Review report of MTG27: Virtual Touch Quantification to diagnose and monitor liver fibrosis in chronic hepatitis B and C

Version no.	Date	Author	Purpose
1	27/9/2019	Jacoby Patterson	For review by MTEP technical lead
2	4/10/2019	Jacoby Patterson	For review by MTEP technical lead
3	11/10/2019	Jacoby Patterson and Joyce Craig	For review by MTEP technical lead
4	18/10/2019	Jacoby Patterson and Joyce Craig	Final version

This medical technology guidance was published in September 2015.

All medical technology guidance is reviewed 3 years after publication.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance needs to be updated at this time.

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Acknowledgements

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Abbreviations

ALD	Alcoholic liver disease
ARFI	Acoustic radiation force impulse imaging which measures tissue elasticity including liver stiffness by way of shear wave speed using a multipurpose diagnostic ultrasound imaging machine
AUROC/ AUC	Area under receiver operating characteristic curve
BI-RADS	Breast Imaging-Reporting and Data System
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CLD	Chronic liver disease
CT	Computerised tomography
Cut-off	The threshold for defining a test as positive
DAX	Deep abdominal transducer
DOR	Diagnostic odds ratio (the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease)
EAC	External Assessment Centre
EASL	European Association for the Study of the Liver
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
F0	No liver fibrosis
F1	Mild liver fibrosis
F2	Moderate liver fibrosis
F3	Severe liver fibrosis
F4	Cirrhosis
FN	False negative
FP	False positive
gIS	Guidance Information Service
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICTRP	International Clinical Trial Registry Platform
INR	International normalised ratio
ISRCTN	International Standard Randomised Controlled Trials Number
JSUM	Japan Society of Ultrasonics in Medicine
kPa	Kilopascal
LB	Liver biopsy
LLL	Left liver lobe
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
m/s	Meters per second
MTEP	Medical Technologies Evaluation Programme
MTG	Medical technologies guidance
NA	Not available
NAFLD	Non-alcoholic fatty liver disease
NICE	National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
pSWE	Point shear wave elastography
QUS	Quantitative ultrasound
ROC	Receiver operating characteristic curve that displays specificity (X-axis) and sensitivity (Y-axis). The best diagnostic tests are positioned in the upper left corner of the ROC, as both sensitivity and specificity are close to 1.
SCoR/BMUS	Society & College of Radiographers and The British Medical Ultrasound Society
SE	Standard error
Sens	Sensitivity
SP	Spleen
Spec	Specificity
SROC	Summary ROC curve
SWE	Shear wave elastography

SWV	Shear-wave velocity
TE	Transient elastography is a non-invasive measure of liver stiffness based on a mechanical wave generated by vibration
TN	True negative
TP	True positive
US	Ultrasound
VTIQ	Virtual Touch Tissue Imaging Quantification
VTq	Virtual Touch Quantification: uses ARFI technology on a traditional ultrasound system
WFUMB	World Federation for Ultrasound in Medicine and Biology
WHO	World Health Organization
YHEC	York Health Economics Consortium
$\chi 2$	Chi square statistic

1. Original objective of guidance

To assess the clinical and cost effectiveness of Virtual Touch Quantification to diagnose and monitor liver fibrosis in chronic hepatitis B and C.

2. Current guidance recommendations

2.1 The case for adopting Virtual Touch Quantification (VTq) software to diagnose and monitor liver fibrosis is supported by the evidence. VTq is as accurate as transient elastography in diagnosing and staging liver fibrosis, and may offer other benefits in terms of imaging the liver and sampling selected areas to assess fibrosis and identify associated pathologies. By avoiding liver biopsies, it may also benefit people whose liver fibrosis needs monitoring. Cost savings through adopting VTq will be greater in hospitals in which liver biopsy is the primary method for diagnosing and monitoring liver fibrosis.

2.2 VTq should be considered as an option for people with chronic hepatitis B or C who need assessment of liver fibrosis.

2.3 Cost modelling suggests that using VTq is cost saving compared with transient elastography and liver biopsy, whether or not a compatible Siemens ultrasound machine needs to be purchased. Compared with transient elastography, the estimated overall cost saving for VTq is around £53 per person. This saving assumes that 10% of the ultrasound machine capacity would be used for VTq measurements, leaving 90% to be applied to other uses. Compared with liver biopsy, the corresponding saving is around £434 per person.

3. Methods of review

Information was obtained from the Guidance Information Service (gIS) literature search (search strategy in Appendix C); national and international guidelines; handsearching of reference lists of review articles, information from the company and the views of national experts. References are listed in Appendix D. The following table provides the Final Scope produced by NICE which guided the search and inclusion and exclusion criteria.

Table 1: Final Scope

Population	Virtual Touch Quantification is intended for use in adults or children with chronic hepatitis B or C in whom assessment of liver fibrosis is indicated.

Intervention	The Virtual Touch Quantification (VTq) software application used with the Siemens Virtual Touch Tissue Imaging systems (the Acuson S2000 or S3000 ultrasound platforms)
Comparator(s)	• Transient elastography (TE) • Liver biopsy
Outcomes	The outcome measures to consider include: • Correlation in assessment of stage of liver disease • Sensitivity and specificity (using AUROC*) in assessment of liver fibrosis • Correlation in assessment of stage of fibrosis using Metavir score** • Use of anti-viral drugs • Quality of life measures • Hospital bed usage and length of stay • Requirement for liver biopsy • Device-related adverse events
Cost analysis	The cost analysis should include both transient elastography and liver biopsy as comparators depending on whether either or both of these represent standard care in the relevant patient population. The use in both primary and secondary care settings should be considered. Scenarios considered in the model should include settings where there is a compatible Siemens ultrasound machine and those without. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared, for example ongoing fibrosis monitoring. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	None

Special considerations, including those related to equality	None

* AUROC = area under receiver operating characteristic curve

[Note: liver biopsy is considered to be the gold standard for assessing liver fibrosis for both hepatitis B and C. Histological assessment uses the METAVIR score (unless otherwise stated), based on an assessment of fibrosis and the degree of liver architecture disorganisation, and classifies the severity of liver disease from none (F0), through mild, moderate and severe (F1–F3), to cirrhosis (F4) (www.nice.org.uk/guidance/mtg27). Important distinctions are identifying people a) with moderate (F2) or greater fibrosis (F≥2), or b) with cirrhosis (F=4) (www.nice.org.uk/guidance/mtg27).]

One reviewer sifted the titles and abstracts and data extracted the included studies. A second reviewer was available to resolve uncertainties on the selection of specific papers and checked a sample of the data extraction tables. Data extracted included study details (e.g. country), participant details (number, diagnosis, age, gender), intervention and reference standard[1] (biopsy or TE), and outcomes relating to diagnostic accuracy. Where the required outcomes were not reported, they were calculated if possible from the data provided.

Patients with a diagnosis of hepatitis B, hepatitis C, or mixed populations, were evaluated separately. The numbers of participants in each fibrosis stage, cut-off values used, true and false positives and negatives, sensitivity, specificity, positive and negative predictive values, AUROC and diagnostic odds ratio (DOR) of the test from the various studies were tabulated. Sensitivity and specificity were shown graphically using forest plots[2] and AUROC curves. Additional analyses were conducted to calculate pooled sensitivity and specificity values and assess the heterogeneity between studies.

4. New evidence

4.1 Changes in technology

The technology is still available in the NHS.

[1] The best available method for identifying patients that have the target condition.
[2] Forest plots are graphs that display sensitivity, specificity, TP, FP, FN and TN

The company notes that there is a new ultrasound system model ACUSON Sequoia, which has an identical function to VTq on the ACUSON S2000 and ACUSON S3000 ultrasound systems. The function is referred to as point shear wave elastography (pSWE).

Two new technologies used for quantitative liver elastography have been added to the ACUSON Sequoia system. These are a deep abdominal transducer (DAX) which extends the depth range of shear wave measurement from 8 cm to 12 cm, for high body mass index (BMI) subjects and two-dimensional shear wave elastography (SWE) which provides a two-dimensional colour coded map of tissue stiffness in kilopascal (kPa) or shear wave velocity, in meters per second (m/s).

The company has added VTq to the ACUSON Juniper system for liver indications. This system has a lower cost than the ACUSON S2000 and ACUSON S3000.

A new system, the ACUSON Redwood, will be released shortly. It will support liver assessment using pSWE technology.

The company has not proposed an expansion to the scope, but has stated that the technology is being used in conditions other than Hepatitis B and C, including non-alcoholic fatty liver disease (NAFLD), portal hypertension, risk of oesophageal varices, breast lesions and the evaluation of thyroid nodules and Hashimoto's thyroiditis.

The company also advises that interpreting the results of a VTq test are a matter for clinical judgement by specialists, taking into account results of other tests and the clinical context. The company noted reference studies can be provided. It added that a paper by Barr et al., 2015 set out a consensus statement by the Society of Radiologists in Ultrasound Consensus. This suggests cut-offs of 1.2 m/s for F2 and 2.2 m/s for F4.

The clinical experts noted the NICE advice on the VTq technology was useful, adding that it can be used in other aspects of hepatological care for assessment of fibrosis in pre-and post- transplant and all liver diseases. One expert noted VTq can be used in other clinical indications such as breast, thyroid and musculoskeletal disorders. He added it can also be used by trained staff in primary and secondary care if the circumstances are correct and the technology is available.

The experts agreed the technology is easy to use by trained personnel and reliable. One expert noted that the equipment has to be calibrated and requires to be stored. Another is concerned about the variation of readings

depending on manufacturer and a slight discrepancy between results offered in kilopascal (kPA) and those in meters per second (m/s).

4.1.1. Adverse events

The MHRA website (http://www.mhra.gov.uk/index.htm) and the MAUDE database section of the FDA medical devices website (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm) were searched on 01/09/2019 for information on VTQ, VTIQ or "Virtual Touch Quantification"; no relevant results were found.

The company also advised no adverse events have been reported for VTq.

4.2. Changes in care pathways

Virtual Touch Quantification is intended for use in adults and children in whom assessment of liver fibrosis is indicated. This evaluation is concerned only with people with chronic hepatitis B or C.

The NICE pathways are Hepatitis B and Hepatitis B and C testing.

NICE Hepatitis B (chronic) clinical pathway indicates that assessment of hepatitis B is usually in primary care where blood tests are undertaken; all patients who are hepatitis B surface antigen (HBsAg) positive should be referred to a hepatologist, gastroenterologist or infectious disease specialist with an interest in hepatology (children to a similar paediatric specialist in a secondary or tertiary centre).

In secondary or tertiary care patients are provided with information on disease progress, long term prognosis, HBV transmission and antiviral treatment options. Adult patients are then offered TE as an initial test for chronic liver disease. Transient elastography (for example, FibroScan) is a non-invasive method of assessing liver fibrosis by measuring liver stiffness based on a mechanical wave generated by vibration. Children, young people and their parents or carers are offered liver biopsy to determine the need for anti-viral therapy, with appropriate information on biopsy limitations and risks.

Hepatitis B (chronic; NICE clinical guideline 165) recommends:

- TE as the initial test for chronic liver disease, offering antiviral treatment (without a liver biopsy) to patients with a transient elastography score ≥11 kPa.
- Considering liver biopsy in patients with a transient elastography score between 6 and 10 kPa.

- Offering liver biopsy to patients with a TE score < 6 kPa if they are <30 years and have HBV DNA >2000 IU/ml and abnormal ALT on 2 consecutive tests conducted months apart.
- Annual reassessment of patients who are not taking antiviral treatment.

NICE is developing a quality standard on hepatitis C with publication date to be confirmed. Patients who are hepatitis C RNA positive on a blood test are referred to a hepatology clinic. The degree of fibrosis is assessed and treatment options are discussed depending on specific patient contraindications and degree of liver disease.

Liver biopsy is considered the gold standard for assessing liver fibrosis for both hepatitis B and C. Histological assessment uses the METAVIR score, based on an assessment of fibrosis and the degree of liver architecture disorganisation and classifies the severity of liver disease from none (grade F0) through mild, moderate, severe to cirrhosis (grade F4).

Two experts have noted that there has been no change to the care pathway since the guidance was published. One expert suggested that VTq technology will be used increasingly in follow up and another expert noted that it offered a good model for centres planning to start a programme from scratch.

4.3. Results from MTEP MTG review

There were no research recommendations in MTG27.

4.4. New studies

Details of the search results are shown in the PRISMA diagram in Appendix B. Reasons for exclusion of studies are also reported in Appendix B.

Details of the new studies are tabulated in Appendix B and summaries of the diagnostic test accuracy outcomes are provided below for patients with hepatitis C, hepatitis B, or mixed populations.

Fifteen of the papers evaluated VTq in adults with hepatitis C only (of which one was a systematic review including a further 6 studies), 4 in adults with hepatitis B only, 2 in mixed populations of hepatitis B and C (shown separately) and 1 in mixed hepatitis B and C (analysed together). Five studies compared VTq with transient elastography and 17 compared VTq with liver biopsy. Optimal cut-off values for VTq measurements were calculated to classify fibrosis stages by METAVIR score. Most studies describe VTq as

acoustic radiation force impulse (ARFI) imaging carried out on a Siemens Acuson S2000 ultrasound machine.

While reporting diagnostic test accuracy parameters, of note, no studies reported outcomes such as use of anti-viral drugs, hospital bed usage, length of stay or quality of life; all outcomes listed in the Final Scope.

Hepatitis C

Our searches for this update (run in July 2019) were from inception of the databases. We included 17 studies (Alem 2019, Bota 2015, Elhosary 2016, Friedrich-Rust 2015, Frulio 2014, Gandy 2016, Joo 2015, LazAr 2018, Lopez 2018, Lupusoru 2016, Nierhoff 2013, Nishimura 2016, Paranagua-Vezozzo 2017, Ragazzo 2017, Sporea 2016, Tai 2015, Tsukano 2018) from our searches providing cross-sectional data comparing the number of patients identified as having significant fibrosis (F≥2) by the VTq method versus a reference standard (usually liver biopsy, unless stated otherwise). The earliest systematic review identified was published in 2013 (Nierhoff 2013) included 6 relevant studies of patients with hepatitis C and used liver biopsy as the gold standard (Fierbinteanu-Braticevici 2009, Lupsor 2009, Song 2010, Fierbinteanu-Braticevici 2011, Rizzo 2011, Sporea 2011b). Three studies, all set in Romania, included overlapping populations (Fierbinteanu-Braticevici [2009,] n=74; Lupsor [2009], n = 112 and Sporea [2011b] n = 543). Hence the two smaller studies were removed from the analysis.

The diagnostic accuracy data (as reported in the papers or calculated) for the remaining studies and subsequent studies are shown below in Table 2 for the outcome of F≥2 and Table 3 for F=4. Full details of the studies are shown in Appendix B. Eight studies did not provide sufficient information to enable their use in a meta-analyses. These are highlighted with grey shading in both Tables. Hence 12 studies were included in the meta-analyses.

Table 2. Diagnostic accuracy parameters for diagnosis of F≥2 in patients with hepatitis C.

Hep C	Fibrosis stage (n) diagnosed by biopsy					For F≥2										
Study	**F0**	**F1**	**F2**	**F3**	**F4**	**Cut-off (m/s)†**	**TP**	**FP**	**FN**	**TN**	**Sens (%)**	**Spec (%)**	**PPV (%)**	**NPV (%)**	**AUROC**	**DOR**
Song 2010	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.89	NA
Fierbinteanu-Braticevici 2011	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.97	NA
Rizzo 2011	13	39	33	24	30	1.31m/s	70	16	17	36	81	70	81.4	67.9	0.86	9.95
Sporea 2011b	54	178	148	139	172	1.29m/s	330	46	129	186	72	80	87.8	59.0	0.81	10.29
Alem 2019**	704	360	260	188	601	1.36 m/s	845	133	204	931	80.6	87.5	86.4	82.0	0.89	29.0
Bota 2015	7	12	58	39	16	1.35 m/s	55	4	44	14	55.6	77.8	93.2	24.1	NA	4.4
Elhosary 2016	0	25	28	29	108	1.32m/s	124	2	41	23	75.0	90.9	90.9	75.0	0.727	34.8
Friedrich-Rust 2015	28	63	30	19	42	1.435 m/s	59	9	32	82	64.84	90.11	86.76	71.93	0.81	16.8
Frulio 2014*	0	31	7	2	6	1.34m/s	12	8	3	23	80.0	74.2	60.0	88.5	NA	11.5
Gandy 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Joo 2015	7	26	29	19	20	1.335 m/s	66	10	2	23	83.8	75.8	87.7	69.4	0.853	75.9
LazAr 2018**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lopez 2018**	0	34	19	10	26	1.43m/s	44	8	11	26	80.0	76.5	84.6	70.3	NA	13.0
Lupusoru 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nishimura 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Paranagua-Vezozzo 2017	5	33	20	12	11	1.22 m/s	34	11	9	27	78	70	85.5	58.4	0.7701	9.3
Ragazzo 2017	8	43	31	23	2	1.22m/s	NA	NA	NA	NA	64	69	67	67	0.67	NA
Sporea 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tai 2015	0	33	29	4	17	1.39 m/s.	NA	NA	NA	NA	76.5	78.8	NA	NA	NA	NA
Tsukano 2018	0	108	93	62	39	1.33 m/s	147	22	47	86	76	80	87.0	64.7	0.822	12.2

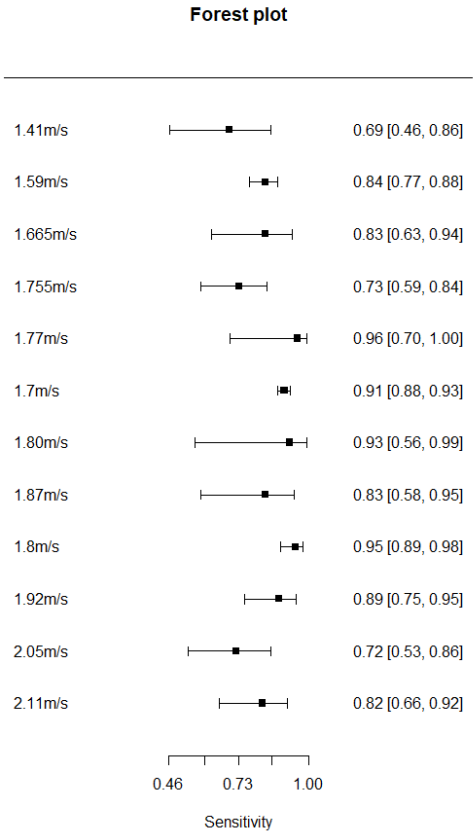
NA Not available

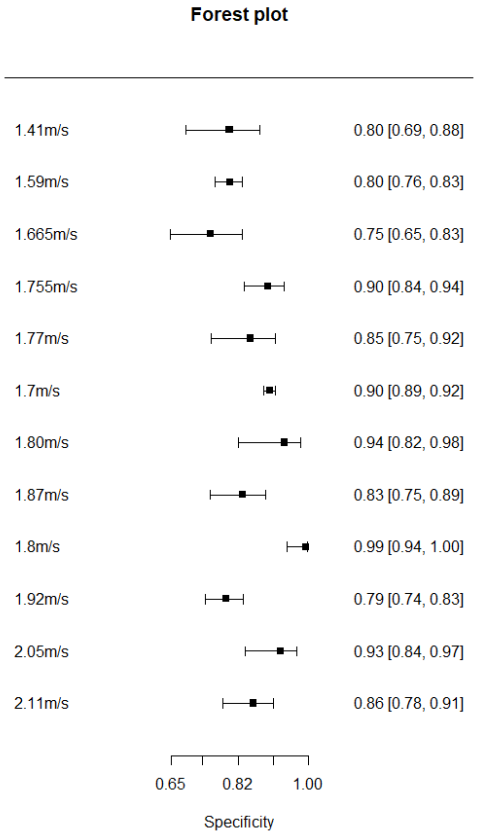
†Of note, differing manufacturers have different cut-offs for shear wave velocities for the various stages of liver disease; practitioners are advised to refer to individual manufacturers' reference ranges (SCoR/BMUS 2019). Also, VTq values should be interpreted taking into account results of other tests and the clinical context (MTG27).

* Reference standard: The presence of cirrhosis was evaluated in all patients histologically (not all had biopsy) and from imaging, clinical and biological results included small nodular and irregular livers with increased echogenicity and/or a significant reduction in Doppler flow in the portal circulation on ultrasound, CT, or MRI.

** Reference standard = TE.

Descriptive statistics for the data set include the sensitivity and specificity of the primary studies and also their DOR. Sensitivity and specificity are presented in forest plots including 95% confidence intervals.

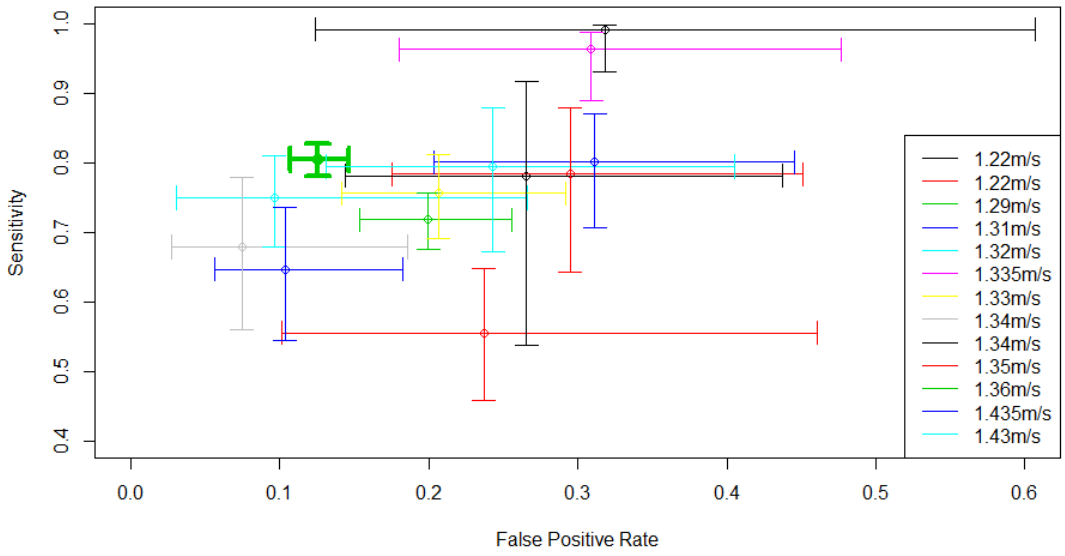




Cut-Off	DOR	2.5%	97.5%
1.22m/s	9.27	3.36	25.60
1.29m/s	10.34	7.06	15.15
1.31m/s	9.27	4.20	20.46
1.32m/s	34.78	7.86	153.93
1.335m/s	75.90	15.47	372.43
1.33m/s	12.23	6.90	21.66
1.34m/s	11.50	2.57	51.50
1.35m/s	4.38	1.35	14.24
1.36m/s	29.00	22.87	36.77
1.435m/s	16.80	7.46	37.83
1.43m/s	13.00	4.63	36.48

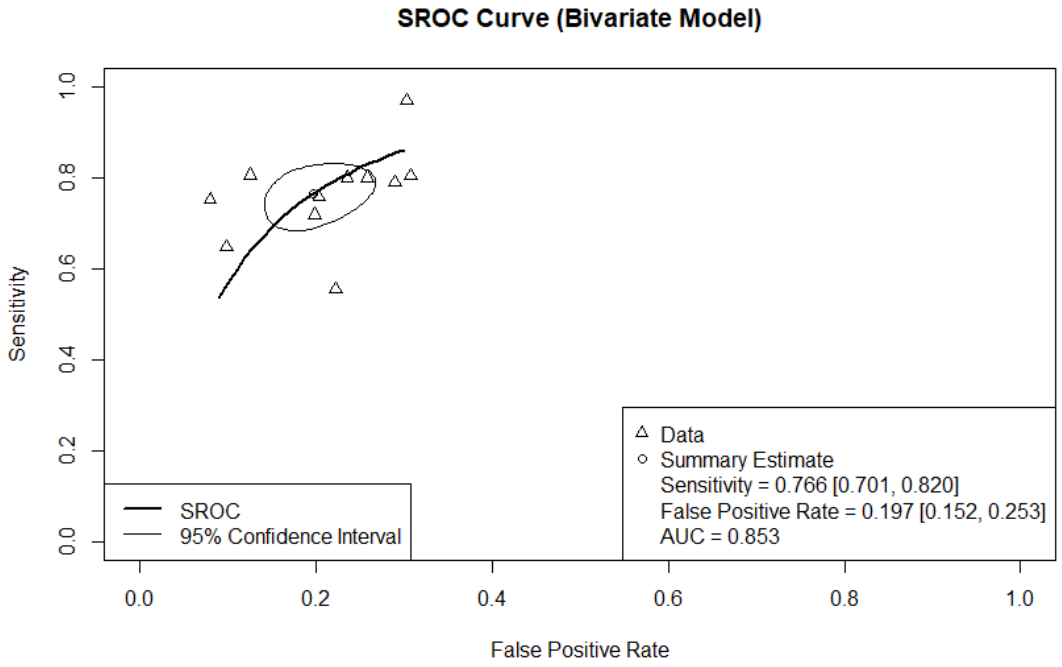
In addition, a crosshair plot with arbitrary colouring is provided to visualise the data. Paired lines show the corresponding 95% confidence intervals for

sensitivity and false positive rate (1-specificity). Crosshairs are weighted, with wider lines indicating increased sample size.



A χ^2 test was used to assess the heterogeneity of sensitivities and specificities. Both test suggest statistical heterogeneity is significant ($\chi^2 = 64.1208, p < 0.01$ and $\chi^2 = 40.4868$, p<0.01 respectively). It is likely that heterogeneity is due to difference in cut-off values.

Finally, a bivariate model (mixed effects) was used to pool the studies. This provided a mean value for sensitivity and false positive rate. A SROC plot for this model is shown.



To summarise, the bivariate model calculates a pooled estimate for sensitivity of 77% and a specificity of 80%. This suggest good estimate accuracy with the summary AUC reaching 0.853.

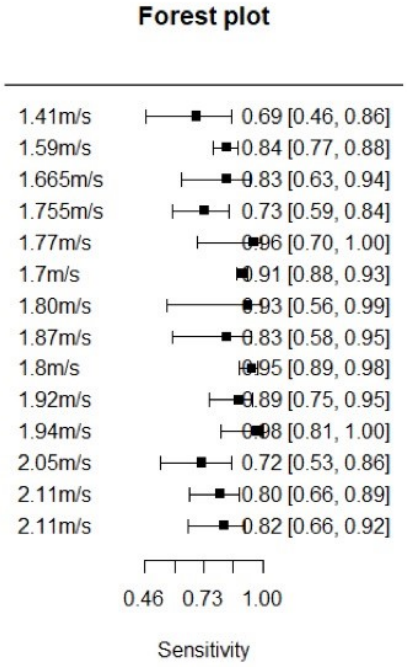
Data reported from all studies for F=4 are reported in Table 3, with the shaded studies excluded from the meta-analyses due to data limitations.

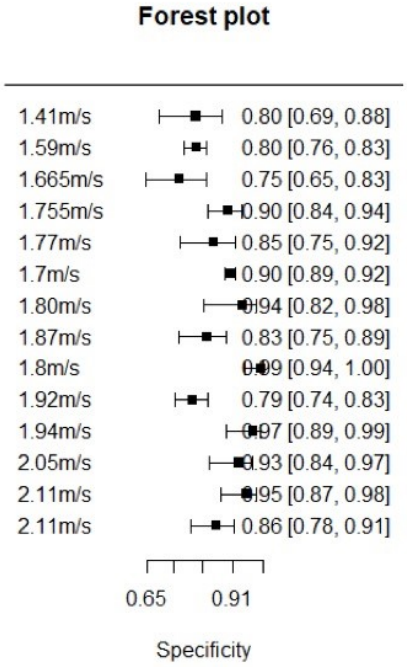
Table 3. Diagnostic accuracy parameters for diagnosis of F=4 in patients with hepatitis C.

Hep C	Fibrosis stage (n) diagnosed by biopsy					For F=4										
Study	F0	F1	F2	F3	F4	Cut-off (m/s)†	TP	FP	FN	TN	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUROC	DOR
Song 2010	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.94	NA
Fierbinteanu-Braticevici 2011	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rizzo 2011	13	39	33	24	30	2.11m/s	25	15	5	94	83	86	62.5	94.9	0.89	29.99
Sporea 2011b	54	178	148	139	172	1.59m/s	144	104	28	415	84	80	58.1	93.7	0.85	21
Alem 2019**	704	360	260	188	601	1.7 m/s	546	147	55	1365	90.9	90.3	78.8	96.1	0.95	92.2
Bota 2015	7	12	58	39	16	1.87m/s	12	17	2	86	85.7	83.5	41.4	97.8	NA	30.4
Elhosary 2016	0	25	28	29	108	1.8m/s	103	0	5	82	95.7	100	100	40.0	0.989	NA
Friedrich-Rust 2015	28	63	30	19	42	1.755m/s	31	14	11	126	73.81	90.00	68.89	91.97	0.89	25.4
Frulio 2014*	0	31	7	2	6	1.80m/s	6	2	0	38	100	95.0	75.0	100	NA	NA
Gandy 2016	NA	NA	NA	NA	26	1.89m/s	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Joo 2015	7	26	29	19	20	1.665 m/s	17	20	3	61	85.0	69.1	40.5	94.9	0.828	17.3
LazAr 2018**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lopez 2018**	0	34	19	10	26	2.05m/s	19	4	7	59	73.1	93.7	82.6	89.4	NA	40.0
Lupusoru 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nishimura 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Paranagua-Vezozzo 2017	5	33	20	12	11	1.77 m/s	11	10	0	60	100	85.7	77.5	100	0.9188	NA
Ragazzo 2017	8	43	31	23	2	2.37m/s	NA	NA	NA	NA	100	94	40	100	0.96	NA
Sporea 2016	NA	NA	NA	NA	NA	1.81 m/s	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tai 2015	0	33	29	4	17	1.41m/s	12	13	5	53	70.6	80.3	48.0	91.4	NA	9.8
Tsukano 2018	0	108	93	62	39	1.92 m/s	35	55	4	208	90.0	84.0	38.9	98.1	0.890	33.1

†Of note, differing manufacturers have different cut-offs for shear wave velocities for the various stages of liver disease; practitioners are advised to refer to individual manufacturers' reference ranges (SCoR/BMUS 2019). Also, VTq values should be interpreted taking into account results of other tests and the clinical context (MTG27).
* Reference standard: The presence of cirrhosis was evaluated in all patients histologically (not all had biopsy) and from imaging, clinical and biological results included small nodular and irregular livers with increased echogenicity and/or a significant reduction in Doppler flow in the portal circulation on ultrasound, CT, or MRI.
** Reference standard = TE.

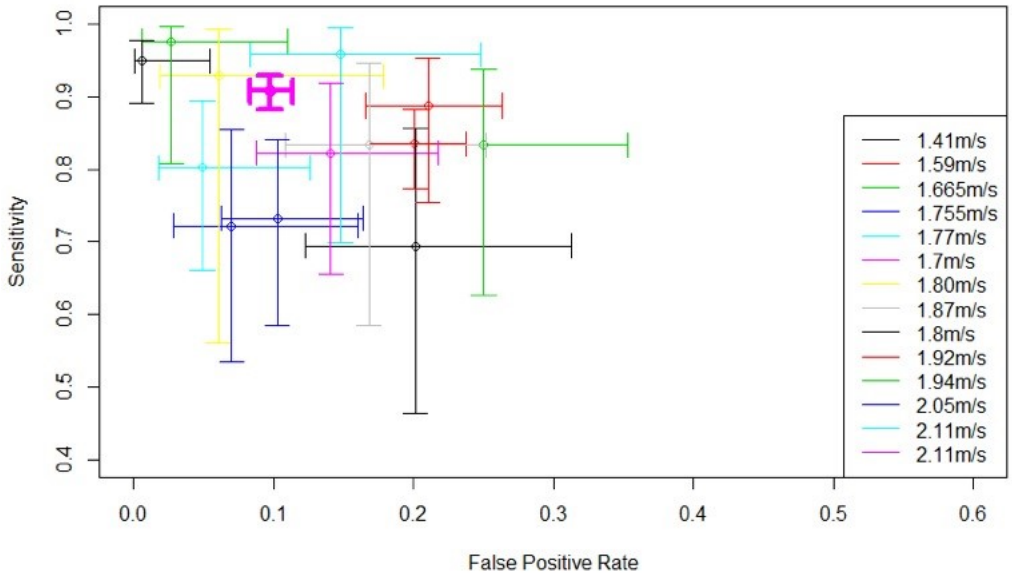
Descriptive statistics for a data set include the sensitivity and specificity of the primary studies and also their DOR. Sensitivity and specificity are presented in forest plots including 95% confidence intervals.





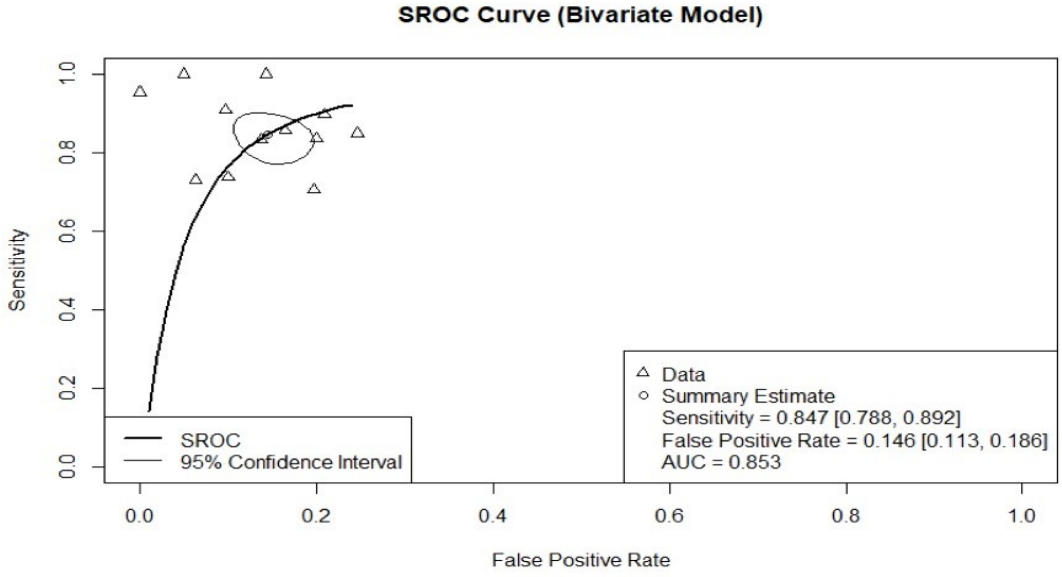
Cut-Off	DOR	2.5%	97.5%
1.41m/s	9.01	2.80	28.94
1.59m/s	20.16	12.79	31.79
1.665m/s	15.00	4.29	52.45
1.755m/s	23.90	10.04	56.86
1.77m/s	132.52	7.25	2423.61
1.7m/s	91.16	65.92	126.06
1.80m/s	200.20	8.60	4662.82
1.87m/s	24.71	5.79	105.55
1.8m/s	3105.00	169.24	56967.93
1.92m/s	29.64	10.64	82.56
2.05m/s	34.38	9.60	123.11
2.11m/s	28.28	9.73	82.13
1.41m/s	9.01	2.80	28.94
1.59m/s	20.16	12.79	31.79

In addition, a crosshair plot with arbitrary colouring was used to visual the data. Paired lines show the corresponding 95% confidence intervals for sensitivity and false positive rate (1-specificity). Crosshairs are weighted, with wider lines indicating increased sample size.



A χ^2 test was used to assess the heterogeneity of sensitivities and specificities. Both test suggest statistical heterogeneity is significant ($\chi^2 = 36.5273, p < 0.01$ and $\chi^2 = 81.5477$, p<0.01 respectively). It is likely that heterogeneity is due to difference in cut-off values.

Finally, a bivariate model (mixed effects) was used to pool the studies. This provided a mean value for sensitivity and false positive rate. A SROC plot for this model is shown.



To summarise, the bivariate model calculates a pooled estimate for sensitivity of 85% and a specificity of 85%. This suggests good estimate accuracy with the summary AUC reaching 0.853.

Evidence from other studies comparing VTq versus liver biopsy or TE have shown high predictive accuracy of VTq in the detection of cirrhosis (F4) in hepatitis C, with AUROC >80%, although some of these studies did not present data to allow 2 x 2 tables to be constructed (Friedrich-Rust 2015, Gandy 2016, Ragazzo 2017, Sporea 2016).

Gandy 2016 included 96 patients with HCV infection, and examined cut-offs for F=4 in group 1) all 96 cases, including 20 patients with co-pathology (HBV, NAFLD, or ALD); group 2) 76 cases with HCV only; and group 3) the 84 cases who had simultaneous biopsy. Cirrhosis was present in 26, 20 and 14 in groups 1, 2 and 3, respectively. Predictive accuracy for Metavir F4 using the reference threshold of 1.75 m/sec was 90%, 92% and 88% in groups 1, 2 and 3, respectively, while a cutoff of 1.89 achieved accuracies of 93%, 96% and 92%, respectively.

Ragazzo 2017 conducted a prospective study of 107 treatment-naïve patients chronically infected with HCV, of whom 51 had VTq. The authors reported an AUROC of 0.67 at a cut-off of 1.22m/s for F≥2 and an AUROC of 0.96 at a cut-off of 2.37m/s for F=4.

Sporea 2016 conducted a prospective study of 40 consecutive patients diagnosed with HCV liver cirrhosis, and found that at a cut-off of 1.81 m/s, 97% of subjects were correctly classified by TE and 97% by VTQ.

Performance for intermediate fibrosis stages and F2 exclusion is less consistent between techniques and across trials (Sherman 2017), although still with AUROC above 67% for VTq (Nishimura 2016, Ragazzo 2017).

In a cross-sectional study involving a total of 1210 patients with chronic liver disease, data were presented for the subgroups of patients with chronic hepatitis B and C separately (n not stated) (Nishimura 2016). The AUC for patients with hepatitis C for F3-4 (advanced fibrosis) was 0.806.

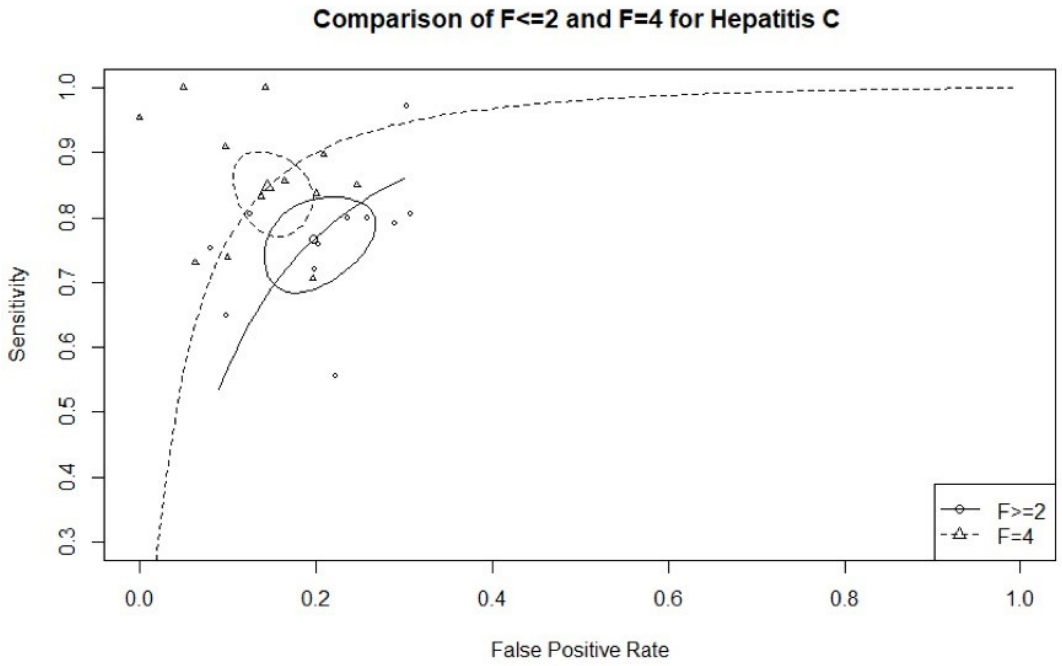
The following studies did not report the AUROC, but reported other measures of the accuracy of VTq for the diagnosis of fibrosis or cirrhosis.

In a retrospective study published only as an abstract (LazAr 2018), involving 102 patients with hepatitis C virus (HCV) compensated liver cirrhosis, TE performed significantly better than VTQ (correctly diagnosing 92.1% versus 79.4% of patients against a “gold standard” of a diagnosis of cirrhosis based on clinical, biological, and ultrasound criteria rather than biopsy, p = 0.04).

In a prospective study of 100 consecutive patients diagnosed with HCV liver cirrhosis, TE elastography had 94.6% accuracy in diagnosing cirrhosis, compared with pSWE (VTq) 79.3% (p=0.06) (Lupusoru 2016).

One study (Lopez 2018), set in a Spanish tertiary hospital, reported on costs for the assessment of liver fibrosis using TE on all patients (current practice) or selecting some patients to have ARFI (VTq) instead of TE. In this study, the authors identified patients in whom the TE and ARFI would likely give concordant results (based on viral load, left liver lobe size and spleen size). Ultrasound normal spleen size (odds ratio [OR], 0.20; 95% CI 0.05–0.91) and high viral load (OR, 0.36; 95% CI 0.17– 0.77) reduced the probability of agreement between TE and ARFI, whereas ultrasound normal left liver lobe size (OR, 3.32; 95% CI, 1.21–9.10) increased this probability. The authors then proposed an algorithm for the assessment of patients. The proposed algorithm starts with the liver ultrasound, as this step is included in the routine evaluation of patients with chronic hepatitis C as screening for hepatocellular carcinoma and portal hypertension. Patients with a probability of concordance of ≥0.70 (47.2% of the sample in this study) would be investigated only with VTq during the ultrasound, while those with a probability <0.70 (the remaining 52.8%) would go on to have TE after the ultrasound. The assessment of LF resulted in a higher cost per patient for TE (€556.93) than for ARFI (€327.93). The incremental cost-effectiveness ratio of TE compared with ARFI to increase concordance by 1% was €8.86. Application of the algorithm generated savings of €108,067 per cohort of 1000 patients. The savings generated by the algorithm would make it possible to study 241 patients more per 1000 patients than when only TE is used.

The summary estimates for diagnostic testing of hepatitis C indicates that diagnostic testing for F = 4 is more accurate than for F>=2; however, the confidence intervals overlap (sensitivity: F≥2: 76.6% [95% CI 70.1%–82.0%]; F=4: 84.7% [78.8%–89.2%]; false positive rate: F≥2: 19.7% [95% CI 15.2%–25.3%]; F=4: 14.6% [95% CI 11.3%–18.6%]).


Comparison of F<=2 and F=4 for Hepatitis C
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
F>=2
F=4

Hepatitis B

We included six studies (Cano 2014, Dong 2015, Dong 2016, Nishimura 2016, Su 2018, Tai 2015) providing cross-sectional data comparing the number of patients identified as having fibrosis by the VTq method versus a reference standard (usually liver biopsy, unless stated to be TE).

A meta-analysis (published only as an abstract) in patients with hepatitis B included 4 studies and a total of 476 patients (Cano 2014). The included studies were not listed in the abstract. VTq had a pooled sensitivity of 67% (95% CI 0.62 to 0.73; P = 0.000) and pooled specificity of 87% (95% CI 0.82 to 0.92; P = 0.4793). The ROC showed a significant diagnostic value of ARFI in assessing liver fibrosis with an AUC of 0.9359.

Five subsequent studies were included.

A cross-sectional study (Dong 2015) involved 81 consecutive patients with chronic hepatitis B (CHB) in China, tested with the SEQUIOA512 color ultrasound diagnostic system (Siemens).

In a cross-sectional study involving a total of 1210 patients with chronic liver disease, data were presented for the subgroups of patients with chronic hepatitis B and C (n not stated) (Nishimura 2016). The AUC for patients with hepatitis B for F3-4 (advanced fibrosis) was 0.695.

In a prospective study involving 206 patients with chronic hepatitis B and 40 healthy volunteers, there was a high correlation between the staging of ARFI and the hepatic histology, with correlation coefficient 0.845 (95% CI 0.805-0.877; p< 0.001) (Dong 2016).

In a retrospective cohort study (Su 2018) of 559 patients with chronic hepatitis B, Pearson correlation showed that the VTq value increased significantly by Metavir fibrosis score (p for trend < 0.001).

Tai 2015 conducted a cross-sectional study involving 121 patients with chronic hepatitis B and 83 with chronic hepatitis C. The 2 x 2 tables could be calculated for F=4 for hepatitis B and C separately. Exclusion of F2 fibrosis may be more accurate when inflammation is less active (Sherman 2017), e.g. the correlation between ARFI and METAVIR fibrosis scores improved after excluding patients with ALT levels ≥5 times the upper limit of normal (Tai 2015).

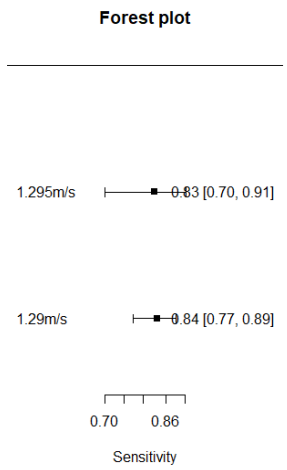
The diagnostic accuracy parameters of these studies are summarised in Table 4 for F≥2 and Table 5 for F=4, and full study details are in Appendix B. Those excluded due to data limitations are shaded grey.

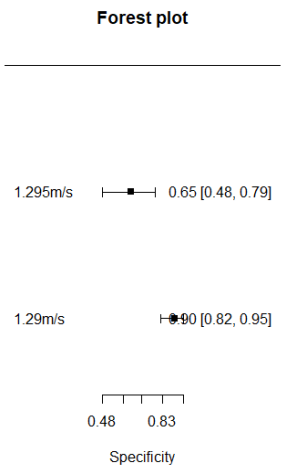
Table 4. Diagnostic accuracy parameters for diagnosis of F≥2 in patients with hepatitis B.

Hep B	Fibrosis stage (n) diagnosed by biopsy					For F≥2										
Study	**F0**	**F1**	**F2**	**F3**	**F4**	**Cut-off (m/s)**	**TP**	**FP**	**FN**	**TN**	**Sens (%)**	**Spec (%)**	**PPV**	**NPV**	**AUROC**	**DOR**
Cano 2014	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	67	87	NA	NA	0.9359	NA
Dong 2015	9	25	25	16	6	1.295m/s	39	12	8	22	82.9	65.0	76.5	73.3	0.762	8.94
Dong 2016	40	41	52	59	54	1.29m/s	138	8	27	73	83.6	90.1	94.5	73.0	0.91	46.6
Nishimura 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Su 2018**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tai 2015	4	29	36	9	43	1.17m/s	NA	NA	NA	NA	76.6	79.3	NA	NA	0.857	NA

** Reference standard = TE.

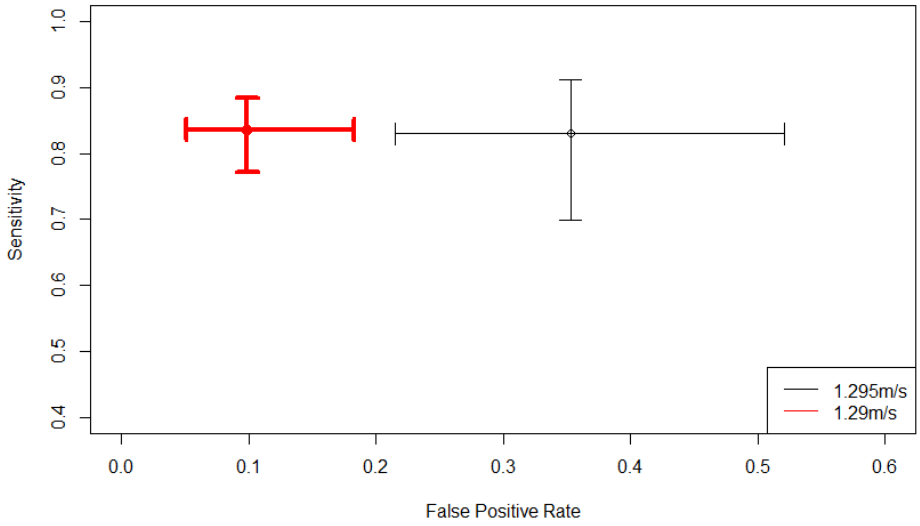
Descriptive statistics for a data set include the sensitivity and specificity of the primary studies and also their DOR. Sensitivity and specificity are presented in forest plots including 95% confidence intervals. Analyses are limited by the small number of studies.





Cut-Off	DOR	2.5%	97.5%
1.295m/s	8.937	3.171	25.187
1.29m/s	46.639	20.167	107.860

A crosshair plot with arbitrary colouring was used to visual the data. Paired lines show the corresponding 95% confidence intervals for sensitivity and false positive rate (1-specificity). Crosshairs are weighted, with wider lines indicating increased sample size.



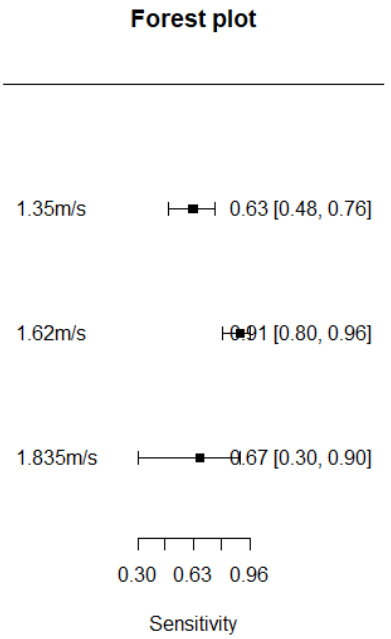
In the presence of between-study heterogeneity, especially with unbalanced study sizes, caution is needed in applying meta-analytical methods to few studies (Seide 2019), so SROC analysis was not conducted.

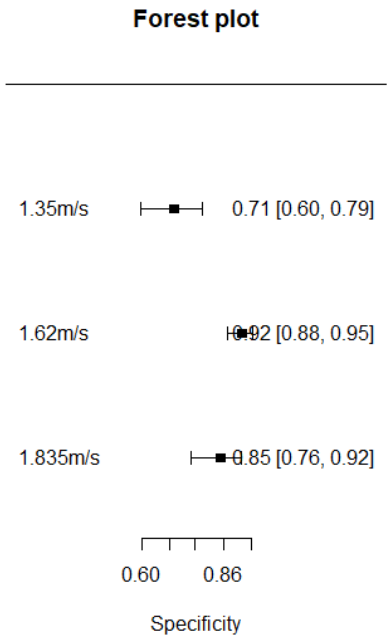
Table 5. Diagnostic accuracy parameters for diagnosis of F=4 in patients with hepatitis B.

Hep B	Fibrosis stage (n) diagnosed by biopsy					For F=4										
Study	**F0**	**F1**	**F2**	**F3**	**F4**	**Cut-off (m/s)**	**TP**	**FP**	**FN**	**TN**	**Sens (%)**	**Spec (%)**	**PPV**	**NPV**	**AUROC**	**DOR**
Cano 2014	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dong 2015	9	25	25	16	6	1.835/s	4	11	2	64	66.7	85.5	26.7	97.0	0.723	11.6
Dong 2016	40	41	52	59	54	1.62m/s	49	15	5	177	90.7	92.2	76.0	97.2	0.96	115.6
Nishimura 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Su 2018**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tai 2015	4	29	36	9	43	1.35m/s	27	23	16	55	62.8	70.5	54	77.5	0.707	4.03

** Reference standard = TE.

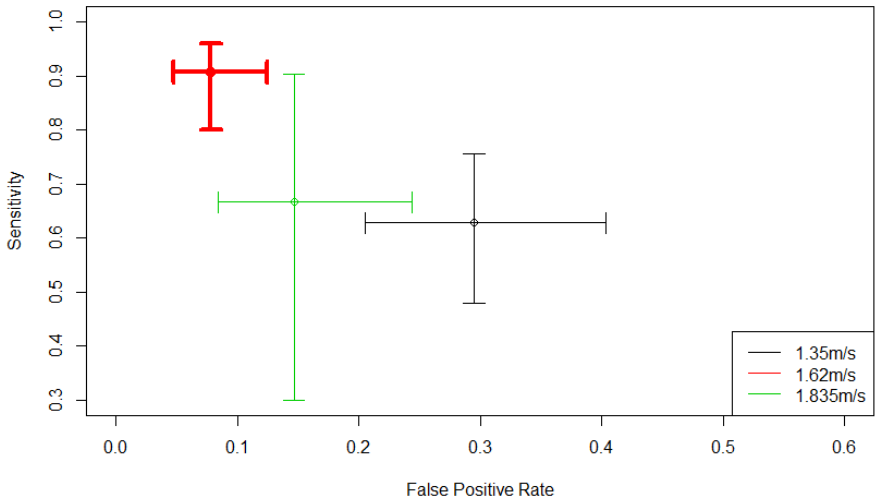
Descriptive statistics for a data set include the sensitivity and specificity of the primary studies and also their DOR. Sensitivity and specificity are presented in forest plots including 95% confidence intervals.





Cut-Off	DOR	2.5%	97.5%
1.35m/s	4.035	1.837	8.864
1.62m/s	115.640	40.047	333.920
1.835m/s	11.636	1.897	71.383

In addition, a crosshair plot is provided.



Mixed population of hepatitis B and C

We included one study (Jain 2016) providing cross-sectional data comparing the number of patients identified as having significant fibrosis (F≥2) or cirrhosis (F=4) by the VTq method versus liver biopsy as the reference standard. (Note Nishimura 2016 and Tai 2015 included patients with hepatitis B or C but reported results separately, so these studies are included separately in both of the above two sections, not here.) This cross-sectional study in India involved 69 patients, mean age 34.7 years, 49 (71%) male, of whom 51 (74%) had HCV infection, 16 (23%) had HBV infection and 2 (3%) had combined HBV and HCV infection (Jain 2016). Diagnostic accuracy was assessed versus liver biopsy using the Ishak scoring system which comprises a seven-point (F0-F6) scale. ARFI liver propagation velocity was positively correlated to histology with Spearman's correlation coefficient rho = 0.789 ($p<0.0001$). Thus the mean shear-wave velocity (SWV) showed an increasing trend with increasing grade of fibrosis. The parameters are shown in Table 6 for F≥2 and Table 7 for F=4. These are not shown graphically as there was only one study.

Table 6. Diagnostic accuracy parameters for diagnosis of F≥2 in patients with hepatitis B or C.

Hep B or C	Fibrosis stage (n) diagnosed by biopsy					F≥2										
Study	F0	F1	F2	F3	F4	Cut-off (m/s)	TP	FP	FN	TN	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUROC	DOR
Jain 2016	13	29	6	5	12	1.347 m/s	21	7	2	35	91.3	83.7	75	95	NA	52.5

Table 7. Diagnostic accuracy parameters for diagnosis of F=4 in patients with hepatitis B or C.

Hep B or C	Fibrosis stage (n) diagnosed by biopsy					F=4										
Study	F0	F1	F2	F3	F4	Cut-off (m/s)	TP	FP	FN	TN	Sens (%)	Spec (%)	PPV	NPV	AUROC	DOR
Jain 2016	13	29	6	5	12	1.92 m/s	11	2	1	51	91.7	96.2	85	98	NA	280.5

Children

As noted in the NICE guidelines on the assessment and management of non-alcoholic fatty liver disease (NAFLD; NG49), few non-invasive techniques to

diagnose advanced liver fibrosis have been assessed in children and young people (NICE 2016). We found no studies in children and young people that had been published in the database searches. We found one completed study in clinicaltrials.gov that involved children (NCT01781208) which reported study results on that website but was not linked to any publications.

Limitations

The main limitation with this review is that studies were only included if the publication stated the technology was “VT’ or ‘virtual touch’, in line with the Scope. However, there is a risk that some studies using this technology were excluded because the software was described using different terms.

4.5. Ongoing trials

The Clinical trials.gov (http://clinicaltrials.gov/ct2/home), WHO International Clinical Trial Registry Platform (ICTRP): (covering a number of registries) (http://apps.who.int/trialsearch/) and the ISRCTN website (http://www.isrctn.com/) were searched between 28/06/2019 – 12/07/2019, and the following completed and ongoing trials were found. Details are reported in Appendix B.

In one study of VTq in children (n=62) undergoing liver biopsy for known or suspected non-neoplastic liver disease (not stated to be hepatitis; NCT01781208), VTq was correlated with liver fibrosis score (correlation oefficient r-0.68). This study was stated to be completed but was not linked to any publications.

One study in Taiwan (NCT01268865) was designed to examine the correlation between VTq and fibrosis stage in HBV or HCV-infected patients; recruitment status was stated to be unknown and no results were posted.

4.6. Changes in costs

The manufacturer advises that as of October 1st 2019 all VTq and pSWE software systems will cost [redacted] excluding VAT. The VTq functionality is provided on the ACUSON S2000 and the S3000 and pSWE functionality on the ACUSON Sequoia. This is slightly lower than the price charged when the NICE guidance was developed [redacted]

The VTq software has also been added to the ACUSON Juniper, for liver indications. The price of VTq on this system is slightly lower being [redacted] excluding VAT. The same price applied when the NICE guidance was developed.

A new system, the ACUSON Redwood, will support liver assessment using pSWE technology. It is due to be launched later this month and until then no prices are available. The company advises it would like this system to form part any updates to the NICE guidance.

The annual maintenance costs and cost of a 1-year warranty and 4 years fully comprehensive contract, all exclusive of VAT are:

- ACUSON S2000, [redacted]
- ACUSON Juniper, [redacted]
- ACUSON S3000 AND ACUSON Sequoia [redacted]

These are the same as those adopted in the cost model informing the NICE guidance.

Hence the VTq costs have not materially changed from those used in the cost model.

4.7. Other relevant information

Across thirty-seven NHS organisations ACUSON S2000, S3000 or Sequoia are being used.

Expert advice was received from 4 clinical experts. All 4 experts have experience using the technology. One expert noted that the technology can be used for other clinical indications (e.g. assessment of breast lesion stiffness or thyroid nodules) if made available in primary and secondary care. The expert also noted that VTq reduces the need for liver biopsy, is a useful tool in non-invasive assessment of liver disease and is more reliable and cost-effective when compared with fibroscan and transient elastography. A clinical expert noted the presence of variations in measurements across manufacturers and the need for the bench marking of multivendor information. The expert also stated that there is a slight discrepancy between results presented in kPa and those in m/s. One expert suggested using the ARFI (VTq) technology for patients who have spurious results from Fibroscan or if they have contraindications in its use.

The company reported that since the guidance, the technology has been explored in other etiologies of liver disease beyond Hepatitis B and C, including NAFLD and evaluation of portal hypertension and risk of oesophageal varices as indicated by spleen stiffness measurement. Two-dimensional SWE (VTIQ on the S2000 and S3000), has been studied in evaluation of breast lesions as complementary to BI-RADS for BI_RADS 3 and 4 lesions, to potentially reduce the number of negative biopsies. In Thyroid applications, there is new evidence that VTIQ can add further characterize thyroid nodules and Hashimoto’s thyroiditis. The technology has

also been studied in lymph nodes for likelihood of malignancy based on increased stiffness above a certain level.

5. Conclusion

Twenty-two papers were included. Fifteen of the papers evaluated VTq in adults with hepatitis C only (of which one was a systematic review that included a further 4 usable studies), 4 in adults with hepatitis B only, 2 in mixed populations of hepatitis B and C (shown separately) and 1 in mixed hepatitis B and C (analysed together). For hepatitis C, analyses for F≥2 yielded a pooled estimate for sensitivity of 77% and a specificity of 80%, suggesting good estimate accuracy with the summary AUC reaching 0.853. For F=4, the pooled estimate for sensitivity was 85% and specificity 85%, suggesting good estimate accuracy with the summary AUC being 0.853.

The evidence is more limited for hepatitis B. We included one meta-analysis (published only as an abstract) which included 4 studies and a total of 476 patients and found a pooled sensitivity of 67% (95% CI 0.62 to 0.73) and pooled specificity of 87% (95% CI 0.82 to 0.92). The ROC showed a significant diagnostic value of ARFI in assessing liver fibrosis with an AUC of 0.9359. We found five subsequent studies but only two had data that could be pooled for F≥2. The sensitivity, specificity and DOR for the two studies were 82.9% and 65.0%; 83.6% and 90.1%; and 8.94 and 46.6, respectively. Three studies had data for F=4. The sensitivity was 66.7%, 90.7% and 62.8%, respectively; specificity was 85.5%, 92.2% and 70.5%, respectively; and DOR was 11.6, 115.6 and 4.03, respectively. Due to the between-study heterogeneity, especially with unbalanced study sizes, SROC analysis was not conducted.

There was significant heterogeneity between studies, which used a variety of cut-off values to define the different thresholds between the fibrosis stages. Of note, guidelines state that differing manufacturers have different cut-offs for shear wave velocities for the various stages of liver disease; practitioners are advised to refer to individual manufacturers' reference ranges (SCoR/BMUS 2019). Also, VTq values should be interpreted taking into account results of other tests and the clinical context (MTG27 and Barr, 2015). These conclusions are in line with the previous guidance.

The additional studies identified in this update provide more robust data for sensitivity and specificity of VTq that could be used in an updated cost-effectiveness model. As shown in Table 8, for hepatitis C, the differences between the updated values and values used in the original model are relatively minor. No updated pooled data are available for hepatitis B because of data limitations. The range of values reported in the studies included in this

evidence update for sensitivity and specificity are wide and their implications for modelling difficult to predict.

Table 8. Comparison of original and updated measures of accuracy by disease

Disease	Sensitivity		Specificity	
	Update	Original	Update	Original
Hep C F≥2	77%	79%	80%	79%
Hep C F=4	85%	85%	85%	82%
Hep C F≥2	83% to 84%	79%	65% to 90%	87%
Hep C F=4	63% to 91%	93%	71% to 92%	77%

In terms of costs, the company advises that the initial purchase price and maintenance costs have been aligned across several models. However, these are essentially the same as those adopted in the cost model informing the NICE guidance.

Only one study was identified, in patients co-infected with HIV and hepatitis C (Lopez 2018). This study identified an algorithm in which patients whose fibrosis could be identified by VTq just as accurately as if they had a TE would only have the VTq during their ultrasound (which they would be having anyway) and hence omit the TE test. Transient elastography would be reserved for those patients in whom TE would be more accurate than VTq. This study may have relevant data to update the cost effectiveness model.

Appendix A – Relevant guidance

NICE guidance – published

- Virtual Touch Quantification to diagnose and monitor liver fibrosis in chronic hepatitis B and C. Medical technologies guidance. Published: 23 September 2015. www.nice.org.uk/guidance/mtg27

Other published NICE guidelines and standards

- Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults NICE clinical guideline 165 (June 2013). Available from http://publications.nice.org.uk/hepatitis-b-chronic-cg165
- Cirrhosis in over 16s: assessment and management (NG50) July 2016. Available from: https://www.nice.org.uk/guidance/ng50
- Hepatitis B (QS65) Quality standard Published July 2014. Available from: https://www.nice.org.uk/search?q=Hepatitis+B
- Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. NICE public health guidance PH43 (December 2012). Available from: http://guidance.nice.org.uk/PH43
- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. NICE diagnostics guidance DG5 (August 2012). Available from: http://guidance.nice.org.uk/DG5
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE Technology appraisal guidance TA253 (April 2012). Available from: http://guidance.nice.org.uk/TA253
- Extracorporeal albumin dialysis for acute liver failure. NICE Interventional procedure guidance IPG316 (September 2009). Available from: http://www.nice.org.uk/guidance/IPG316
- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance TA153 (August 2008). Available from: http://www.nice.org.uk/guidance/TA153 Date for review: October 2011 Review decision.
- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance TA252 (April 2012). Available from: http://guidance.nice.org.uk/TA252
- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance TA96 (February 2006) Available from: http://www.nice.org.uk/guidance/TA96 Date for review: October 2011 Review decision

- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal guidance TA106 (August 2006) Available from: http://www.nice.org.uk/guidance/TA106
- Tenofovir disoproxil fumarate for the treatment of hepatitis B. NICE technology appraisal guidance TA173 (July 2009) Available from: http://guidance.nice.org.uk/TA173
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance TA75 (January 2004). Available from: http://guidance.nice.org.uk/TA75
- Telbivudine for the treatment of chronic hepatitis B. NICE Technology appraisal guidance TA154 (August 2008). Available from: http://guidance.nice.org.uk/TA154
- Hepatitis C - peginterferon alfa and ribavirin. NICE Technology appraisal guidance TA200 (September 2010). Available from: http://guidance.nice.org.uk/TA200
- Subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites. NICE interventional procedure guidance IPG479 (February 2014). Available from http://publications.nice.org.uk/subcutaneous-implantation-of-a-battery-powered-catheter-drainage-system-for-managing-refractory-and-ipg479

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Subcutaneous implantation of the ALFA pump System to manage ascites in patients with cirrhosis of the liver. NICE interventional procedure guidance expected: unknown https://www.nice.org.uk/guidance?action=byId&o=13735
- A proposed quality standard on Hepatitis C [GID-QS10126] Expected publication date: To be confirmed https://www.nice.org.uk/guidance/proposed/gid-qs10126

NICE pathways

- Hepatitis B (chronic) (2019) NICE pathway: this pathway states that the case for adopting Virtual Touch Quantification (VTq) software to diagnose and monitor liver fibrosis is supported by the evidence (referenced to MTG27).
- Hepatitis B and C testing. Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. Available from: https://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator and NICE CKS

- None relevant.

Guidance from professional bodies other than NICE

Guidelines reporting on VTq separately

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines **2017** update (Dietrich 2017) on the use of liver ultrasound elastography state that:

- In patients with chronic hepatitis C (CHC):
    - VTq cut-offs of 1.21–1.34m/s predict significant fibrosis (F ≥2) (AUROC 0.85–0.89);
    - the diagnostic performance of VTQ is comparable to TE with high accuracy for predicting severe fibrosis (F ≥3, AUROC 0.91);
    - cut-offs of 1.55–2m/s (AUROC 0.89–0.93) predict cirrhosis;
    - discordance (>one fibrosis stage) between VTQ and histology can occur, so pSWE results require cautious interpretation.
- In chronic hepatitis B (CHB):
    - VTQ has a lower failure rate and similar diagnostic performance to TE;
    - the best cut-off for ≥F2 was 1.35m/s (AUROC 0.88)
    - the best cut-off for ≥F4 was 1.87m/s (AUROC 0.93).

The European Association for the Study of the Liver (EASL) guidelines (Castera **2015**) reported the diagnostic performance of pSWE using ARFI (VTq; Siemens) for F≥2 and F4 in chronic liver diseases including HBV and HCV. The largest study evaluating pSWE/ARFI for staging of chronic hepatitis C was a retrospective pooled analysis of 914 international patient data (Sporea 2012), part of which were published in smaller single centre studies previously (Fierbinteanu-Braticevici 2009, Friedrich-Rust 2009, Takahashi 2010, Piscaglia 2011, Sporea 2011, Ebinuma 2011). It reported sensitivity and specificity of pSWE/ARFI for the diagnosis of significant fibrosis of 0.69 and 0.80 and for the diagnosis of liver cirrhosis of 0.84 and 0.76, respectively. (Castera 2015).

The Japan Society of Ultrasonics in Medicine (JSUM) ultrasound elastography practice guidelines (Kudo 2013) recommended that VTQ is indicated for

patients with chronic liver disease, particularly viral hepatitis, requiring the diagnosis of liver fibrosis. This was based on data from the following studies:

- Friedrich-Rust et al. (2009), who included patients with hepatitis B or C, and used the cut-off value of 1.75 m/s for fibrosis of F2 or above and obtained a sensitivity of 81.8%, specificity of 91.5%, positive predictive value of 78.3%, negative predictive value of 93.1% and AUC of 0.82 (95% CI 0.73–0.91).
- Sporea et al (2012), who included patients with hepatitis C, and reported the following cut-off values and diagnostic accuracy parameters:

	Cut-off (m/s)	**AUROC**	**Sensitivity (%)**	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**	**Accuracy (%)**
F≥1	>1.19	0.779	69.9	80	95.4	16	70.4
F≥2	>1.33	0.792	69.1	79.8	87.3	56.1	72.6
F≥3	>1.43	0.829	74.8	81.5	76.3	79.8	78.2
F= 4	>1.55	0.842	84.3	76.3	53.1	93.7	77.9

Guidelines reporting on SWE including VTq

The World Federation for Ultrasound in Medicine and Biology (WFUMB) published guidelines in **2018** on liver ultrasound elastography, and included the VTq ACUSON S2000 and 3000 in the point shear wave elastography section, but not the Jupiter (Ferraioli 2018). They note that:

- Cut-offs for staging liver fibrosis are system-specific.
- The impact of hepatic steatosis on liver stiffness is uncertain. Clinicians should exercise caution when interpreting liver stiffness results in patients with severe steatosis and obesity.
- SWE is useful to exclude significant fibrosis and diagnose cirrhosis in patients with untreated chronic hepatitis B.
- In hepatitis B, liver stiffness usually decreases during antiviral treatment with analogues. Screening for hepatocellular carcinoma and portal hypertension should continue despite decreased liver stiffness in patients with advanced disease.
- SWE is the preferred method as the first-line assessment for the severity of liver fibrosis in untreated patients with chronic viral hepatitis C. It is useful to rule out advanced disease.

- Liver stiffness decreases significantly after sustained virological response to treatment of hepatitis C with interferon-based therapies or direct-acting antiviral agents. However, liver stiffness cannot be used to stage liver fibrosis or rule out cirrhosis, given the loss of accuracy of cutoffs defined in viremic patients. Screening for hepatocellular carcinoma and portal hypertension should continue despite decrease in liver stiffness in patients with advanced disease.
- SWE can be used for liver stiffness assessment in NAFLD patients to rule out advanced fibrosis and select patients for further assessment.
- SWE can be used for liver stiffness assessment in patients with ALD to rule out advanced disease. Caution is needed in patients with ongoing alcohol abuse or with acute alcoholic hepatitis.
- SWE has high diagnostic accuracy for detecting cirrhosis, better at ruling out (high negative predictive value >90%) than ruling in.
- There is insufficient evidence to make a recommendation on the use of SWE for liver stiffness assessment in pediatric patients.
- There is insufficient evidence to make a recommendation on the use of SWE for differentiation between benign and malignant lesions and characterization of focal liver lesions.
- Interpretation of liver stiffness measurements needs to be taken in context with the other clinical and laboratory data.

The Society of Radiologists in Ultrasound consensus panel (of radiology, hepatology, pathology, basic science and physics specialists) on elastography in the assessment of liver fibrosis in chronic liver disease (Barr, 2015) recommended that:

- Patients with decompensated cirrhosis can be diagnosed clinically; those without overt decompensated cirrhosis can be assessed with elastography.
    - Those with normal elastography values have a low likelihood of cirrhosis (stage F0 or F1) and may not require additional follow-up,
    - those with high elastography values have a high likelihood of cirrhosis,
    - and those in between who have moderate to severe fibrosis (stages F2 and F3) may be at risk for progression of the fibrosis.
- Suggested thresholds for elastography measurements of liver stiffness in hepatitis C for Siemens technologies (m/sec; not only VTq) are:
    - Fibrosis ≥2: 1.34 (5.7)
    - Fibrosis ≥3: 1.55 (7.3)
    - Fibrosis ≥4: 1.80 (10)

Guidelines with no mention of VTq

The Canadian Agency for Drugs and Technologies in Health (CADTH rapid response report: Non-Invasive Imaging Modalities for the Diagnosis and Monitoring of Liver Fibrosis: Diagnostic Accuracy, Clinical Effectiveness/ Utility, Cost-Effectiveness, and Guidelines (CADTH 2017) did not mention VTq.

The update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver (Myers 2015) did not mention VTq.

The WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015) also did not mention VTq.

The WHO guidelines for the screening, care and treatment of persons with hepatitis C infection (WHO 2014) also did not mention VTq.

Other

- Patient (2019) Chronic hepatitis. This reference states that "Point shear wave elastography and transient elastography have been shown to be simple and effective methods of assessing liver fibrosis" referenced to Jiang W, Huang S, Teng H, et al; Diagnostic accuracy of point shear wave elastography and transient elastography for staging hepatic fibrosis in patients with non-alcoholic fatty liver disease: a meta-analysis. BMJ Open. 2018 Aug 238(8):e021787. doi: 10.1136/bmjopen-2018-021787. This reference (Jiang 2018) excluded patients with hepatitis B or C.
- Patient (2019) Cirrhosis. This reference states that: "Either transient elastography or acoustic radiation force impulse imaging (whichever is available) should be used to diagnose cirrhosis for people with NAFLD and advanced liver fibrosis. Liver biopsy should be considered to diagnose cirrhosis in people for whom transient elastography is not suitable" referenced to Cirrhosis in over 16s - assessment and management; NICE Guideline (July 2016), but is for patients with NAFLD not hepatitis.
- The Society & College of Radiographers and The British Medical Ultrasound Society (SCoR/BMUS) (2105 revision December 2018 and minor amendments March 2019) Guidelines for professional ultrasound practice. This document states: "Recent (2015) advice from NICE (MTG27), advocates elastography in the diagnosis and monitoring of fibrosis in chronic hepatitis. The economic benefits of using elastography is explored in the guideline, a saving of around £434 per patient is quoted when using Virtual Touch Quantification (VTq) over

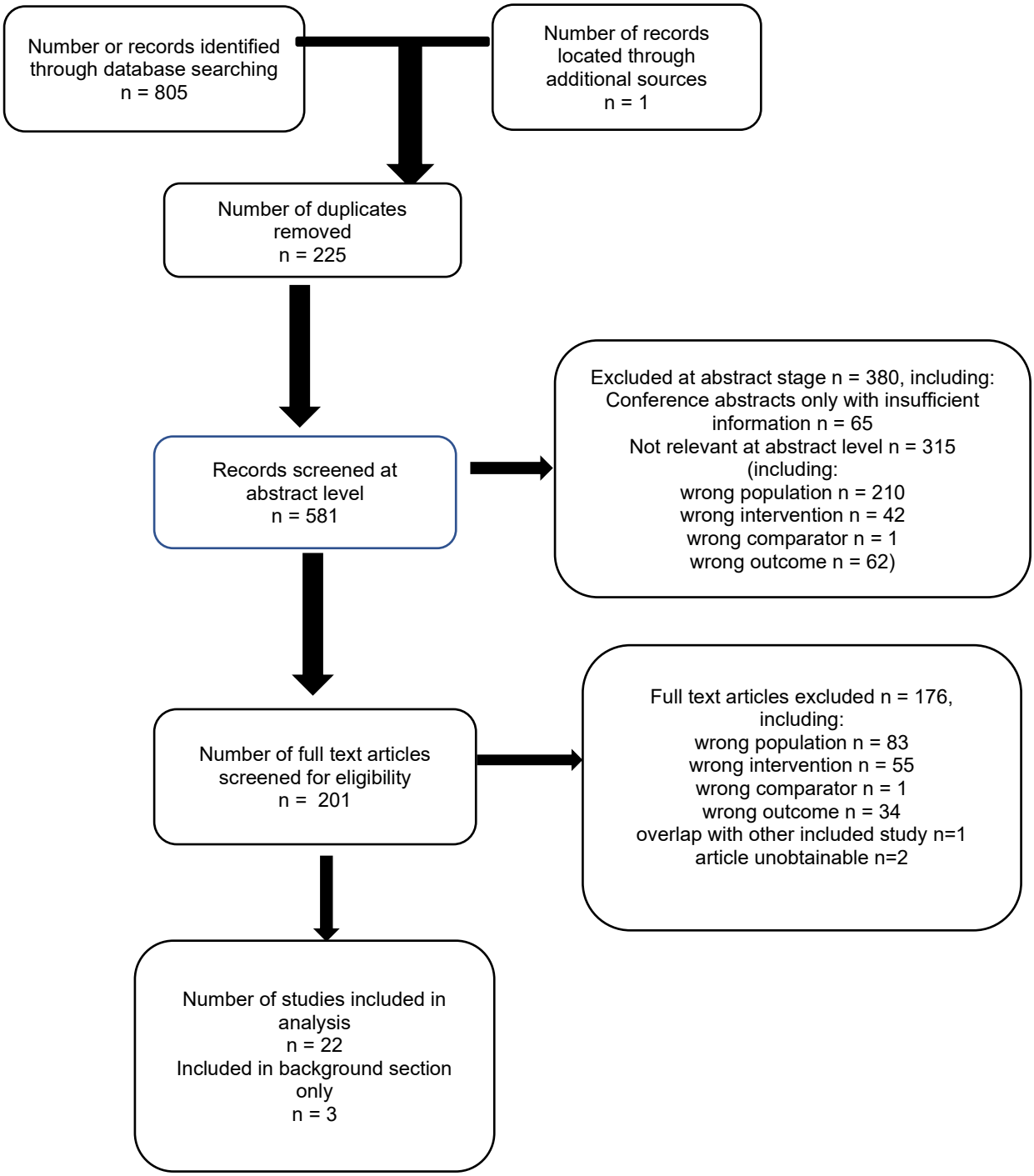
conventional liver biopsy. The safety implications to patients should also be considered as well as its tolerability and its ability to be undertaken in an outpatient setting. Giving the economic challenges facing healthcare today, this technique could have the potential to deliver large savings. http://nice.org.uk/guidance/mtg27." It goes on to state (under "Clinical Application") that: "Whilst differing manufacturers have different shear wave velocities for stages of liver disease it is noted that the following (based on the VTq imaging as described in the NICE publication [i.e. MTG27]) are given as examples of disease staging

- Normal < 1.2 m/s
- Fibrosis ≥ 1.21 – 1.34 m/s
- Cirrhosis ≥ 1.55 – 2.00 m/s

Extreme caution is required when quoting shear wave velocities in ultrasound reports. It is useful to report the shear wave velocity and quote the relevant reference values for the machine used to minimise confusion between normal and abnormal readings compared to the stage of liver disease. Practitioners are advised to refer to individual manufacturers' reference ranges when reporting shear wave studies in liver disease."

Appendix B – Details of included and excluded studies in the review and completed/ongoing trials

PRISMA diagram



List of studies excluded at full text and reasons

Ahn SJ, Lee JM, Chang W, Lee SM, Kang H-J, Yang H, et al. Prospective Validation of Intra- and Interobserver Reproducibility of a New Point Shear Wave Elastographic Technique for Assessing Liver Stiffness in Patients with Chronic Liver Disease. Korean journal of radiology. 2017;18(6):926-35.	Wrong population
Akdogan E, Yilmaz FG. The role of acoustic radiation force impulse elastography in the differentiation of benign and malignant focal liver masses. Turkish Journal of Gastroenterology. 2018;29(4):456-63.	Wrong population
Alem, S. A. et al. Improvement of liver stiffness measurement, acoustic radiation force impulse measurements, and noninvasive fibrosis markers after direct-acting antivirals for hepatitis C virus G4 recurrence post living donor liver transplantation: Egyptian cohort. Journal of Medical Virology 2018; 90(9): 1508-1515.	Wrong outcome
Alfageme Zubillaga, M. et al. ARFI elastography: changes after direct-acting antiviral treatment in transplanted livers with relapse of hepatitis C virus infection. Radiologia 2017; 59(2): 139-146.	Wrong outcome
Alkhouri N. Putting it all together: Noninvasive diagnosis of fibrosis in nonalcoholic fatty liver disease in adults and children. Clinical Liver Disease. 2017;9(6):134-7.	Wrong population
Almpanis Z, Demonakou M, Tiniakos D. Evaluation of liver fibrosis: "Something old, something new...". Annals of Gastroenterology. 2016;29(4):445-53.	Wrong intervention
Amador Carrascal C, Chen S, Urban MW, Greenleaf JF. Acoustic Radiation Force-Induced Creep-Recovery (ARFICR): A Noninvasive Method to Characterize Tissue Viscoelasticity. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2018;65(1):3-13.	Wrong population
Anonymous. Erratum to: Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis. Journal of Gastroenterology. 2015;50(6):705.	Wrong population
Aoki T, Iijima H, Nakano C, Ishii A, Takashima T, Aizawa N, et al. VF map scores (virtual touch quantification, fasting plasma glucose, male, age, platelets) for prediction of hepato-carcinogenesis. Liver Cancer. 2015;4(SUPPL. 1):232-3.	Wrong outcomes
Asrani, S. K. Incorporation of Noninvasive Measures of Liver Fibrosis Into Clinical Practice: Diagnosis and Prognosis. Clinical Gastroenterology and Hepatology 2015; 13(12): 2190-2204	Overlap with other included study
Attia, Dina et al. Different kinetics of liver stiffness using shear wave elastography in patients with chronic hepatitis C infection treated with interferon-free regimens. European journal of gastroenterology & hepatology 2019; 31(1): 67-74	Article unobtainable
Belei O, Sporea I, Gradinaru-Tascau O, Olariu L, Popescu A, Simedrea I, et al. Comparison of three ultrasound based elastographic techniques in children and adolescents with chronic diffuse liver diseases. Medical Ultrasonography. 2016;18(2):145-50.	Wrong population
Bert F, Stahmeyer JT, Rossol S. Ultrasound Elastography Used for Preventive Non-Invasive Screening in Early Detection of Liver Fibrosis. Journal of clinical medicine research. 2016;8(9):650-5.	Wrong population
Berzigotti A, Reverter E, Garcia-Criado A, Abraldes JG, Cerini F, Garcia-Pagan JC, et al. Reliability of the estimation of total hepatic blood flow by Doppler ultrasound in patients with cirrhotic portal hypertension. Journal of hepatology. 2013;59(4):717-22.	Wrong outcomes

Bignulin S, Falleti E, Cmet S, Cappello D, Cussigh A, Lenisa I, et al. Usefulness of acoustic radiation force impulse and fibrotest in liver fibrosis assessment after liver transplant. Annals of hepatology. 2016;15(2):200-6.	Wrong population
Bignulin S, Falleti E, Cmet S, Cappello D, Cussigh A, Lenisa I, et al. Usefulness of acoustic radiation force impulse and fibrotest in liver fibrosis assessment after liver transplant. Annals of Hepatology. 2016;15(2):200-6.	Wrong population
Brener S. Transient elastography for assessment of liver fibrosis and steatosis: An evidence-based analysis. 2015;15(18).	Wrong intervention
Cafolla A, Gentile G. Anticoagulant therapy with fondaparinux in a liver transplant patient with thrombosis and liver fibrosis: a case report. Clinical Case Reports. 2017;5(3):342-5.	Wrong population
Canas T, Macia A, Munoz-Codoceo RA, Fontanilla T, Gonzalez-Rios P, Miralles M, et al. Hepatic and Splenic Acoustic Radiation Force Impulse Shear Wave Velocity Elastography in Children with Liver Disease Associated with Cystic Fibrosis. BioMed Research International. 2015;2015:517369.	Wrong population
Cantero I, Abete I, Marin-Alejandre A, Monreal JI, Elorz M, Herrero JI, et al. Retinol-binding protein-4 levels and liver fat content in subjects with non-alcoholic fatty liver disease and obesity. Annals of Nutrition and Metabolism. 2018;73(Supplement 2):45.	Wrong population
Carvalho Santos J, Doria Batista A, Maria Mola Vasconcelos C, Souza Lemos R, Romao de Souza Junior V, Dessein A, et al. Liver ultrasound elastography for the evaluation of periportal fibrosis in schistosomiasis mansoni: A cross-sectional study. PLoS Neglected Tropical Diseases. 2018;12(11):e0006868.	Wrong population
Cassinotto C, De Ledinghen V. Reply to: "New imaging assisted methods for liver fibrosis quantification: Is it really favorable to classical transient elastography?". Journal of Hepatology. 2015;63(3):767.	Wrong intervention
Cassinotto C, Lapuyade B, Mouries A, Hiriart JB, Vergniol J, Gaye D, et al. Non-invasive assessment of liver fibrosis with impulse elastography: Comparison of Supersonic Shear Imaging with ARFI and FibroScan. Journal of Hepatology. 2014;61(3):550-7.	Wrong intervention
Cebreiros Lopez I, Guzman Aroca F, Noguera Velasco JA, Ramirez Ruiz C, Martinez Villanueva M, De Miguel Elizaga I, et al. Clinical usefulness of ELF index in the assessment of non alcoholic fatty liver disease. Clinical Chemistry and Laboratory Medicine. 2014;52(11):eA355.	Wrong population
Cebreiros Lopez I, Guzman Aroca F, Noguera Velasco JA, Ramirez Ruiz C, Martinez Villanueva M, De Miguel Elizaga I, et al. Evaluation of ELF index as non-invasive marker of liver fibrosis in patients with hepatitis C. Clinical Chemistry and Laboratory Medicine. 2014;52(11):eA369.	Wrong outcomes
Cebreiros Lopez I, Noguera-Velasco JA, Guzman-Aroca F, Frutos-Bernal MD, Lujan-Mompean JA, Bas A. Non-invasive evaluation of non-alcoholic fatty liver disease using liver fibrosis biomarkers and acoustic radiation force-based shear stiffness. Inflammatory Intestinal Diseases. 2017;2(1):15-6.	Wrong population
Cebreiros-Lopez I, Guzman-Aroca F, Noguera-Velasco JA, Ramirez-Ruiz C, Martinez-Villanueva M, De Miguel-Elizaga I, et al. Non-invasive markers of liver fibrosis in patients with hepatitis C: Evaluation of ELF test and its correlation with acoustic radiation force impulse elastography (ARFI). Clinical Chemistry and Laboratory Medicine. 2014;52(SUPPL. 1):S1213.	Wrong outcomes
Cebreiros-Lopez I, Guzman-Aroca F, Noguera-Velasco JA, Ramirez-Ruiz C, Martinez-Villanueva M, De Miguel-Elizaga I, et al. Usefulness of ELF test as predictor of steatohepatitis and liver fibrosis in obese patients undergoing bariatric surgery. Clinical Chemistry and Laboratory Medicine. 2014;52(SUPPL. 1):S1379.	Wrong population
Cebreiros-Lopez I, Noguera-Velasco JA, Guzman-Aroca F, Martinez-Villanueva M, Ramirez-Ruiz C, Frutosbernal MD, et al. Elf test in the assessment of non alcoholic fatty liver disease. Clinical Chemistry and Laboratory Medicine. 2015;53(SUPPL. 1):S1391.	Wrong population

Chakravartty S, Jaffer O, Zen Y, Dent J, Clarke J, Sidhu P, et al. Non invasive monitoring of fatty livers in morbidly obese patients: Preliminary evaluation with acoustic radiation force impulse imaging. Gut. 2014;63(SUPPL. 1):A248-A9.	Wrong population
Chen S-H, Lai H-C, Chiang IP, Su W-P, Lin C-H, Kao J-T, et al. Changes in liver stiffness measurement using acoustic radiation force impulse elastography after antiviral therapy in patients with chronic hepatitis C. PloS one. 2018;13(1):e0190455.	Wrong intervention
Chen S-H, Peng C-Y, Chiang IP, Lai H-C, Lee C-J, Su W-P, et al. Comparison of collagen proportionate areas in liver fibrosis quantification between chronic hepatitis B and C. Medicine. 2016;95(35):e4736.	Wrong intervention
Chen S-H, Peng C-Y, Lai H-C, Chang IP, Lee C-J, Su W-P, et al. Head-to-Head Comparison between Collagen Proportionate Area and Acoustic Radiation Force Impulse Elastography in Liver Fibrosis Quantification in Chronic Hepatitis C. PloS one. 2015;10(10):e0140554.	Wrong intervention
Chen X, Wen H, Zhang X, Dong C, Lin H, Guo Y, et al. Development of a Simple Noninvasive Model to Predict Significant Fibrosis in Patients with Chronic Hepatitis B: Combination of Ultrasound Elastography, Serum Biomarkers, and Individual Characteristics. Clinical and Translational Gastroenterology. 2017;8(4):e84.	Wrong intervention
Chen Y-P, Peng J, Hou J-L. Non-invasive assessment of liver fibrosis in patients with chronic hepatitis B. Hepatology international. 2013;7(2):356-68.	Wrong intervention
Chin JL, Pavlides M, Moolla A, Ryan JD. Non-invasive markers of liver fibrosis: Adjuncts or alternatives to liver biopsy? Frontiers in Pharmacology. 2016;7(JUN):159.	Wrong population
Choi M, Kwon H, Cho J, Oh J, Nam K, Kang M, et al. Serial change of liver stiffness measured by acoustic radiation force impulse imaging in chronic liver disease: Correlation with biochemical markers. Journal of Medical Ultrasonics. 2014;41(3):311-7.	Wrong intervention
Chung JH, Ahn HS, Kim SG, Lee YN, Kim YS, Jeong SW, et al. The usefulness of transient elastography, acoustic-radiation-force impulse elastography, and real-time elastography for the evaluation of liver fibrosis. Clinical and molecular hepatology. 2013;19(2):156-64.	Wrong intervention
Conti CB, Cavalcoli F, Fraquelli M, Conte D, Massironi S. Ultrasound elastographic techniques in focal liver lesions. World Journal of Gastroenterology. 2016;22(9):2647-56.	Wrong population
Coppola, Antonio. Noninvasive assessment of liver fibrosis in patients with chronic hepatitis C (and congenital bleeding disorders): where do we stand? Seminars in thrombosis and hemostasis 2013; 39(7): 803-15	Wrong intervention
Cui J, Heba E, Hernandez C, Haufe W, Hooker J, Andre MP, et al. Magnetic resonance elastography is superior to acoustic radiation force impulse for the Diagnosis of fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease: A prospective study. Hepatology. 2016;63(2):453-61.	Wrong population
Cui J, Loomba R. Reply. Hepatology. 2016;64(6):2263.	Wrong population
De Robertis R, D'Onofrio M, Demozzi E, Crosara S, Canestrini S, Pozzi Mucelli R. Noninvasive diagnosis of cirrhosis: a review of different imaging modalities. World journal of gastroenterology. 2014;20(23):7231-41.	Wrong intervention
Dillman JR, Heider A, Bilhartz JL, Smith EA, Keshavarzi N, Rubin JM, et al. Ultrasound shear wave speed measurements correlate with liver fibrosis in children. Pediatric Radiology. 2015;45(10):1480-8.	Wrong population
Dina I, Braticevici CF. Idiopathic colonic varices: Case report and review of literature. Hepatitis Monthly. 2014;14(7):e18916.	Wrong outcomes
Dong Y, Potthoff A, Klinger C, Barreiros AP, Pietrawski D, Dietrich CF. Ultrasound findings in autoimmune hepatitis. World Journal of Gastroenterology. 2018;24(15):1583-90.	Wrong population

Dumitrascu DL, Neuman MG. Non-alcoholic fatty liver disease: An update on diagnosis. Clujul Medical. 2018;91(2):147-50.	Wrong population
Elias J, Nogueira-Barbosa MH. Ultrasonography: The Global Imaging Solution. Current Radiology Reports. 2016;4(11):60.	Wrong outcomes
Enomoto M, Morikawa H, Tamori A, Kawada N. Noninvasive assessment of liver fibrosis in patients with chronic hepatitis B. World Journal of Gastroenterology. 2014;20(34):12031-8.	Wrong intervention
Ersoy MA, Yilmaz FG. Evaluation of fibrosis using a non-invasive, fast, reliable method in chronic hepatitis cases: ARFI (Acoustic radiation force impulse) elastography. Acta Medica Mediterranea. 2019;35(1):137-42.	Wrong population
Expert Panel on Gastrointestinal I, Horowitz JM, Kamel IR, Arif-Tiwari H, Asrani SK, Hindman NM, et al. ACR Appropriateness Criteria Chronic Liver Disease. Journal of the American College of Radiology : JACR. 2017;14(11S):S391-S405.	Wrong population
Fitzpatrick E, Dhawan A. Noninvasive biomarkers in non-alcoholic fatty liver disease: Current status and a glimpse of the future. World Journal of Gastroenterology. 2014;20(31):10851-63.	Wrong population
Galgenmueller S, Jaeger H, Kratzer W, Schmidt SA, Oeztuerk S, Haenle MM, et al. Parameters affecting different acoustic radiation force impulse applications in the diagnosis of fibrotic liver changes. World Journal of Gastroenterology. 2015;21(27):8425-32.	Wrong population
Gersak MM, Sorantin E, Windhaber J, Dudea SM, Riccabona M. The influence of acute physical effort on liver stiffness estimation using Virtual Touch Quantification (VTQ). Preliminary results. Medical ultrasonography. 2016;18(2):151-6.	Wrong population
Gibiino G, Garcovich M, Ainora ME, Zocco MA. Spleen ultrasound elastography: State of the art and future directions - A systematic review. European Review for Medical and Pharmacological Sciences. 2019;23(10):4368-81.	Wrong intervention
Goertz RS, GaBmann L, Strobel D, Wildner D, Schellhaas B, Neurath MF, et al. Acoustic Radiation Force Impulse (ARFI) Elastography in Autoimmune and Cholestatic Liver Diseases. Annals of hepatology. 2019;18(1):23-9.	Wrong population
Goertz RS, Gasmann L, Strobel D, Wildner D, Schellhaas B, Neurath MF, et al. Acoustic Radiation Force Impulse (ARFI) Elastography in Autoimmune and Cholestatic Liver Diseases. Annals of hepatology. 2018;18(1):23-9.	Wrong population
Goertz RS, Sturm J, Pfeifer L, Wildner D, Wachter DL, Neurath MF, et al. ARFI cut-off values and significance of standard deviation for liver fibrosis staging in patients with chronic liver disease. Annals of hepatology. 2013;12(6):935-41.	Wrong population
Guerra JAAA, Trippia M, Pissaia Junior A, Teixeira BCA, Ivantes CAP. Acoustic radiation force impulse is equivalent to liver biopsy to evaluate liver fibrosis in patients with chronic hepatitis C and nonalcoholic fatty liver disease. Arquivos de Gastroenterologia. 2015;52(3):234-8.	Wrong intervention
Gungoren MS, Efe C, Kav T, Akbiyik F. Comparison of enhanced liver fibrosis test and acoustic radiation force impulse elastography with liver biopsy in patients with autoimmune hepatitis: Preliminary results. Clinical Chemistry and Laboratory Medicine. 2014;52(SUPPL. 1):S1205.	Wrong population
Guo Y, Parthasarathy S, Goyal P, McCarthy RJ, Larson AC, Miller FH. Magnetic resonance elastography and acoustic radiation force impulse for staging hepatic fibrosis: a meta-analysis. Abdominal Imaging. 2015;40(4):818-34.	Wrong intervention
Hassan S, Syed S, Kehar SI. Review of diagnostic techniques of hepatic fibrosis. Journal of the Pakistan Medical Association. 2014;64(8):941-5.	Wrong intervention
Heo JY, Kim BK, Park JY, Kim DY, Ahn SH, Tak WY, et al. Multicenter retrospective risk assessment of esophageal variceal bleeding in patients with cirrhosis: An acoustic radiation force impulse elastography-based prediction model. Gut and Liver. 2019;13(2):206-14.	Wrong outcomes

Heo JY, Kim BK, Park JY, Kim DY, Ahn SH, Tak WY, et al. Multicenter Retrospective Risk Assessment of Esophageal Variceal Bleeding in Patients with Cirrhosis: An Acoustic Radiation Force Impulse Elastography-Based Prediction Model. Gut and liver. 2019;13(2):206-14.	Wrong outcomes
Horowitz JM, Kamel IR, Arif-Tiwari H, Asrani SK, Hindman NM, Kaur H, et al. ACR Appropriateness Criteria Chronic Liver Disease. Journal of the American College of Radiology. 2017;14(11 Supplement):S391-S405.	Wrong population
Horowitz JM, Venkatesh SK, Ehman RL, Jhaveri K, Kamath P, Ohliger MA, et al. Evaluation of hepatic fibrosis: a review from the society of abdominal radiology disease focus panel. Abdominal Radiology. 2017;42(8):2037-53.	Wrong intervention
Hsu SJ. Acoustic Radiation Force and Elasticity Imaging. Journal of Medical Ultrasound. 2016;24(1):1-2.	Wrong outcomes
Hu X, Qiu L, Liu D, Qian L. Acoustic Radiation Force Impulse (ARFI) Elastography for non-invasive evaluation of hepatic fibrosis in chronic hepatitis B and C patients: A systematic review and meta-analysis. Medical Ultrasonography. 2017;19(1):23-31.	Wrong intervention
Huang TL, Chen TY, Tsang LC, Ou HY, Yu CY, Hsu HW, et al. Acoustic Radiation Force Impulse Elastography in Post-transplant Recurrent Hepatitis C in Living Donor Liver Transplantation. Transplantation Proceedings. 2018;50(9):2695-8.	Wrong intervention
Huang Y-Q. Recent advances in the diagnosis and treatment of primary biliary cholangitis. World journal of hepatology. 2016;8(33):1419-41.	Wrong population
Imajo K, Takahashi H, Ogawa Y, Eguchi Y, Sumida Y, Yoneda M, et al. Clinical strategy of diagnosing and following patients with nonalcoholic fatty liver disease based on invasive and noninvasive methods. Journal of Gastroenterology. 2018;53(2):181-96.	Wrong population
Jenkins P, Zadar Z, Dua J, Mahadevan V. Evaluating the long term effects of the fontan procedure on the hepatic system. Cardiology in the Young. 2017;27(4):S125.	Wrong population
Jeong WK, Lim HK, Lee H-K, Jo JM, Kim Y. Principles and clinical application of ultrasound elastography for diffuse liver disease. Ultrasonography (Seoul, Korea). 2014;33(3):149-60.	Wrong intervention
Kamble R, Sodhi KS, Thapa BR, Saxena AK, Bhatia A, Dayal D, et al. Liver acoustic radiation force impulse (ARFI) in childhood obesity: comparison and correlation with biochemical markers. Journal of Ultrasound. 2017;20(1):33-42.	Wrong population
Karanjia RN, Crossey MME, Cox IJ, Fye HKS, Njie R, Goldin RD, et al. Hepatic steatosis and fibrosis: Non-invasive assessment. World Journal of Gastroenterology. 2016;22(45):9880-97.	Wrong outcomes
Karatzas A, Konstantakis C, Aggeletopoulou I, Kalogeropoulou C, Thomopoulos K, Triantos C. Non-invasive screening for esophageal varices in patients with liver cirrhosis. Annals of Gastroenterology. 2018;31(3):305-14.	Wrong outcomes
Karlas T, Dietrich A, Peter V, Wittekind C, Lichtinghagen R, Garnov N, et al. Evaluation of transient elastography, Acoustic Radiation Force Impulse Imaging (ARFI), and Enhanced Liver Function (ELF) score for detection of fibrosis in morbidly obese patients. PLoS ONE. 2015;10(11):e0141649.	Wrong population
Karlas T, Dietrich A, Peter V, Wittekind C, Lichtinghagen R, Garnov N, et al. Evaluation of Transient Elastography, Acoustic Radiation Force Impulse Imaging (ARFI), and Enhanced Liver Function (ELF) Score for Detection of Fibrosis in Morbidly Obese Patients. Plos one. 2015;10(11):e0141649.	Wrong population
Karlas T, Neuschulz M, Oltmanns A, Wirtz H, Keim V, Wiegand J. ARFI and transient elastography for characterization of cystic fibrosis related liver disease: first longitudinal follow-up data in adult patients. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2013;12(6):826-7.	Wrong population
Karlas T, Weber J, Nehring C, Kronenberger R, Tenckhoff H, Mossner J, et al. Value of liver elastography and abdominal ultrasound for detection of	Wrong population

complications of allogeneic hemopoietic SCT. Bone Marrow Transplantation. 2014;49(6):806-11.	
Keller J, Kaltenbach TE-M, Haenle MM, Oeztuerk S, Graeter T, Mason RA, et al. Comparison of Acoustic Structure Quantification (ASQ), shearwave elastography and histology in patients with diffuse hepatopathies. BMC medical imaging. 2015;15:58.	Wrong population
Khallafi H, Qureshi K. Imaging based methods of liver fibrosis assessment in viral hepatitis: A practical approach. Interdisciplinary Perspectives on Infectious Diseases. 2015;2015:809289.	Wrong outcomes
Kiani A, Brun V, Laine F, Turlin B, Morcet J, Michalak S, et al. Acoustic radiation force impulse imaging for assessing liver fibrosis in alcoholic liver disease. World Journal of Gastroenterology. 2016;22(20):4926-35.	Wrong population
Kim HP, Moon AM, Dellon ES. Noninvasively Predicting Hemodynamic Response to Carvedilol in Cirrhotic Patients With Varices: You Have Some Ex-Spleening to Do. Gastroenterology. 2019;156(8):2347-9.	Wrong outcomes
Kim HY, Jin EH, Kim W, Lee JY, Woo H, Oh S, et al. The Role of Spleen Stiffness in Determining the Severity and Bleeding Risk of Esophageal Varices in Cirrhotic Patients. Medicine. 2015;94(24):e1031.	Wrong outcomes
Kohla, M. A. S. et al. Assessment of liver fibrosis with acoustic radiation force impulse imaging versus liver histology in patients with chronic hepatitis C: A pilot study. European Journal of Gastroenterology and Hepatology 2017; 29(8): 951-955.	Article unobtainable
Konerman MA, Lok ASF. Hepatitis C treatment and barriers to eradication. Clinical and Translational Gastroenterology. 2016;7(9):e193.	Wrong intervention
Kubo K, Kawakami H, Kuwatani M, Nishida M, Kawakubo K, Kawahata S, et al. Liver elasticity measurement before and after biliary drainage in patients with obstructive jaundice: a prospective cohort studya prospective cohort study. BMC gastroenterology. 2016;16(1):65.	Wrong population
Kumar R, Teo EK, How HC, Wong TY, Ang TL. A practical clinical approach to liver fibrosis. Singapore Medical Journal. 2018;59(12):628-33.	Wrong population
Lanthier N, Starkel P, Horsmans Y. New imaging assisted methods for liver fibrosis quantification: Is it really favorable to classical transient elastography? Journal of Hepatology. 2015;63(3):765-6.	Wrong outcomes
Lee CK. Biomarkers and imaging studies to predict portal hypertension and varices. Clinical Liver Disease. 2017;9(4):94-8.	Wrong outcomes
Lee MS, Bae JM, Joo SK, Woo H, Lee DH, Jung YJ, et al. Correction: Prospective comparison among transient elastography, supersonic shear imaging, and ARFI imaging for predicting fibrosis in nonalcoholic fatty liver disease (PLoS ONE (2017) 12:11 (e0188321) DOI: 10.1371/journal.pone.0188321). PLoS ONE. 2018;13(6):e0200055.	Wrong population
Lee MS, Bae JM, Joo SK, Woo H, Lee DH, Jung YJ, et al. Prospective comparison among transient elastography, supersonic shear imaging, and ARFI imaging for predicting fibrosis in nonalcoholic fatty liver disease. PLoS ONE. 2017;12(11):e0188321.	Wrong population
Lee S, Kim DY. Non-invasive diagnosis of hepatitis B virus-related cirrhosis. World journal of gastroenterology. 2014;20(2):445-59.	Wrong intervention
Li C, Zhang C, Li J, Huo H, Song D. Diagnostic accuracy of real-time shear wave elastography for staging of liver fibrosis: A meta-analysis. Medical Science Monitor. 2016;22:1349-59.	Wrong intervention
Li J, Yu J, Peng XY, Du TT, Wang JJ, Tong J, et al. Acoustic radiation force impulse (Arfi) elastography and serological markers in assessment of liver fibrosis and free portal pressure in patients with hepatitis B. Medical Science Monitor. 2017;23:3585-92.	Wrong intervention
Li JH, Zhu N, Min YB, Shi XZ, Duan YY, Yang YL. Ultrasonic assessment of liver stiffness and carotid artery elasticity in patients with chronic viral hepatitis 11 Medical and Health Sciences 1103 Clinical Sciences. BMC Gastroenterology. 2018;18(1):181.	Wrong intervention

Li S-M, Li G-X, Fu D-M, Wang Y, Dang L-Q. Liver fibrosis evaluation by ARFI and APRI in chronic hepatitis C. World journal of gastroenterology. 2014;20(28):9528-33.	Wrong intervention
Li X, Xu L, Li H, Zhao L, Luo Y, Zhu Z, et al. Cetuximab-induced insulin-like growth factor receptor i activation mediates cetuximab resistance in gastric cancer cells. Molecular Medicine Reports. 2015;11(6):4547-54.	Wrong population
Lin Y-H, Yeh M-L, Huang C-I, Yang J-F, Liang P-C, Huang C-F, et al. The performance of acoustic radiation force impulse imaging in predicting liver fibrosis in chronic liver diseases. The Kaohsiung journal of medical sciences. 2016;32(7):362-6.	Wrong population
Lin YS. Ultrasound Evaluation of Liver Fibrosis. Journal of Medical Ultrasound. 2017;25(3):127-9.	Wrong intervention
Liu H, Fu J, Hong R, Liu L, Li F. Acoustic radiation force impulse elastography for the non-invasive evaluation of hepatic fibrosis in non-alcoholic fatty liver disease patients: A systematic review & meta-analysis. PLoS ONE. 2015;10(7):e0127782.	Wrong population
Liu J, Ji Y, Ai H, Ning B, Zhao J, Zhang Y, et al. Liver shear-wave velocity and serum fibrosis markers to diagnose hepatic fibrosis in patients with chronic viral hepatitis B. Korean Journal of Radiology. 2016;17(3):396-404.	Wrong intervention
Liu Y, Dong Cf, Yang G, Liu J, Yao S, Li Hy, et al. Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B. Liver International. 2015;35(3):816-25.	Wrong intervention
Lombardi R, Buzzetti E, Roccarina D, Tsochatzis EA. Non-invasive assessment of liver fibrosis in patients with alcoholic liver disease. World Journal of Gastroenterology. 2015;21(39):11044-52.	Wrong population
Loy M, Serra G, Chessa L. The prevalence of bright liver echo pattern in patients with chronic hepatitis C: correlation with steatosis and fibrosis. Journal of Ultrasound. 2016;19(2):91-8.	Wrong intervention
Lucero C, Brown RS. Noninvasive measures of liver fibrosis and severity of liver disease. Gastroenterology and Hepatology. 2016;12(1):33-40.	Wrong intervention
Lurie Y, Webb M, Cytter-Kuint R, Shteingart S, Lederkremer GZ. Non-invasive diagnosis of liver fibrosis and cirrhosis. World Journal of Gastroenterology. 2015;21(41):11567-83.	Wrong intervention
Marin-Alejandre BA, Abete I, Cantero I, Riezu-Boj JI, Milagro FI, Monreal JI, et al. Association between sleep disturbances and liver status in obese subjects with nonalcoholic fatty liver disease: A comparison with healthy controls. Nutrients. 2019;11(2):322.	Wrong population
Mazur R, Celmer M, Silicki J, Holownia D, Pozowski P, Miedzybrodzki K. Clinical applications of spleen ultrasound elastography - a review. Journal of ultrasonography. 2018;18(72):37-41.	Wrong intervention
Mebus S, Kugel J, Zachoval R, Braun S, Haverkamper G, Opgen-Rhein B, et al. Noninvasive assessment of liver function in adults with congenital heart disease (ACHD) by transient elastography (Fibroscan), acoustic radiation force impulse imaging (ARFI) and biochemical markers. Cardiology in the Young. 2014;24(Supplement 1):S114.	Wrong population
Morishita N, Hiramatsu N, Oze T, Harada N, Yamada R, Miyazaki M, et al. Erratum to: Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis. Journal of gastroenterology. 2015;50(6):705.	Wrong outcomes
Mostafavi B, Diaz S, Tanash HA, Piitulainen E. Liver function in alpha-1-antitrypsin deficient individuals at 37 to 40 years of age. Medicine. 2017;96(12):e6180.	Wrong population
Mueller S, Seitz HK, Rausch V. Non-invasive diagnosis of alcoholic liver disease. World Journal of Gastroenterology. 2014;20(40):14626-41.	Wrong population
Mulabecirovic A, Mjelle AB, Gilja OH, Vesterhus M, Havre RF. Repeatability of shear wave elastography in liver fibrosis phantoms-Evaluation of five different systems. PloS one. 2018;13(1):e0189671.	Wrong population

Nacif LS, Paranagua-Vezozzo DC, Matsuda A, Alves VAF, Carrilho FJ, Farias AQ, et al. HIGHER VALUES IN LIVER ELASTOGRAPHY AND MELD SCORE ARE MORTALITY PREDICTORS ON LIVER TRANSPLANT WAITING LIST. Arquivos brasileiros de cirurgia digestiva : ABCD = Brazilian archives of digestive surgery. 2018;31(1):e1360.	Wrong population
Nishikawa H, Nishimura T, Enomoto H, Iwata Y, Ishii A, Miyamoto Y, et al. Impact of virtual touch quantification in acoustic radiation force impulse for skeletal muscle mass loss in chronic liver diseases. Nutrients. 2017;9(6):620.	Wrong outcomes
Nishikawa T, Hashimoto S, Kawabe N, Harata M, Nitta Y, Murao M, et al. Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C. World journal of gastroenterology. 2014;20(5):1289-97.	Wrong intervention
Nishimura T, Nakano C, Aoki T, Aizawa N, Shimono Y, Kishino K, et al. Noninvasive diagnosis of malignant liver tumors using shear wave ultrasound elastography. Liver Cancer. 2015;4(SUPPL. 1):231-2.	Wrong population
Omar H, Said M, Eletreby R, Mehrez M, Bassam M, Abdellatif Z, et al. Longitudinal assessment of hepatic fibrosis in responders to direct-acting antivirals for recurrent hepatitis C after liver transplantation using noninvasive methods. Clinical Transplantation. 2018;32(8):e13334.	Wrong outcomes
Omote K, Nagai T, Asakawa N, Aikawa T, Tokuda Y, Kato Y, et al. Clinical value of a non-invasive measurement of increased liver stiffness by using virtual touch quantification for predicting elevated right atrial pressure in heart failure patients. European Heart Journal. 2018;39(Supplement 1):786-7.	Wrong population
Omote K, Nagai T, Asakawa N, Komoriyama H, Kato Y, Aikawa T, et al. Long-term prognostic significance of liver stiffness non-invasively measured by the virtual touch quantification in patients with acute decompensated heart failure. European Heart Journal. 2018;39(Supplement 1):583-4.	Wrong population
Osakabe K, Ichino N, Nishikawa T, Sugiyama H, Kato M, Shibata A, et al. Changes of shear-wave velocity by interferon-based therapy in chronic hepatitis C. World journal of gastroenterology. 2015;21(35):10215-23.	Wrong intervention
Ozalper V, Ozturker C, Sonmez G. Usefulness of acoustic radiation force impulse in liver fibrosis assessment after liver transplant. Annals of Hepatology. 2016;15(6):946.	Wrong population
Ozkan MB, Bilgici MC, Eren E, Caltepe G, Yilmaz G, Kara C, et al. Role of Point Shear Wave Elastography in the Determination of the Severity of Fibrosis in Pediatric Liver Diseases With Pathologic Correlations. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2017;36(11):2337-44.	Wrong population
Ozturker C, Karagoz E, Mutlu H. How useful is ARFI elastography for predicting the significant fibrosis and compensated liver cirrhosis? Medical Ultrasonography. 2016;18(1):131.	Wrong outcomes
Ozturker C, Karagoz E, Sildiroglu HO. IS ARFI A USEFUL TOOL FOR NON-INVASIVE EVALUATION OF LIVER STIFFNESS IN NONALCOHOLIC FATTY LIVER DISEASE AND HEPATITIS C? Arquivos de gastroenterologia. 2016;53(3):212.	Wrong outcomes
Ozturker C, Karagoz E, Sivrioglu AK, Kara K. Clinical usefulness and performance of acoustic radiation force impulse in patients with chronic hepatitis B. European Journal of Gastroenterology and Hepatology. 2017;29(6):663-8.	Wrong outcomes
Ozturker C, Karagoz E, Tanoglu A. RE: Liver shear-wave velocity to diagnose hepatic fibrosis in patients with chronic viral hepatitis B. Korean Journal of Radiology. 2016;17(5):822.	Wrong outcomes
Park MS, Kim SW, Yoon KT, Kim SU, Park SY, Tak WY, et al. Factors influencing the diagnostic accuracy of acoustic radiation force impulse elastography in patients with chronic hepatitis B. Gut and Liver. 2016;10(2):275-82.	Wrong intervention

Park Y, Kim SU, Park SY, Kim BK, Park JY, Kim DY, et al. A novel model to predict esophageal varices in patients with compensated cirrhosis using acoustic radiation force impulse elastography. PloS one. 2015;10(3):e0121009.	Wrong outcomes
Pawlowska M, Sobolewska-Pilarczyk M, Domagalski K. Hepatitis C virus infection in children in the era of directacting antiviral. World Journal of Gastroenterology. 2018;24(24):2555-66.	Wrong intervention
Porra L, Swan H, Ho C. The effect of applied transducer force on acoustic radiation force impulse quantification within the left lobe of the liver. Australasian journal of ultrasound in medicine. 2015;18(3):100-6.	Wrong population
Reiter R, Wetzel M, Hamesch K, Strnad P, Asbach P, Haas M, et al. Comparison of non-invasive assessment of liver fibrosis in patients with alpha1-antitrypsin deficiency using magnetic resonance elastography (MRE), acoustic radiation force impulse (ARFI) Quantification, and 2D-shear wave elastography (2D-SWE). PLoS ONE. 2018;13(4):e0196486.	Wrong population
Rix A, Lederle W, Theek B, Lammers T, Moonen C, Schmitz G, et al. Advanced ultrasound technologies for diagnosis and therapy. Journal of Nuclear Medicine. 2018;59(5):740-6.	Wrong intervention
Rizzo L, Attanasio M, Pinzone MR, Berretta M, Malaguarnera M, Morra A, et al. A new sampling method for spleen stiffness measurement based on quantitative acoustic radiation force impulse elastography for noninvasive assessment of esophageal varices in newly diagnosed HCV-related cirrhosis. BioMed research international. 2014;2014:365982.	Wrong outcomes
Sagir A, Ney D, Oh J, Pandey S, Kircheis G, Mayatepek E, et al. Evaluation of Acoustic Radiation Force Impulse Imaging (ARFI) for the Determination of Liver Stiffness Using Transient Elastography as a Reference in Children. Ultrasound international open. 2015;1(1):E2-7.	Wrong population
Schmillevitch J, Chammas MC, Pugliese V, Abdala E, Rizzon AC, Alves V, et al. Acoustic radiation force impulse (ARFI) elastography compared with biopsy for evaluating hepatic fibrosis after liver transplantation: A cross-sectional diagnostic study. Sao Paulo Medical Journal. 2016;134(6):513-8.	Wrong population
Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, et al. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. Hepatology International. 2017;11(1).	Wrong outcomes
Shin HJ, Kim M-J, Yoon C-S, Lee K, Lee KS, Park J-C, et al. Motion effects on the measurement of stiffness on ultrasound shear wave elastography: a moving liver fibrosis phantom study. Medical ultrasonography. 2018;1(1):14-20.	Wrong population
Silva Junior, R. G. et al. Acoustic radiation force impulse elastography and serum fibrosis markers in chronic hepatitis C. Scandinavian Journal of Gastroenterology 2014; 49(8): 986-992.	Wrong intervention
Sirli R, Sporea I, Popescu A, Danila M. Ultrasound-based elastography for the diagnosis of portal hypertension in cirrhotics. World Journal of Gastroenterology. 2015;21(41):11542-51.	Wrong outcomes
Sporea I, Bota S, Gradinaru-Tascau O, Sirli R, Popescu A. Comparative study between two point Shear Wave Elastographic techniques: Acoustic Radiation Force Impulse (ARFI) elastography and ElastPQ. Medical Ultrasonography. 2014;16(4):309-14.	Wrong outcomes
Sporea I, Gilja OH, Bota S, Sirli R, Popescu A. Liver elastography - an update. Medical ultrasonography. 2013;15(4):304-14.	Wrong intervention
Sporea I, Mare R, Lupusoru R, Popescu A, Danila M, Bende F, et al. Comparative study between four ultrasound Shear Waves Elastographic methods for liver fibrosis assessment. Medical Ultrasonography. 2018;20(3):265-71.	Wrong population
Stal P. Liver fibrosis in non-alcoholic fatty liver disease-Diagnostic challenge with prognostic significance. World Journal of Gastroenterology. 2015;21(39):11077-87.	Wrong population

Stasi C, Milani S. Evolving strategies for liver fibrosis staging: Non-invasive assessment. World journal of gastroenterology. 2017;23(2):191-6.	Wrong intervention
Staufer K, Halilbasic E, Trauner M, Kazemi-Shirazi L. Cystic fibrosis related liver disease-another black box in hepatology. International Journal of Molecular Sciences. 2014;15(8):13529-49.	Wrong population
Summers JA, et al. Virtual Touch Quantification to Diagnose and Monitor Liver Fibrosis in Hepatitis B and Hepatitis C: A NICE Medical Technology Guidance. Applied Health Economics and Health Policy. 2017;15(2):139-54.	Wrong outcomes
Sun XL, Liang LW, Cao H, Men Q, Hou KZ, Chen Z, et al. Liver reserve function assessment by acoustic radiation force impulse imaging. World Journal of Gastroenterology. 2015;21(32):9648-55.	Wrong outcomes
Tachi Y, Hirai T, Kojima Y, Ishizu Y, Honda T, Kuzuya T, et al. Liver stiffness measurement predicts hepatocellular carcinoma development in patients treated with direct-acting antivirals. JGH Open. 2017;1(1):44-9.	Wrong intervention
Tachi Y, Hirai T, Kojima Y, Ishizu Y, Honda T, Kuzuya T, et al. Liver stiffness reduction correlates with histological characteristics of hepatitis C patients with sustained virological response. Liver international : official journal of the International Association for the Study of the Liver. 2018;38(1):59-67.	Wrong intervention
Tachi Y, Hirai T, Kojima Y, Miyata A, Ohara K, Ishizu Y, et al. Liver stiffness measurement using acoustic radiation force impulse elastography in hepatitis C virus-infected patients with a sustained virological response. Alimentary pharmacology & therapeutics. 2016;44(4):346-55.	Wrong intervention
Tang A, Cloutier G, Szeverenyi NM, Sirlin CB. Ultrasound elastography and MR elastography for assessing liver fibrosis: Part 1, principles and techniques. American Journal of Roentgenology. 2015;205(1):22-32.	Wrong outcomes
Taura K, Nishio T, Koyama Y, Tanabe K, Yamamoto G, Okuda Y, et al. Liver stiffness measurement for the prediction of posthepatectomy liver failure after liver resection for hepatocellular carcinoma. Liver Cancer. 2015;4(SUPPL. 1):161.	Wrong population
Tovo CV, De Mattos AZ, Coral GP, Branco FS, Suwa E, De Mattos AA. Noninvasive imaging assessment of non-alcoholic fatty liver disease: Focus on liver scintigraphy. World Journal of Gastroenterology. 2015;21(15):4432-9.	Wrong population
Trivedi HD, Patwardhan VR, Malik R. Chronic hepatitis C infection - Noninvasive assessment of liver fibrosis in the era of direct acting antivirals. Digestive and Liver Disease. 2019;51(2):183-9.	Wrong intervention
Tseng C-H, Chang C-Y, Mo L-R, Lin J-T, Tai C-M, Perng D-S, et al. Acoustic Radiation Force Impulse Elastography with APRI and FIB-4 to Identify Significant Liver Fibrosis in Chronic Hepatitis B Patients. Annals of hepatology. 2018;17(5):789-94.	Wrong intervention
Wang CC, Tsai MC, Lin CP, Chang MH, Yang TW, Tsai CH, et al. Acoustic radiation force impulse sonography-based noninvasive prediction of cirrhosis and esophageal varices. Advances in Digestive Medicine. 2019.	Wrong intervention
Wildner D, Strobel D, Konturek PC, Gortz RS, Croner RS, Neurath MF, et al. Impact of acoustic radiation force impulse imaging in clinical practice of patients after orthotopic liver transplantation. Medical Science Monitor. 2014;20:2027-35.	Wrong population
Woo H, Lee JY, Yoon JH, Kim W, Cho B, Choi BI. Comparison of the Reliability of Acoustic Radiation Force Impulse Imaging and Supersonic Shear Imaging in Measurement of Liver Stiffness. Radiology. 2015;277(3):881-6.	Wrong intervention
Wu C-H, Ho M-C, Jeng Y-M, Liang P-C, Hu R-H, Lai H-S, et al. Assessing hepatic fibrosis: comparing the intravoxel incoherent motion in MRI with acoustic radiation force impulse imaging in US. European radiology. 2015;25(12):3552-9.	Wrong intervention
Wu SD, Ding H, Liu LL, Zhuang Y, Liu Y, Cheng LS, et al. Longitudinal monitoring of liver stiffness by acoustic radiation force impulse imaging in	Wrong intervention

patients with chronic hepatitis B receiving entecavir. Clinics and Research in Hepatology and Gastroenterology. 2018;42(3):227-36.	
Xu X, Luo L, Chen J, Wang J, Zhou H, Li M, et al. Acoustic radiation force impulse elastography for efficacy evaluation after hepatocellular carcinoma radiofrequency ablation: a comparative study with contrast-enhanced ultrasound. BioMed research international. 2014;2014:901642.	Wrong population
Yamada R, Hiramatsu N, Oze T, Morishita N, Harada N, Miyazaki M, et al. Significance of liver stiffness measurement by acoustic radiation force impulse (ARFI) among hepatitis C patients. Journal of medical virology. 2014;86(2):241-7.	Wrong intervention
Yoo H, Lee JM, Yoon JH, Lee DH, Chang W, Han JK. Prospective comparison of liver stiffness measurements between two point shear wave elastography methods: Virtual touch quantification and elastography point quantification. Korean Journal of Radiology. 2016;17(5):750-7.	Wrong population
Yoshitani T, Asakawa N, Sakakibara M, Noguchi K, Tokuda Y, Kamiya K, et al. Value of virtual touch quantification elastography for assessing liver congestion in patients with heart failure. Circulation Journal. 2016;80(5):1187-95.	Wrong population
Zarebska-Michaluk D, Jaroszewicz J, Janczewska E, Berak H, Horban A, Sitko M, et al. Interferon free therapy with and without ribavirin for genotype 1 HCV cirrhotic patients in the real world experience. Hepatitis Monthly. 2018;18(8):e80761.	Wrong intervention
Zentner D, Phan K, Gibson R, Sood S, Grigg L, Nicoll A. Acoustic radiation force imaging of the fontan liver-adding to the diagnostic armamentarium. Cardiology in the Young. 2017;27(4):S94.	Wrong population
Zhang D, Chen M, Wang R, Liu Y, Zhang D, Liu L, et al. Comparison of acoustic radiation force impulse imaging and transient elastography for non-invasive assessment of liver fibrosis in patients with chronic hepatitis B. Ultrasound in medicine & biology. 2015;41(1):7-14.	Wrong intervention
Zhang E, Wartelle-Bladou C, Lepanto L, Lachaine J, Cloutier G, Tang A. Cost-utility analysis of nonalcoholic steatohepatitis screening. European Radiology. 2015;25(11):3282-94.	Wrong population
Zhang E, Wartelle-Bladou C, Lepanto L, Lachaine J, Cloutier G, Tang A. Cost-utility analysis of screening strategies for nonalcoholic steatohepatitis. Value in Health. 2014;17(7):A367.	Wrong population
Zhang H-C, Hu R-F, Zhu T, Tong L, Zhang Q-Q. Primary biliary cirrhosis degree assessment by acoustic radiation force impulse imaging and hepatic fibrosis indicators. World journal of gastroenterology. 2016;22(22):5276-84.	Wrong population
Zhang Y, Mao D-F, Zhang M-W, Fan X-X. Clinical value of liver and spleen shear wave velocity in predicting the prognosis of patients with portal hypertension. World journal of gastroenterology. 2017;23(45):8044-52.	Wrong outcomes
Zheng X-Z, Wu J, Tan X-Y. A novel approach to assessing fetal tissue stiffness using virtual touch tissue quantification. Medical ultrasonography. 2016;18(1):70-4.	Wrong population
Zopf S, Rosch L, Konturek PC, Goertz RS, Neurath MF, Strobel D. Low pretreatment acoustic radiation force impulse imaging (ARFI) values predict sustained virological response in antiviral Hepatitis C virus (HCV) therapy. Medical Science Monitor. 2016;22:3500-5.	Wrong comparator

Included Studies

The tables of included studies below show “2 x 2 tables” where these are given in the papers or can be calculated, as shown below:

2 x 2 table:

	Person really has the condition; “gold standard” is positive	**Person really does not have the condition; “gold standard” is negative**	**Total**
Test is positive	TP: True positive (test correctly identifies the person as having the condition)	FP: False positive (test incorrectly identifies the person when they really do not have the condition)	TP+FP
Test is negative	FN: False negative (test misses the condition)	TN: True negative (test correctly identifies the person as not having the condition)	FN+TN
Total	TP+FN	FP+TN	TP+FP+FN+TN

Sensitivity: how many people who have the condition who are identified in the test: TP/(TP+FN)

Specificity: How many people who do not have the condition who are rules out by the test: TN/(FP+TN)

PPV: Positive predictive value: How likely the person is to have the condition if the test is positive: TP/(TP+FP)

NPV: Negative predictive value: How likely the person is to not have the condition if the test is negative: TN/(FN+TN)

DOR: the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease: (TP/FP)/(FN/TN). It can also be calculated as (sensitivity/1-sensitivity) x (specificity/1-specificity).

The sensitivity, specificity, PPV and NPV can be calculated if the numbers for TP, FP, FN and TN are known. Similarly, TP, FP, FN and TN can be calculated if sensitivity, specificity and the column totals are known.

<table>
<tr><td>Study details</td><td>Alem, S. A. et al. Diagnostic accuracy of acoustic radiation force impulse elastography (ARFI) in comparison to other non-invasive modalities in staging of liver fibrosis in chronic HCV patients: single-center experience. Abdominal Radiology 2019; 44: 2751–2758.</td></tr>
<tr><td>Design</td><td>Prospective study</td></tr>
<tr><td>Country</td><td>Egypt</td></tr>
<tr><td>Participants</td><td>2103 patients with chronic hepatitis C; aged 18–75 years with HCV RNA positive for > 6 months. Patients who had hepatitis B virus co-infection, HIV or associated liver pathology e.g. autoimmune hepatitis, decompensated liver cirrhosis, hepatocellular carcinoma or extra-hepatic malignancy were excluded.</td></tr>
<tr><td>Age and gender</td><td>Median 48 years (range 36–56)
Male 1258 (59.9%)
Female 844 (40.1%)</td></tr>
<tr><td>Assigned interventions</td><td>VTq</td></tr>
<tr><td>Comparator</td><td>TE (the reference method)</td></tr>
<tr><td>Outcomes</td><td>Diagnostic accuracy</td></tr>
<tr><td>Statistics</td><td>ROC curves. AUC values were interpreted as follows: 0.90–1.0 = excellent; 0.80–0.90 = good; 0.70–0.80 = fair; and less than 0.70 = poor.</td></tr>
<tr><td>Effect size</td><td>Cut-off value; AUC; sensitivity; specificity; accuracy:
≥ F2: 1.36 m/s, AUC 0.89, 80.6%, 87.5%, 84.1%
≥ F3: 1.45 m/s, AUC 0.94, 90.3%, 87.5%, 88.5%
F4: 1.7 m/s, AUC 0.95, 90.9%, 90.3%, 90.4%
Stages of hepatic fibrosis using TE
as the reference method were as follows: F0 in 704 (33.5%), F1 in 360 (17%), F2 in 260 (12%), F3 in 188 (8.9%), F4 in 601 (28.6%).
Using these figures, the 2 x 2 table could be calculated:
For F≥2
<table>
<tr><td></td><td>TE ≥2</td><td>TE <2</td><td>Total</td></tr>
<tr><td>VTq ≥1.36 m/s</td><td>845</td><td>133</td><td>978</td></tr>
<tr><td>VTq <1.36 m/s</td><td>204</td><td>931</td><td>1135</td></tr>
<tr><td>Total</td><td>1049</td><td>1064</td><td>2113</td></tr>
</table>
For F=4
<table>
<tr><td></td><td>TE =4</td><td>TE <4</td><td>Total</td></tr>
<tr><td>VTq ≥1.7 m/s</td><td>546</td><td>147</td><td>693</td></tr>
<tr><td>VTq <1.7 m/s</td><td>55</td><td>1365</td><td>1420</td></tr>
<tr><td>Total</td><td>601</td><td>1512</td><td>2113</td></tr>
</table>
</td></tr>
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<table>
<tr><td>Study details</td><td>Bota, S et al. 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): 200-5.</td></tr>
<tr><td>Design</td><td>Retrospective study</td></tr>
<tr><td>Country</td><td>Romania</td></tr>
<tr><td>Participants</td><td>132 patients with chronic hepatitis C. None of the patients had coinfection with hepatitis B virus or human immunodeficiency virus. None of the patients had liver focal liver lesions
or ascites on abdominal ultrasound examination.</td></tr>
<tr><td>Age and gender</td><td>Median (range) age 53 (21-65) years
45 (34.1%) male; 87 (65.9%) female</td></tr>
<tr><td>Assigned interventions</td><td>VTq</td></tr>
<tr><td>Comparator</td><td>TE in some patients
Liver biopsy as reference standard</td></tr>
<tr><td>Outcomes</td><td>Diagnostic accuracy</td></tr>
<tr><td>Statistics</td><td>Sensitivity and specificity; positive and negative predictive value</td></tr>
<tr><td>Effect size</td><td>Assessed using the cut-offs published in the Nierhoff 2013 meta-analysis, of 1.35 m/s for at least significant fibrosis (F2) and 1.87m/s for cirrhosis (F4).
F≥2:
<table>
<tr><td></td><td>F≥2 on biopsy:</td><td>F<2 on biopsy</td><td>Total</td></tr>
<tr><td>VTq ≥1.35m/s</td><td>55</td><td>4</td><td>59</td></tr>
<tr><td>VTq <1.35m/s</td><td>55</td><td>14</td><td>58</td></tr>
<tr><td>Total</td><td>99</td><td>18</td><td>117</td></tr>
</table>
Sensitivity = 55/99 = 55.6%
Specificity = 14/18 = 77.8%
Positive predictive value for at least significant fibrosis (F2), i.e. chance of having the condition if the test is positive = 55/59 = 93.2%
Negative predictive value for at least significant fibrosis (F2), i.e. chance of not having the condition if the test is negative = 14/58 = 24.1%.

F≥4:
<table>
<tr><td></td><td>F≥4 on biopsy:</td><td>F<4 on biopsy</td><td>Total</td></tr>
<tr><td>VTq ≥1.87m/s</td><td>12</td><td>17</td><td>29</td></tr>
<tr><td>VTq <1.87m/s</td><td>2</td><td>86</td><td>88</td></tr>
<tr><td>Total</td><td>14</td><td>103</td><td>117</td></tr>
</table>
Sensitivity = 12/14 = 85.7%
Specificity = 86/103 = 83.5%
Positive predictive value for cirrhosis (F4), i.e. chance of having the condition if the test is positive = 12/29 = 41.4%
Negative predictive value for cirrhosis (F4), i.e. chance of not having the condition if the test is negative = 86/88 = 97.8%.</td></tr>
</table>

Study details	Cano J, Acosta KR, Bisnar J, et al. Diagnostic performance of acoustic radiation force impulse versus transient elastography in assessing liver fibrosis; A meta-analysis. Clin Gastro Hepatol 2014;12:156 (abstract).
Design	Meta-analysis
Country	NA
Participants	Cross-sectional and cohort studies involving adult patients with chronic hepatitis B and chronic liver disease who underwent percutaneous liver biopsy during the last 12-15 months. 476 patients in 4 included studies were analysed for the diagnostic accuracy of ARFI.
Age and gender	NA
Assigned interventions	VTq (ARFI/SWE)
Comparator	Liver biopsy
Outcomes	Diagnostic performance
Statistics	Sensitivity and specificity; receiver operating characteristic curve (ROC) and area under curve (AUC)
Effect size	ARFI had a pooled sensitivity of 67% (95% CI 0.62 to 0.73; P = .000) and pooled specificity of 87% (95% CI 0.82 to 0.92; P = .4793). The ROC showed a significant diagnostic value of ARFI in assessing liver fibrosis with an AUC of 0.9359.

Study details	Dong, Dao-Ran et al. Acoustic radiation force impulse elastography, FibroScan, Forns' index and their combination in the assessment of liver fibrosis in patients with chronic hepatitis B, and the impact of inflammatory activity and steatosis on these diagnostic methods. Molecular medicine reports 2015; 11(6): 4174-82.
Design	Cross-sectional study
Country	China
Participants	81 consecutive patients with chronic hepatitis B (CHB):Inclusion criteria: i) Age, 18-65 years, irrespective of gender; ii) CHB of various degrees in association with liver fibrosis; iii) no intake of medication known to inhibit liver enzymes within two weeks prior to biochemical blood analysis; iv) history of abnormal transaminase; and v) provision of signed informed consent by the patient. The criteria for study exclusion were: i) Unavailability of patient consent; ii) other complicated liver conditions, including other types of viral hepatitis, alcoholic and nonalcoholic fatty liver disease, autoimmune hepatitis and inherited metabolic liver disease; iii) hepatic decompensation, including the presence of ascites; iv) body mass index (BMI) ≥30; v) non-healed upper quadrant abdominal wound; vi) space-occupying tumors or cysts in the right lobe of the liver or various space-occupying tumors and cysts; and vii) acute hepatitis or cholestatic hepatitis.
Age and gender	41±11.4 years 71 (87.7%) male
Assigned interventions	SEQUIOA512 color ultrasound diagnostic system (Siemens)
Comparator	TE Liver biopsy: Liver fibrosis was scored according to the biopsy criteria of the Chinese Program of Prevention and Cure for Viral Hepatitis (equivalent to METAVIR fibrosis stages): 0 Absent 1 Portal fibrosis to be enlarged, localized perisinusoidal and intralobular fibrosis 2 Periportal fibrosis, several fibrous septa with lobule structure remaining 3 Numerously fibrous septa companied, Lobule structure distortion, without cirrhosis 4 Early cirrhosis
Outcomes	Diagnostic accuracy
Statistics	AUROC, sensitivity, specificity, as well as positive and negative predictive values

<table>
<tr>
<td>Effect size</td>
<td>
Stage ≥1: Cut-off 1.295; AUROC (95% CI) 0.720 (0.524-0.916); sensitivity 68.3%; specificity 80.0%
Stage ≥2: Cut-off 1.295; AUROC (95% CI) 0.762 (0.627-0.896); sensitivity 82.9%; specificity 65.0%
Stage ≥3: Cut-off 1.54; AUROC (95% CI) 0.884 (0.798-0.970); sensitivity 76.2%; specificity 90.0%
Stage ≥4: Cut-off 1.835; AUROC (95% CI) 0.723 (0.501-0.944); sensitivity 66.7%; specificity 85.5%.
Numbers in each group were: F0: 9; F1: 25; F2: 25; F3: 16; F4: 6.
2 x 2 tables were calculated:
F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.295m/s</td><td>39</td><td>12</td><td>51</td></tr>
<tr><td>VTq < 1.295m/s</td><td>8</td><td>22</td><td>30</td></tr>
<tr><td>Total</td><td>47</td><td>34</td><td>81</td></tr>
</table>
F=4:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.835m/s</td><td>4</td><td>11</td><td>15</td></tr>
<tr><td>VTq < 1.835m/s</td><td>2</td><td>64</td><td>66</td></tr>
<tr><td>Total</td><td>6</td><td>75</td><td>81</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td>Study details</td><td>Dong, C-F et al. Combined acoustic radiation force impulse, aminotransferase to platelet ratio index and Forns index assessment for hepatic fibrosis grading in hepatitis B. World J Hepatol 2016 May 18; 8(14): 616-624</td></tr>
<tr><td>Design</td><td>Prospective study</td></tr>
<tr><td>Country</td><td>China</td></tr>
<tr><td>Participants</td><td>206 patients with chronic hepatitis B. Patients with NAFLD, jaundice, alcoholic steatosis, HCV infection, auto-immune liver disease, were aged < 18 or > 65, who received antiviral treatment before this study or declined to participate were excluded.</td></tr>
<tr><td>Age and gender</td><td>F0 (n = 40) 39.8 ± 11.45 years
F1 (n = 41) 33.07 ± 7.97 years
F2 (n = 52) 38.27 ± 7.662 years
F3 (n = 59) 39.83 ± 8.732 years
F4 (n = 54) 43.85 ± 10.81 years
Overall, 197 male, 49 female</td></tr>
<tr><td>Assigned interventions</td><td>VTq (Siemens Acuson S2000)</td></tr>
<tr><td>Comparator</td><td>Liver biopsy</td></tr>
<tr><td>Outcomes</td><td>Diagnostic accuracy</td></tr>
<tr><td>Statistics</td><td>Correlation; ROC; AUROC; cut-off value, sensitivity, specificity, positive predictive values, negative predictive values</td></tr>
<tr><td>Effect size</td><td>There was a high correlation between the staging of ARFI and the hepatic histology, with correlation coefficient 0.845 (95% CI 0.805-0.877; p< 0.001).

Cut-off values; AUROC (95% CI); sensitivity (95% CI); specificity (95% CI); positive predictive value (95% CI); negative predictive value (95% CI):
F1: 1.26m/s; 0.90 (0.86-0.94); 76.2% (69.80-81.90); 95.0% (83.10-99.40); 99.1% (96.20-99.90); 35.9% (22.50-47.40).
≥F2: 1.29m/s; 0.91 (0.87-0.95); 83.6% (77.10-88.90); 90.1% (89.50-97.60); 94.5% (91.90-99.10); 73.0% (63.10-81.40).
≥F3: 1.43m/s; 0.94 (0.90-0.96); 82.3% (74.00-88.80); 89.5% (83.00-94.10); 86.9% (79.10-92.70); 85.6% (78.60-91.00).
≥F4: 1.62m/s; 0.96 (0.93-0.98); 90.7% (79.70-96.90); 92.2% (87.40-95.60); 76.0% (64.40-86.30); 97.2% (93.70-99.10).

From the liver biopsy, F0=40 (healthy volunteers); F1=41; F2=52; F3=59 and F4=54 people.
The 2 x 2 tables could be calculated:
For F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥1.29m/s</td><td>138</td><td>8</td><td>146</td></tr>
<tr><td>VTq <1.29m/s</td><td>27</td><td>73</td><td>100</td></tr>
<tr><td>Total</td><td>165</td><td>81</td><td>246</td></tr>
</table>
For F=4:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥1.62m/s</td><td>49</td><td>15</td><td>64</td></tr>
<tr><td>VTq <1.62m/s</td><td>5</td><td>177</td><td>182</td></tr>
<tr><td>Total</td><td>54</td><td>192</td><td>246</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Study details</td><td>Elhosary, YA et al. Diagnostic Accuracy of Acoustic Radiation Force Impulse (ARFI) in Diagnosis of Liver Fibrosis among Egyptian Patients with Chronic HCV Infection. Open Access Macedonian Journal of Medical Sciences. 2016 Sep 15; 4(3):374-380.</td></tr>
<tr><td>Design</td><td>Cross-sectional</td></tr>
<tr><td>Country</td><td>Egypt</td></tr>
<tr><td>Participants</td><td>190 patients with chronic HCV infection. Excluded patients with a history of renal disorder; recent history of cardiovascular disease; hepatitis B or HIV; autoimmune or metabolic liver diseases; abnormal coagulation profiles that preclude liver biopsies; INR > 1.5; prothrombin time > 50 s; platelet count < 50,000/mL; contraindications to liver biopsy, e.g. biliary ductal dilatation, ascites; hepatocellular carcinoma.</td></tr>
<tr><td>Age and gender</td><td>Mean (SD) 53.74 ± 12.05 years
Male 142 (74.7%)
Female 48 (25.3%)</td></tr>
<tr><td>Assigned interventions</td><td>VTq (Siemens Acuson S3000 Virtual Touch)</td></tr>
<tr><td>Comparator</td><td>Liver biopsy</td></tr>
<tr><td>Outcomes</td><td>Diagnostic accuracy of ARFI technique for liver fibrosis detection</td></tr>
<tr><td>Statistics</td><td>ROC curves and AUROC; sensitivity and specificity; positive predictive value and negative predictive value</td></tr>
<tr><td>Effect size</td><td>Cut-off values; AUROC; sensitivity and specificity; positive predictive value and negative predictive value:
F1: 1.22m/s; 0.639; 67.6% and 75%; 87.50% and 60%.
≥F2: 1.32m/s; 0.727; 75.0% and 90.9%; 90.9% and 75.0%.
≥F3: 1.44ms/; 0.905; 96.6% and 75%; 96.6% and 100%.
≥F4: 1.8m/s; 0.989; 95.7% and 100%; 100% and 40%.
The numbers of patients in each group were:
F1: 25; F2: 28; F3: 29 and F4: 108.
The 2 x 2 tables were calculated:
For F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥1.32m/s</td><td>124</td><td>2</td><td>126</td></tr>
<tr><td>VTq <1.32m/s</td><td>41</td><td>23</td><td>64</td></tr>
<tr><td>Total</td><td>165</td><td>25</td><td>190</td></tr>
</table>
For F=4:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥1.8m/s</td><td>103</td><td>0</td><td>103</td></tr>
<tr><td>VTq <1.8m/s</td><td>5</td><td>82</td><td>87</td></tr>
<tr><td>Total</td><td>108</td><td>82</td><td>190</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Study details</td><td>Friedrich-Rust M, Lupsor M, de Knegt R, et al. Point shear wave elastography by acoustic radiation force impulse quantification in comparison to transient elastography for the noninvasive assessment of liver fibrosis in chronic hepatitis C: a prospective international multicenter study. Ultraschall in Med 2015;36:239–47.</td></tr>
<tr><td>Design</td><td>Prospective cohort</td></tr>
<tr><td>Country</td><td>European multicenter study</td></tr>
<tr><td>Participants</td><td>241 patients with chronic hepatitis C at 7 European study sites</td></tr>
<tr><td>Age and gender</td><td>48 (11) years
103 (57%) male</td></tr>
<tr><td>Assigned interventions</td><td>VTq (pSWE)</td></tr>
<tr><td>Comparator</td><td>TE
Liver biopsy as gold standard</td></tr>
<tr><td>Outcomes</td><td>Diagnostic accuracy</td></tr>
<tr><td>Statistics</td><td>Paired comparison of the diagnostic accuracy of pSWE and TE</td></tr>
<tr><td>Effect size</td><td>No significant difference between the two methods in the 'intention to diagnose' and 'per protocol' analysis of diagnostic accuracy (0.81 vs. 0.85 for F ≥ 2, p = 0.15; 0.88 vs. 0.92 for F ≥ 3, p = 0.11; 0.89 vs. 0.94 for F = 4, p = 0.19).
The 2 x 2 tables were calculated:

F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.435/s</td><td>59</td><td>9</td><td>68</td></tr>
<tr><td>VTq < 1.435m/s</td><td>32</td><td>82</td><td>114</td></tr>
<tr><td>Total</td><td>91</td><td>91</td><td>182</td></tr>
</table>
F=4:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.755m/s</td><td>31</td><td>14</td><td>45</td></tr>
<tr><td>VTq < 1.755m/s</td><td>11</td><td>126</td><td>137</td></tr>
<tr><td>Total</td><td>42</td><td>140</td><td>182</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Study details</td><td>Frulio, N et al. Acoustic Radiation Force Impulse (ARFI) and Transient Elastography (TE) for evaluation of liver fibrosis in HIV-HCV co-infected patients. BMC Infectious Diseases 2014, 14:405</td></tr>
<tr><td>Design</td><td>Prospective study</td></tr>
<tr><td>Country</td><td>France</td></tr>
<tr><td>Participants</td><td>46 HIV-HCV co-infected patients. Missing data, delay (>6 months) between ARFI and TE or repeated examinations for the same patient were excluded.</td></tr>
<tr><td>Age and gender</td><td>Median (IQR) 48 (45-51) years
Male 32 (69.6%) Female 14 (30.4%)</td></tr>
<tr><td>Assigned interventions</td><td>VTq (Siemens Acuson S2000 using the virtual touch tissue quantification system)</td></tr>
<tr><td>Comparator</td><td>TE
The presence of cirrhosis was evaluated in all patients histologically (not all had biopsy) and from imaging, clinical and biological results included small nodular and irregular livers with increased echogenicity and/or a significant reduction in Doppler flow in the portal circulation on ultrasound, CT, or MRI.</td></tr>
<tr><td>Outcomes</td><td>Correlations between TE and ARFI measurements</td></tr>
<tr><td>Statistics</td><td>Spearman’s correlation coefficient and its two-sided 95% confidence interval (CI), as calculated with Fisher's z transformation.</td></tr>
<tr><td>Effect size</td><td>Spearman correlation analysis showed that the correlation coefficient between ARFI and TE measurements was 0.76 [95% CI, 0.61–0.86].
Overall agreement between the two methods was very good [concordance 69.6%, weighted Kappa = 0.82; 95% CI = 0.70–0.95].
Agreement was also very good for predicting severe fibrosis (≥F3) [concordance 93.5%, Kappa = 0.80, 95% CI = 0.59–1.00], and was moderate for predicting significant fibrosis (≥F2) [concordance 76.1%, Kappa = 0.5, 95% CI = 0.25–0.75].
TE cut=offs used were: 7.1, 9.5 and 12.5 kPa for liver fibrosis scores of F ≥ 2, F ≥3, and F = 4, respectively.
Cut-offs for VTq were 1.34, 1.55, 1.80 m/s for liver fibrosis scores of F ≥ 2, F ≥3, and F = 4, respectively.

The 2 x 2 table could be calculated:
For F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥1.34m/s</td><td>12</td><td>8</td><td>20</td></tr>
<tr><td>VTq <1.34m/s</td><td>3</td><td>23</td><td>26</td></tr>
<tr><td>Total</td><td>15</td><td>31</td><td>46</td></tr>
</table>
For F=4:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.80m/s</td><td>6</td><td>2</td><td>8</td></tr>
<tr><td>VTq <1.80m/s</td><td>0</td><td>38</td><td>38</td></tr>
<tr><td>Total</td><td>6</td><td>40</td><td>46</td></tr>
</table>
</td></tr>
</table>

Study details	Gandy N et al. PWE-037 Reliability of Arfi Shear Velocity Cut-Off for Diagnosis of Cirrhosis in Chronic Hepatitis C: A "Real World" Two Centre Simultaneous Biopsy-Controlled Study in the UK. Gut 2016;65:A157
Design	Retrospective study
Country	UK
Participants	96 patients with HCV infection. Three subgroups were analysed: 1) all 96 cases, including 20 patients with co-pathology (HBV, NAFLD, or ALD); 2) 76 cases with HCV only; 3) 84 cases who had simultaneous biopsy.
Age and gender	NA
Assigned interventions	VTq
Comparator	Liver biopsy or B-mode US imaging criteria
Outcomes	Diagnostic performance of ARFI was determined by ROC analysis, using a) reference SV cut-off values for Metavir stage, and b) optimal SV thresholds for cirrhosis derived from the authors' local data, including subgroup analysis.
Statistics	ROC.
Effect size	Cirrhosis was present in 26, 20 and 14 in groups 1, 2 and 3, respectively. Predictive accuracy for Metavir F4 using the reference threshold of 1.75 m/sec was 90%, 92% and 88% in groups 1, 2 and 3, respectively. Using new thresholds required a higher cutoff of 1.99 in group 1 compared with 1.64 in groups 2 and 3 to achieve accuracies of 87%–93%, whereas more consistent performance across all groups was achieved with median SVs at a cutoff of 1.89, achieving accuracies of 93%, 96% and 92%, respectively.

Study details	Jain, V. et al. Can acoustic radiation force impulse elastography be a substitute for liver biopsy in predicting liver fibrosis? Clinical radiology 2016; 71(9): 869-75.
Design	Cross-sectional study
Country	India
Participants	69 patients referred for an ultrasound with a clinical diagnosis of CLD (defined as persistently elevated aspartate aminotransferase [AST]/alanine aminotransferase [ALT] for >6 months); and patients with a clinical diagnosis of chronic hepatitis B or C (based on hepatitis B antigen [HBsAg] or anti-HCV antibody positivity) attending the gastroenterology/medicine outpatient departments for various complaints. The exclusion criteria for patients included patients with alcoholic liver disease with significant alcohol intake (defined as alcohol intake of 40-80 g/day in males and >20 g/day in females for a decade); patients with hepatocellular carcinoma diagnosed at imaging or serology; and patients who were pregnant or breast feeding.
Age and gender	Mean 34.71 years 49 (71.0%) male
Assigned interventions	VTq
Comparator	Liver biopsy
Outcomes	Diagnostic accuracy versus Ishak scoring system using a seven-point (F0-F6) scale (see table showing scoring systems)
Statistics	AUC

<table>
<tr>
<td>Effect size</td>
<td>
ARFI liver propagation velocity was positively correlated to histology with Spearman’s correlation coefficient rho = 0.789 (p<0.0001). Thus the mean shear-wave velocity (SWV) showed an increasing trend with increasing grade of fibrosis.
Applying an SWV cut-off of 1.347 m/s for detection of significant fibrosis (≥F3 on the Ishak scale; equivalent to F≥2 on the METAVIR scale), the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 91.3%, 83.7%, 75%, and 95%, respectively. Similarly, a cut-off of 1.92 m/s for the detection of cirrhosis (F5 or 6 on the ISHAK scale, or frankly cirrhotic without biopsy, equivalent to F=4 on the METAVIR scale) resulted in a sensitivity of 91.7%, specificity of 96.2%, PPV of 85%, and NPV of 98%.

The 2 x 2 tables could be calculated (transformed to METAVIR notation):

For F≥2 METAVIR:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.347 m/s</td><td>21</td><td>7</td><td>28</td></tr>
<tr><td>VTq <1.347 m/s</td><td>2</td><td>35</td><td>37</td></tr>
<tr><td>Total</td><td>23</td><td>42</td><td>65</td></tr>
</table>
For F=4 METAVIR:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.92 m/s</td><td>11</td><td>2</td><td>13</td></tr>
<tr><td>VTq < 1.92 m/s</td><td>1</td><td>51</td><td>52</td></tr>
<tr><td>Total</td><td>12</td><td>53</td><td>65</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td>Study details</td><td>Joo, Sae Kyung, et al. Prospective Comparison of Noninvasive Fibrosis Assessment to Predict Advanced Fibrosis or Cirrhosis in Asian Patients With Hepatitis C. Journal of clinical gastroenterology 2015; 49(8): 697-704.</td></tr>
<tr><td>Design</td><td>Cross-sectional study</td></tr>
<tr><td>Country</td><td>Republic of Korea</td></tr>
<tr><td>Participants</td><td>101 antiviral-naive patients with HCV. Excluded patients with HCV given antiviral treatment with conventional or pegylated interferon-α before study enrolment; other causes of chronic liver disease; decompensated liver cirrhosis or Child-Pugh class B/C; overt hypothyroidism or hyperthyroidism; absolute neutrophil count <1000/mL, platelet count <50,000/mL and haemoglobin <12g/dL (male) or 11g/dL (female); elevated serum creatinine >1.5 mg/dL; pregnancy or lactation.</td></tr>
<tr><td>Age and gender</td><td>Median (IQR) 59 (50-66) years
43 (42.6%) male; 58 (57.4%)</td></tr>
<tr><td>Assigned interventions</td><td>VTq</td></tr>
<tr><td>Comparator</td><td>Liver biopsy</td></tr>
<tr><td>Outcomes</td><td>Diagnostic accuracy</td></tr>
<tr><td>Statistics</td><td>AUROC</td></tr>
<tr><td>Effect size</td><td>Cut-off; AUROC (95% CI); sensitivity; specificity; positive predictive value; negative predictive value:
F≥1: 1.190; 0.872 (0.776-0.969); 84.0; 85.7; 98.8; 28.6
F≥2: 1.335; 0.853 (0.767-0.939); 83.8; 75.8; 87.7; 69.4
F≥3: 1.645; 0.840 (0.763-0.916); 79.5; 75.8; 67.4; 85.5
F=4: 1.665; 0.828 (0.740-0.916); 85.0; 69.1; 40.5; 94.9
The numbers of people in each group were: F0: 7; F1: 26; F2: 29; F3: 19; F4: 20.
The 2 x 2 tables could be calculated:
For F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.335m/s</td><td>66</td><td>10</td><td>76</td></tr>
<tr><td>VTq <1.335m/s</td><td>2</td><td>23</td><td>25</td></tr>
<tr><td>Total</td><td>68</td><td>33</td><td>101</td></tr>
</table>
For F=4:
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.665m/s</td><td>17</td><td>20</td><td>37</td></tr>
<tr><td>VTq <1.665m/s</td><td>3</td><td>61</td><td>64</td></tr>
<tr><td>Total</td><td>20</td><td>81</td><td>101</td></tr>
</table>
</td></tr>
</table>

Study details	LazAr, A et al. Diagnostic accuracy of three non-invasive methods to evaluate fibrosis in patients with HCV compensated liver cirrhosis. Journal of Gastrointestinal and Liver Diseases 2018; 27 Supplement 1: 37-38 (abstract)
Design	Retrospective study
Country	Romania
Participants	102 patients with hepatitis C virus (HCV) compensated liver cirrhosis
Age and gender	Mean age 61 +/- 8 years. 68 (67%) women and 34 (33%) men
Assigned interventions	VTq
Comparator	TE The diagnosis of cirrhosis was established based on clinical, biological, and ultrasound criteria (not biopsy).
Outcomes	Diagnostic accuracy
Statistics	Not stated
Effect size	For the diagnosis of liver cirrhosis: cut-off for VTq was 1.81 m/s. VTQ correctly diagnosed 81 out of 102 (79%) patients. Transient elastography correctly diagnosed 94 patients out of 102 (92%). Transient elastography performed significantly better than VTQ (92.1% versus 79.4%, p = 0.04)

Study details	Lopez, J. J. et al. Optimal Use of Transient Elastography and Acoustic Radiation Force Impulse to Stage Liver Fibrosis in HIV/HCV-Coinfected Patients in Clinical Practice. Journal of ultrasound in medicine: official journal of the American Institute of Ultrasound in Medicine 2018; 37(1): 113-121.
Design	Cross-sectional study
Country	Spain
Participants	89 consecutive HIV/HCV-coinfected patients. The main exclusion criteria included a daily alcohol intake of more than 20 g in women and 40 g in men, active drug abuse, a body mass index greater than 30 kg/m2, presence of active infections or neoplasms, and diagnosis of liver disease other than chronic HCV infection.
Age and gender	Median (IQR) 50 (46.5–53.0) years 76 (68%) male
Assigned interventions	VTq
Comparator	TE as reference standard
Outcomes	Diagnostic accuracy
Statistics	Concordance between VTq and TE; costs were reported in 2015 Euros. Sensitivity, specificity, positive and negative predictive values could be calculated.

<table>
<tr><td>Effect size</td><td>The cut-offs of liver stiffness by ARFI used to diagnose the fibrosis stage were those reported by Frulio 2014, as follows: F0 to F1, <1.43m/s; ≥F2 to F3, ≥1.43m/s; ≥F3, ≥1.73m/s; and F4, ≥2.05m/s.
More patients were classified as having fibrosis stage ≥F2, ≥F3, and cirrhosis by TE than by ARFI (VTq). Concordance between TE and ARFI was weak for fibrosis stages ≥F2 and ≥F3, and moderate for cirrhosis.
2 x 2 tables could be calculated:
≥F2:
<table>
<tr><td></td><td>TE ≥2</td><td>TE <2</td><td>Total</td></tr>
<tr><td>VTq ≥1.43m/s</td><td>44</td><td>8</td><td>52</td></tr>
<tr><td>VTq <1.43m/s</td><td>11</td><td>26</td><td>37</td></tr>
<tr><td>Total</td><td>55</td><td>34</td><td>89</td></tr>
</table>
Sensitivity: 44/55 = 80.0%
Specificity: 26/34 = 76.5%
Positive predictive value: 44/52 = 84.6%
Negative predictive value: 26/37 = 70.3%

F4:
<table>
<tr><td></td><td>TE =4</td><td>TE <4</td><td>Total</td></tr>
<tr><td>VTq ≥2.05m/s</td><td>19</td><td>4</td><td>23</td></tr>
<tr><td>VTq <2.05m/s</td><td>7</td><td>59</td><td>66</td></tr>
<tr><td>Total</td><td>26</td><td>63</td><td>89</td></tr>
</table>
Sensitivity: 19/26 = 73.1%
Specificity: 59/63 = 93.7%
Positive predictive value: 19/23 = 82.6%
Negative predictive value: 59/66 = 89.4%

The assessment of liver fibrosis resulted in a higher cost per patient for TE (€556.93) than for ARFI (€327.93).</td></tr>
</table>

Study details	Lupusoru, R et al. Prospective comparison of noninvasive techniques for the assessment of liver stiffness in a cohort of compensated HCV liver cirrhosis. United European Gastroenterology Journal 2016; 4(5 Supplement 1): A157-A158
Design	Prospective study
Country	Romania
Participants	100 consecutive patients diagnosed with HCV liver cirrhosis.
Age and gender	Mean (SD) 60+/-5.3 years 40 (40%) men and 60 (60%) women
Assigned interventions	VTQ
Comparator	TE
Outcomes	Accuracy in diagnosing cirrhosis
Statistics	Not stated
Effect size	TE elastography had 94.6% accuracy, pSWE (VTq) 79.3% (p=0.06).

Study details	Nierhoff, J et al. The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. European Radiology 2013; 23(11): 3040-53.
Design	Systematic review
Country	NA
Participants	Studies were included if they evaluated the performance of ARFI of the liver in adults with liver biopsy as the reference standard and chronic liver diseases (CLDs). Further, the studies had to use a comparable liver biopsy staging system (METAVIR, Ishak, Brunt, Ludwig's, Knodell, Desmet, Scheuer), assess the AUROC value for the fibrosis stages F≥2, F≥3 or F=4 according to METAVIR or a comparable staging system and/or assess sensitivity, specificity, positive predictive value (PPV) or negative predictive value (NPV) for the diagnosis of a fibrosis stage based on some cut-offs for liver stiffness. Studies were excluded if they were abstracts or full papers with data already published as a full paper. In the case of abstracts, which obviously present data of the same study at different meetings, only the most recent abstract was included. Authors of abstracts were contacted to confirm that the abstracts presented the data of the same patients before exclusion. Reviews, corresponding letters or editorials not reporting their own results were excluded too. Subgroup of patients with hepatitis C only (n=6 studies; total of 1280 participants) included here: Fierbinteanu-Braticevici 2009, Lupsor 2009, Song 2010, Fierbinteanu-Braticevici 2011, Rizzo 2011, Sporea 2011b). [Note 3 studies included overlapping populations (Fierbinteanu-Braticevici 2009 and Lupsor 2009) and these were excluded from the meta-analyses.]
Age and gender	Mean age varied from 49 to 64 years between studies. % male varied from 40 to 59% between studies
Assigned interventions	VTq
Comparator	Liver biopsy
Outcomes	Diagnostic accuracy
Statistics	AUROC and 95% CI; diagnostic odds ratio (DOR), calculated by [sensitivity/(1 – sensitivity)] × [specificity/(1 – specificity)]. A continuity correction of 0.5 was applied to each cell with a zero cell count. The Ishak score, using a scale from 0 to 6, was transformed into METAVIR.
Effect size	For the studies examining chronic hepatitis C (HCV)-infected patients only: F≥2: AUROC: 0.88 (0.81-0.96) F≥3: AUROC: 0.93 (0.89-0.97) F≥4: AUROC: 0.92 (0.86-0.99)

Study details	Nishimura, T et al. The diagnostic accuracy for liver fibrosis using shear wave elastography according to etiology of liver disease and the presence or absence of anti-viral therapy. Hepatology 2016; 64(1 Supplement 1): 327A-328A
Design	Cross-sectional study
Country	Japan
Participants	Included patients with chronic hepatitis B and C; outcomes shown separately.
Age and gender	NA
Assigned interventions	VTQ
Comparator	Liver biopsy
Outcomes	Diagnostic accuracy
Statistics	Not stated
Effect size	The optimal cutoff values for F3-4 (advanced fibrosis) were 1.49 m/s for hepatitis B and 1.43 m/s for hepatitis C. AUCs were 0.695 and 0.806, respectively.

Study details	Paranagua-Vezozzo, DC et al. Concordance of non-invasive mechanical and serum tests for liver fibrosis evaluation in chronic hepatitis C. World Journal of Hepatology 2017; 9(8): 436-442.
Design	Cross-sectional study
Country	Brazil
Participants	81 patients with chronic hepatitis C. Inclusion criteria were: (1) HCV polymerase chain reaction (PCR) RNA positivity for at least 6 mo, and clinical or histopathological diagnosis of chronic HCV; and (2) representative liver biopsy (minimum of 10 portal spaces, non subcapsular fragment) carried out until 30 d prior to LSM and SM. Exclusion criteria were: (1) patient under 18 years of age; (2) hepatitis B virus (HBV) or HIV co-infection; (3) other chronic liver disease (cholestasis, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease); (4) decompensated cirrhosis; (5) biopsies performed for more than 30 d of the evaluation; and (6) non-representative liver biopsy.
Age and gender	Median (IQR) 51 (30-78) years 40 (49.4%) male; 41 (50.6%) female
Assigned interventions	VTq
Comparator	METAVIR score from liver biopsy
Outcomes	Diagnostic performance
Statistics	Receiver operating characteristic curves

<table>
<tr>
<td>Effect size</td>
<td>
The best cut-off values for predicting fibrosis stage were:
F ≥ 2: 1.22 m/s;
F ≥ 3: 1.48 m/s;
F = 4: 1.77 m/s.
AUC (95% CI) were:
F ≥ 2: 0.7701 (0.6653-0.8749);
F ≥ 3: 0.8669 (0.7756-0.9583);
F = 4: 0.9188 (0.8592-0.9784).
Sensitivity and specificity were:
F ≥ 2: 78% and 70%;
F ≥ 3: 82.60% and 82.80%;
F = 4: 100% and 85.70%.
PPV and NPV were:
F ≥ 2: 85.50% and 58.40%;
F ≥ 3: 83.90% and 81.40%;
F = 4: 77.50% and 100%.
Overall accuracy:
F ≥ 2: 74.10%;
F ≥ 3: 82.70%;
F = 4: 87.70%.
The 2 x 2 tables were calculated:
For F≥2:
<table>
<tr><td></td><td>F≥2</td><td>F<2</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.22 m/s</td><td>34</td><td>11</td><td>45</td></tr>
<tr><td>VTq <1.22 m/s</td><td>9</td><td>27</td><td>36</td></tr>
<tr><td>Total</td><td>43</td><td>38</td><td>81</td></tr>
</table>
For F=4
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥ 1.77 m/s</td><td>11</td><td>10</td><td>21</td></tr>
<tr><td>VTq <1.77 m/s</td><td>0</td><td>60</td><td>60</td></tr>
<tr><td>Total</td><td>11</td><td>70</td><td>81</td></tr>
</table>
</td>
</tr>
</table>

Study details	Ragazzo TG, Paranagua-Vezozzo D, Lima FR, Mazo DF, Pessoa MG, Oliveira CP, et al. Accuracy of transient elastography-FibroScan, acoustic radiation force impulse (ARFI) imaging, the enhanced liver fibrosis (ELF) test, APRI, and the FIB-4 index compared with liver biopsy in patients with chronic hepatitis C. Clinics. 2017;72(9):516-525
Design	Prospective study
Country	Brazil
Participants	51 treatment-naïve patients chronically infected with HCV. Exclusions: 1. refusal to provide informed consent; 2. patient under 18 or over 70 years of age; 3. unavailability of liver biopsy (contraindication); 4. biopsies performed more than 60 days before the evaluation; 5. non-representative liver biopsy; 6. clinical suspicion or image evidence of HCC; 7. ascites; 8. body mass index (BMI) ≥30kg/m2; 9. previous treatment for HCV. 10. unreliable FibroScans results.
Age and gender	Overall: Age (years) F0 (n=8): 40.6±9.8 F1 (n=43): 44.8±10.9 F2 (n=31): 49.9±9.9 F3 (n=23): 53.8±8.9 F4 (n=2): 56.5±3.5 54 (50.4%) female
Assigned interventions	VTq (Siemens Acuson S2000)
Comparator	Liver biopsy
Outcomes	Diagnostic accuracy
Statistics	ROC; AUROC; cut-off points of different degrees of liver fibrosis in terms of sensitivity and specificity
Effect size	Cut-off; AUROC; sensitivity (95% CI); specificity (95% CI); positive predictive value (95% CI); negative predictive value (95% CI): ≥F2: 1.22m/s; 0.67 (0.51 - 0.82); 0.64 (0.43 - 0.82); 0.69 (0.48 - 0.86); 0.67 (0.45 - 0.84); 0.67 (0.45 - 0.84). ≥F3: 1.41m/s; 0.74 (0.57 - 0.90); 0.57 (0.29 - 0.82); 0.84 (0.68 - 0.94); 0.57 (0.35 - 0.82); 0.84 (0.61 - 0.94). ≥F4: 2.37m/s; 0.96 (0.90 – 1); 1 (0.16 – 1); 0.94 (0.83 - 0.99); 0.4 (0.18 – 1); 1 (0.81 – 1). Only 51 of the 107 patients had ARFI (VTq) and the numbers in each fibrosis stage were not shown for the ARFI (VTq) subgroup separately, so the 2 x 2 tables could not be calculated.

Study details	Sporea, I et al. Which is the best noninvasive method to diagnose compensated HCV liver cirrhosis? Gastroenterology 2016; 150(4 SUPPL. 1): S1169
Design	Prospective study
Country	NA
Participants	40 consecutive patients diagnosed with HCV liver cirrhosis. Patients with co-infection with HBV or HIV were excluded.
Age and gender	Mean (SD) 60.4 (8.4) years. 25 (62.5%) women and 15 (37.5%) men
Assigned interventions	VTq
Comparator	TE Cirrhosis diagnosed by liver biopsy, TE >12.5 kPa or by clinical, biologic ultrasonographic and endoscopic criteria.
Outcomes	Diagnosis of cirrhosis
Statistics	Published cut-offs were used to diagnose cirrhosis: VTQ-1.81 m/s
Effect size	Subjects were correctly classified by: TE in 97% of cases and VTQ in 97%.

Study details	Su, Tung-Hung et al. Acoustic Radiation Force Impulse US Imaging: Liver Stiffness in Patients with Chronic Hepatitis B with and without Antiviral Therapy. Radiology 2018; 288:293–299
Design	Retrospective cohort study
Country	Taiwan
Participants	559 patients with chronic hepatitis B aged 20 years or older and who received regular follow-up in the liver clinic. Patients with short-term (< 1 year) antiviral therapy or coinfection with hepatitis C virus, hepatitis D virus, or HIV were excluded.
Age and gender	Mean (SD) 49 (12); range 21–90 years; 302 (54%) male
Assigned interventions	VTq
Comparator	Severity of liver fibrosis from Metavir F0 through F4 according to the FibroScan (TE) results
Outcomes	Correlation between VTq and Metavir score
Statistics	Pearson correlation
Effect size	The ARFI value increased significantly by fibrosis score (P for trend < 0.001)

Study details	Tai, Dar-In et al. Differences in liver fibrosis between patients with chronic hepatitis B and C: evaluation by acoustic radiation force impulse measurements at 2 locations. J Ultrasound Med 2015; 34:813–821.
Design	Cross-sectional study
Country	Taiwan
Participants	121 patients with chronic hepatitis B and 83 with chronic hepatitis C. Patients with dual hepatitis B and C virus infection, HIV, alcoholic beverage consumption > 40 g/d, or histories of autoimmune liver diseases, metabolic liver diseases, or hepatocellular carcinoma were excluded.
Age and gender	Age Hepatitis B: 48.47 ± 10.76 Hepatitis C: 52.92 ± 11.29 (p=0.005) Male, n (%) Hep B: 98 (81.0) Hep C: 48 (57.8) p=0.001
Assigned interventions	VTq at two locations (A and B, mainly situated in segments 5 and 8, respectively)
Comparator	Liver biopsy
Outcomes	Diagnosis of liver cirrhosis (METAVIR F4)
Statistics	ROC curves were constructed, and AUROC values were calculated for evaluation of the best prediction tests

<table>
<tr><td>Effect size</td><td>
Within individuals, there were differences in ARFI values between locations A and B (149 [73.0%] of patients had variations ≤0.2 m/s; larger variations were seen in 55 [27.0%]).
F4:
AUROC (SE; p; 95% CI) were calculated overall and by hepatitis type separately, and within these groups by location, and by the lower, higher or mean ARFI value:
Total
ARFI location A 0.746 (0.036; <.001; 0.676–0.817)
ARFI location B 0.720 (0.037; <.001; 0.647–0.793)
Lower ARFI value 0.750 (0.035; <.001; 0.682–0.818)
Higher ARFI value 0.730 (0.037; <.001; 0.657–0.803)
Mean ARFI value 0.744 (0.036; <.001; 0.673–0.814)
Hepatitis B
ARFI location A 0.700 (0.048; <.001; 0.606–0.793)
ARFI location B 0.681 (0.048; .001; 0.587–0.775)
Lower ARFI value 0.707 (0.046; <.001; 0.616–0.798)
Higher ARFI value 0.690 (0.048; .001; 0.596–0.785)
Mean ARFI value 0.702 (0.047; <.001; 0.610–0.795)
Hepatitis C
ARFI location A 0.821 (0.059; <.001; 0.706–0.937)
ARFI location B 0.802 (0.067; <.001; 0.670–0.934)
Lower ARFI value 0.824 (0.060; <.001; 0.707–0.942)
Higher ARFI value 0.795 (0.068; <.001; 0.661–0.929)
Mean ARFI value 0.808 (0.065; <.001; 0.681–0.935)
Sensitivity and specificity for diagnosis of liver cirrhosis (F4)
Hepatitis B: 0.628 and 0.705, when the low ARFI cutoff value was set at 1.35 m/s.
Hepatitis C: 0.706 and 0.803 when the low ARFI cutoff value was set at 1.41 m/s.

METAVIR fibrosis score <2:
AUROC:
Hepatitis B: 0.857. The correlation between ARFI and METAVIR fibrosis scores improved with removal of patients with chronic hepatitis B with ALT levels ≥5 times the upper limit of normal.
Hepatitis C: not stated
Sensitivity and specificity for diagnosis of METAVIR <2:
Hepatitis B: 0.766 and 0.793 when the low ARFI cutoff value was set at 1.17 m/s.
Hepatitis C: 0.765 and 0.788 when the low ARFI cutoff value was set at 1.39 m/s.

The 2 x 2 tables could be calculated for F=4 for hepatitis B and C separately.

For F=4 (hepatitis B):
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
<tr><td>VTq ≥1.35m/s</td><td>27</td><td>23</td><td>50</td></tr>
<tr><td>VTq < 1.35m/s</td><td>16</td><td>55</td><td>71</td></tr>
<tr><td>Total</td><td>43</td><td>78</td><td>121</td></tr>
</table>
For F=4 (hepatitis C):
<table>
<tr><td></td><td>F=4</td><td>F<4</td><td>Total</td></tr>
</table>
</td></tr>
</table>

VTq ≥1.41m/s	12	13	25
VTq < 1.41m/s	5	53	58
Total	17	66	83

Study details	Tsukano, N et al. Usefulness of virtual touch quantification for staging liver fibrosis in patients with hepatitis C, and factors affecting liver stiffness measurement failure compared with liver biopsy. Hepatology Research 2018; 48(5): 373-382.
Design	Cross-sectional
Participants	302 patients with hepatitis C. Patients with HBV co-infection or other various liver diseases, or who were 18 years of age or younger, were excluded.
Assigned interventions	VTq
Comparator	Liver biopsy
Outcomes	Diagnostic accuracy
Statistics	ROC, AUROC
Effect size	The VTQ cut-off values, AUROCs, sensitivity and specificity were: ≥F2: 1.33 m/s; 0.822; sensitivity 76%, specificity 80%. ≥F3: 1.51 m/s; 0.836; sensitivity 80%, specificity 79%. F4: 1.92 m/s; 0.890; sensitivity 90%, specificity 84%. The 2 x 2 tables were calculated: For F≥2:

	F≥2	F<2	Total
VTq ≥1.33m/s	147	22	169
VTq <1.33m/s	47	86	133
Total	194	108	302

For F=4:

	F=4	F<4	Total
VTq ≥1.92m/s	35	55	90
VTq <1.92m/s	4	208	212
Total	39	263	302

Completed (but unpublished) and ongoing trials

Completed

Clinical Trials Identifier	Title	Sponsor	Participants	Intervention	Comparator	Outcomes
NCT01781208	Ultrasound Based Acoustic Radiation Force Impulse Imaging	University of Michigan	62 children undergoing liver biopsy for known or suspected non-neoplastic liver disease, to assess liver fibrosis and inflammation. Mean age 8 years; 33 (53.2%) male	ARFI/VTQ	Liver biopsy: the histologic scoring system (Ishak) ranged from 0 to 6, where 0 = no fibrosis and 6 = cirrhosis.	49 (79.0%) children underwent successful (diagnostic) liver ARFI/VTQ) assessment and liver histologic fibrosis scoring. 13 (21.0%) subjects had non-diagnostic ARFI/VTQ exams. Pearson Correlation between ARFI (VTQ) liver shear wave speed and liver histologic fibrosis score: r=0.68, unadjusted for age, gender, and histologic inflammation. There were no adverse events.

Ongoing

Clinical Trials Identifier	Title	Sponsor	Participants	Intervention	Comparator	Study type
NCT01268865	Acoustic Radiation Force Impulse (ARFI) Technology in Prediction of Liver Fibrosis (ARFI)	China Medical University Hospital	Adults infected with HBV only or HCV only	VTq	Liver biopsy	Cohort

Appendix C – Literature search strategy

Databases searched

Databases	Date searched	No retrieved	Version/files
MEDLINE (Ovid)	11/07/2019	196	1946 to July 10, 2019>
MEDLINE In-Process (Ovid)	11/07/2019	38	1946 to July 10, 2019>
EMBASE (Ovid)	12/07/2019	291 (251 conference abstracts)	1974 to 2019 July 11
Ovid ePubs	11/07/2019	4	1946 to July 10, 2019>
CDSR (Wiley)	12/07/2019	0	Issue 7 of 12, July 2019
*Database of Abstracts of Reviews of Effects – DARE (CRD)	12/07/2019	0	-
HTA database (CRD)	12/07/2019	1	-
CENTRAL (Wiley)	12/07/2019	18	Issue 7 of 12, July 2019
*NHS EED (CRD	12/07/2019	0	-
Econlit (for economic searches)	12/07/2019	1	1886 to July 04, 2019
Total		799	
Total after de-duplication		596	

**From January 2015 no new records/commentaries will be added to DARE or NHS EED.*

Search strategies

Database: MEDLINE
Strategy used: Database: Ovid MEDLINE(R) <1946 to July 10, 2019> Search Strategy: --- 1 acuson*.tw. (397) 2 (virtual* adj4 touch* adj4 quantificat*).tw. (185) 3 (VTQ* or VTIQ*).tw. (135) 4 (acoustic adj4 radiation adj4 force adj4 impuls*).tw. (682) 5 ARFI*.tw. (653) 6 or/1-5 (1270) 7 Liver diseases/ (66682) 8 (liver adj4 (fibros* or inflam* or disease*)).tw. (102890) 9 Liver Cirrhosis/ (70020)

10 cirrhosis.tw. (76524)
11 hepatitis/ or hepatitis, chronic/ or hepatitis b, chronic/ or hepatitis c, chronic/ or hepatitis, viral, human/ (72757)
12 hepatitis.tw. (187588)
13 ((liver* or hepat*) adj4 stiff*).tw. (1808)
14 or/7-13 (370599)
15 6 and 14 (353)
16 animals/ not humans/ (4564528)
17 15 not 16 (341)
18 limit 17 to english language (322)
19 Predictive value of tests/ (192263)
20 predictive.tw. (246643)
21 ROC Curve/ (52754)
22 "ROC curve".tw. (18210)
23 (receiver adj4 operating adj4 characteristic*).tw. (48996)
24 (sensitiv: or predictive value:).mp. or accurac:.tw. (1787924)
25 incidence.sh. (245384)
26 exp mortality/ (361563)
27 follow-up studies.sh. (617224)
28 prognos:.tw. (480072)
29 predict:.tw. (1204967)
30 course:.tw. (524247)
31 or/25-30 (2903624)
32 (sensitiv: or diagnos:).mp. or di.fs. (5469959)
33 31 or 32 (7287160)
34 18 and 33 (311)
35 limit 34 to ed=20140601-20190731 (196)

Database: MEDLINE in PROCESS

Strategy used:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 10, 2019>
Search Strategy:
---
1 acuson*.tw. (35)
2 (virtual* adj4 touch* adj4 quantificat*).tw. (31)
3 (VTQ* or VTIQ*).tw. (21)
4 (acoustic adj4 radiation adj4 force adj4 impuls*).tw. (119)
5 ARFI*.tw. (156)
6 or/1-5 (236)
7 Liver diseases/ (0)
8 (liver adj4 (fibros* or inflam* or disease*)).tw. (14001)
9 Liver Cirrhosis/ (0)

10 cirrhosis.tw. (8106)
11 hepatitis/ or hepatitis, chronic/ or hepatitis b, chronic/ or hepatitis c, chronic/ or hepatitis, viral, human/ (0)
12 hepatitis.tw. (17239)
13 ((liver* or hepat*) adj4 stiff*).tw. (453)
14 or/7-13 (31184)
15 6 and 14 (70)
16 animals/ not humans/ (0)
17 15 not 16 (70)
18 limit 17 to english language (70)
19 Predictive value of tests/ (0)
20 predictive.tw. (34593)
21 ROC Curve/ (0)
22 "ROC curve".tw. (3412)
23 (receiver adj4 operating adj4 characteristic*).tw. (8616)
24 (sensitiv: or predictive value:).mp. or accurac:.tw. (203227)
25 incidence.sh. (0)
26 exp mortality/ (0)
27 follow-up studies.sh. (0)
28 prognos:.tw. (62824)
29 predict:.tw. (213075)
30 course:.tw. (50464)
31 or/25-30 (302243)
32 (sensitiv: or diagnos:).mp. or di.fs. (378325)
33 31 or 32 (612132)
34 18 and 33 (48)
35 limit 34 to dt=20140601-20190731 (38)

Database: MEDLINE ePUB ahead of print

Strategy used:
Database: Ovid MEDLINE(R) Epub Ahead of Print <July 10, 2019>
Search Strategy:
---
1 acuson*.tw. (9)
2 (virtual* adj4 touch* adj4 quantificat*).tw. (9)
3 (VTQ* or VTIQ*).tw. (8)
4 (acoustic adj4 radiation adj4 force adj4 impuls*).tw. (21)
5 ARFI*.tw. (21)
6 or/1-5 (38)
7 Liver diseases/ (0)
8 (liver adj4 (fibros* or inflam* or disease*)).tw. (2121)
9 Liver Cirrhosis/ (0)
10 cirrhosis.tw. (1145)

11 hepatitis/ or hepatitis, chronic/ or hepatitis b, chronic/ or hepatitis c, chronic/ or hepatitis, viral, human/ (0)
12 hepatitis.tw. (2578)
13 ((liver* or hepat*) adj4 stiff*).tw. (91)
14 or/7-13 (4667)
15 6 and 14 (7)
16 animals/ not humans/ (0)
17 15 not 16 (7)
18 limit 17 to english language (7)
19 Predictive value of tests/ (0)
20 predictive.tw. (6793)
21 ROC Curve/ (0)
22 "ROC curve".tw. (679)
23 (receiver adj4 operating adj4 characteristic*).tw. (2002)
24 (sensitiv: or predictive value:).mp. or accurac:.tw. (26770)
25 incidence.sh. (0)
26 exp mortality/ (0)
27 follow-up studies.sh. (0)
28 prognos:.tw. (10809)
29 predict:.tw. (33433)
30 course:.tw. (7778)
31 or/25-30 (47401)
32 (sensitiv: or diagnos:).mp. or di.fs. (53555)
33 31 or 32 (89310)
34 18 and 33 (5)

Database: EMBASE

Strategy used:
Database: Embase <1974 to 2019 July 11>
Search Strategy:
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1 acuson*.tw. (1010)
2 acuson*.dm. (1642)
3 (virtual* adj4 touch* adj4 quantificat*).tw. (411)
4 (VTQ* or VTIQ*).tw. (316)
5 ((virtual* adj4 touch* adj4 quantificat*) or (VTQ* or VTIQ*)).dv. (16)
6 acoustic radiation force impulse imaging/ (972)
7 (acoustic adj4 radiation adj4 force adj4 impuls*).tw. (1356)
8 ARFI*.tw. (1511)
9 ((acoustic adj4 radiation adj4 force adj4 impuls*) or ARFI*).dv. (7)
10 or/1-9 (4580)
11 Liver disease/ or liver fibrosis/ (129585)
12 (liver adj4 (fibros* or inflam* or disease*)).tw. (183593)

13 Liver Cirrhosis/ (121269)
14 cirrhosis.tw. (126546)
15 hepatitis/ or chronic hepatitis/ or chronic hepatitis B/ or chronic hepatitis C/ or virus hepatitis/ (105446)
16 hepatitis.tw. (279173)
17 liver stiffness/ (3308)
18 ((liver* or hepat*) adj4 stiff*).tw. (5961)
19 or/11-18 (552905)
20 10 and 19 (1176)
21 nonhuman/ not human/ (4426395)
22 20 not 21 (1155)
23 limit 22 to english language (1104)
24 Predictive value of tests/ (80077)
25 predictive.tw. (427153)
26 receiver operating characteristic/ (107674)
27 "ROC curve".tw. (40711)
28 (receiver adj4 operating adj4 characteristic*).tw. (78104)
29 (sensitiv: or predictive value:).mp. or accurac:.tw. (2393752)
30 incidence.sh. (360504)
31 exp mortality/ (996425)
32 follow-up studies.sh. (107)
33 prognos:.tw. (833407)
34 predict:.tw. (1941711)
35 course:.tw. (784203)
36 or/30-35 (4223184)
37 (sensitiv: or diagnos:).mp. or di.fs. (7385428)
38 36 or 37 (10157409)
39 23 and 38 (921)
40 limit 39 to dc=20140601-20190731 (542)
41 limit 40 to (conference abstract or conference paper or "conference review") (251)
42 40 not 41 (291)

Database: Cochrane

Strategy used:
Search Name: MTG review - Virtual Touch Quantification
Date Run: 12/07/2019 10:20:53
Comment:

ID	Search	Hits
#1	(acuson*):ti,ab,kw	45
#2	((virtual* near/4 touch* near/4 quantificat*)):ti,ab,kw	10
#3	((VTQ* or VTIQ*)):ti,ab,kw	8

#4 ((acoustic near/4 radiation near/4 force near/4 impuls*)):ti,ab,kw 50
#5 (ARFI*):ti,ab,kw 55
#6 #1 or #2 or #3 or #4 or #5 111
#7 MeSH descriptor: [Liver Diseases] this term only 1051
#8 ((liver near/4 (fibros* or inflam* or disease*))):ti,ab,kw 11733
#9 MeSH descriptor: [Liver Cirrhosis] this term only 2300
#10 (cirrhosis):ti,ab,kw 9172
#11 MeSH descriptor: [Hepatitis] this term only 1275
#12 MeSH descriptor: [Hepatitis, Chronic] this term only 767
#13 MeSH descriptor: [Hepatitis B, Chronic] this term only 1109
#14 MeSH descriptor: [Hepatitis C, Chronic] this term only 1788
#15 MeSH descriptor: [Hepatitis, Viral, Human] this term only 136
#16 (hepatitis):ti,ab,kw 19708
#17 (((liver* or hepat*) near/4 stiff*)):ti,ab,kw 307
#18 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 32861
#19 MeSH descriptor: [Predictive Value of Tests] this term only 7016
#20 (predictive):ti,ab,kw 27303
#21 MeSH descriptor: [ROC Curve] this term only 1207
#22 ("ROC curve"):ti,ab,kw 2308
#23 ((receiver near/4 operating near/4 characteristic*)):ti,ab,kw 4676
#24 ((sensitiv* or predictive value* or accurac*)):ti,ab,kw 96297
#25 MeSH descriptor: [Mortality] explode all trees 12722
#26 (prognos*):ti,ab,kw 41822
#27 (predict*):ti,ab,kw 91925
#28 (course*):ti,ab,kw 63335
#29 ((sensitiv* or diagnos*)):ti,ab,kw 261661
#30 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 397935
#31 #6 and #18 and #30 with Publication Year from 2014 to 2019, with Cochrane Library publication date Between Jun 2014 and Jul 2019, in Trials 18

Database: CRD

Strategy used:

	Line	Search	Hits	
	1	(acuson*)	3	Delete
	2	((virtual* and touch* and quantificat*))	0	Delete
	3	((VTQ* or VTIQ*))	0	Delete

	4	((acoustic and radiation and force and impuls*))	4	Delete
	5	(ARFI*)	1	Delete
	6	#1 OR #2 OR #3 OR #4 OR #5	8	Delete
	7	MeSH DESCRIPTOR Liver diseases	93	Delete
	8	(liver) AND ((fibros* or inflam* or disease*))	1236	Delete
	9	MeSH DESCRIPTOR Liver Cirrhosis	260	Delete
	10	(cirrhosis)	623	Delete
	11	MeSH DESCRIPTOR hepatitis	10	Delete
	12	MeSH DESCRIPTOR hepatitis, chronic	12	Delete
	13	MeSH DESCRIPTOR hepatitis b, chronic	181	Delete
	14	MeSH DESCRIPTOR hepatitis c, chronic	317	Delete
	15	MeSH DESCRIPTOR hepatitis, viral, human	11	Delete
	16	(hepatitis)	1348	Delete
	17	((liver* or hepat*)) AND (stiff*)	16	Delete
	18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	2369	Delete
	19	#6 AND #18	4	Delete

Database: Econlit

Strategy used:
Database: Econlit <1886 to July 04, 2019>
Search Strategy:

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1 acuson*.tw. (1)
2 (virtual* adj4 touch* adj4 quantificat*).tw. (1)
3 (VTQ* or VTIQ*).tw. (1)

4 (acoustic adj4 radiation adj4 force adj4 impuls*).tw. (0)
5 ARFI*.tw. (333)
6 or/1-5 (334)
7 [Liver diseases/] (0)
8 (liver adj4 (fibros* or inflam* or disease*)).tw. (31)
9 [Liver Cirrhosis/] (0)
10 cirrhosis.tw. (25)
11 [hepatitis/ or hepatitis, chronic/ or hepatitis b, chronic/ or hepatitis c, chronic/ or hepatitis, viral, human/] (0)
12 hepatitis.tw. (88)
13 ((liver* or hepat*) adj4 stiff*).tw. (1)
14 or/7-13 (132)
15 6 and 14 (1)
16 [animals/ not humans/] (0)
17 15 not 16 (1)
18 limit 17 to english language [Limit not valid; records were retained] (1)
19 [Predictive value of tests/] (0)
20 predictive.tw. (6598)
21 [ROC Curve/] (0)
22 "ROC curve".tw. (50)
23 (receiver adj4 operating adj4 characteristic*).tw. (83)
24 (sensitiv: or predictive value:).mp. or accurac:.tw. (31526)
25 incidence.sh. (0)
26 [exp mortality/] (0)
27 follow-up studies.sh. (0)
28 prognos:.tw. (556)
29 predict:.tw. (60032)
30 course:.tw. (10781)
31 or/25-30 (70580)
32 (sensitiv: or diagnos:).mp. or di.fs. (27820)
33 31 or 32 (95938)
34 18 and 33 (1)

Appendix D – References

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