 107(12):1862-1871

160 Wong VW-S, Vergniol J, Wong GL-H, Foucher J, Chan HLY, Le Bail B et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010; 51(2):454-462

161 Yamada H, Ebara M, Yamaguchi T, Okabe S, Fukuda H, Yoshikawa M et al. A pilot approach for quantitative assessment of liver fibrosis using ultrasound: preliminary results in 79 cases. Journal of Hepatology. 2006; 44(1):68-75

162 Yoneda M, Yoneda M, Mawatari H, Fujita K, Endo H, Iida H et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Digestive and Liver Disease. 2008; 40(5):371-378

163 Yoneda M, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K et al. Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. Radiology. 2010; 256(2):640-647

164 Zarski JP, Sturm N, Guechot J, Paris A, Zafrani ES, Asselah T et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. Journal of Hepatology. 2012; 56(1):55-62