Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease (Review)

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[Diagnostic Test Accuracy Review]

Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

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ABSTRACT

Background

The presence and progression of hepatic (liver) fibrosis into cirrhosis is a prognostic variable having impact on survival in people with alcoholic liver disease. Liver biopsy, although an invasive method, is the recommended 'reference standard' for diagnosis and staging of hepatic fibrosis in people with liver diseases. Transient elastography is a non-invasive method for assessing and staging hepatic fibrosis.

Objectives

To determine the diagnostic accuracy of transient elastography for diagnosis and staging hepatic fibrosis in people with alcoholic liver disease when compared with liver biopsy. To identify the optimal cut-off values for differentiating the five stages of hepatic fibrosis.

Search methods

The Cochrane Hepato-Biliary Group Controlled and Diagnostic Test Accuracy Studies Registers, *The Cochrane Library*, MEDLINE (OvidSP), EMBASE (OvidSP), and the Science Citation Index Expanded (last search August 2014).

Selection criteria

Diagnostic cohort and diagnostic case-control study designs that assessed hepatic fibrosis in participants with alcoholic liver disease with transient elastography and liver biopsy, irrespective of language or publication status. The study participants could be of any sex and ethnic origin, above 16 years old, hospitalised or managed as outpatients. We excluded participants with viral hepatitis, autoimmunity, metabolic diseases, and toxins.

Data collection and analysis

We followed the guidelines in the draft *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.*

Main results

Five retrospective and nine prospective cohort studies with 834 participants provided data for the review analyses. Authors of seven of those studies sent us individual participant data. The risk of bias in the included studies was high in all but three studies. We could identify no serious concerns regarding the applicability of the studies in answering the main study question of our review, namely to use transient elastography to diagnose hepatic fibrosis. We could not identify the optimal cut-off values for the fibrosis stages. The definition of the diagnosis of alcoholic liver disease was not provided in one study and was not clearly defined in two studies, but it was clear in the remaining 11 studies. The study authors used different liver stiffness cut-off values of transient elastography for the hepatic fibrosis stages.

There was only one study (103 participants) with data on hepatic fibrosis stage F1 or worse, with a cut-off of 5.9 kPa, and reporting sensitivity of 0.83 (95% confidence interval (CI) 0.74 to 0.90) and specificity of 0.88 (95% CI 0.47 to 1.00). The summary sensitivity and specificity of transient elastography for F2 or worse (seven studies with 338 participants and with cut-offs around 7.5 kPa (range 7.00 to 7.8 kPa)) were 0.94 and 0.89 with LR+ 8.2 and LR- 0.07, which suggests that transient elastography could be useful to rule out the presence of significant hepatic fibrosis, thus avoiding liver biopsy.

Due to the wide range of cut-off values (from 8.0 to 17.0 kPa) found in the 10 studies with 760 participants with hepatic fibrosis F3 or worse, we fitted a hierarchical summary receiver operating characteristic (HSROC) model and estimated a summary ROC (SROC) curve. The sensitivity of the 10 studies varied from 72% to 100% and the specificity from 59% to 89%. We performed an additional analysis by including the studies with a cut-off value of around and equal to 9.5 kPa (range 8.0 to 11.0 kPa). The summary sensitivity and specificity of transient elastography (eight studies with 564 participants) were 0.92 and 0.70 with LR+ 3.1 and LR- 0.11, which suggests that transient elastography could also be useful to rule out the presence of severe hepatic fibrosis (F3 or worse), avoiding liver biopsy. We carried out a sensitivity analysis by considering only the studies with a cut-off value equal to 9.5 kPa and the result did not differ.

We performed an HSROC analysis and reported an SROC curve for hepatic fibrosis stage F4 (cirrhosis). The HSROC analysis suggested that when the cut-off value changes, there is a wide variation in specificity and a more limited variation in sensitivity. We performed an additional analysis with the studies with the most commonly used cut-off value of 12.5 kPa. The summary sensitivity and specificity of transient elastography (seven studies with 330 participants) were 0.95 and 0.71 with LR+ 3.3 and LR- 0.07, which again suggests that transient elastography could be useful to rule out the presence of cirrhosis, avoiding liver biopsy.

Authors' conclusions

We identified a small number of studies with a few participants and were unable to include several studies, which raises the risk of outcome reporting bias. With these caveats in mind, transient elastography may be used as a diagnostic method to rule out liver cirrhosis (F4) in people with alcoholic liver disease when the pre-test probability is about 51% (range 15% to 79%). Transient elastography may also help in ruling out severe fibrosis (F3 or worse). Liver biopsy investigation remains an option if the certainty to rule in or rule out the stage of hepatic fibrosis or cirrhosis remains insufficient after a clinical follow-up or any other non-invasive test considered useful by the clinician.

The proposed cut-off values for the different stages of hepatic fibrosis may be used in clinical practice, but caution is needed, as those values reported in this review are only the most common cut-off values used by the study authors. The best cut-off values for hepatic fibrosis in people with alcoholic liver disease could not be established yet.

In order to diagnose correctly the stage of hepatic fibrosis in people with alcoholic liver disease using transient elastography assessment, the studies should consider a single aetiology. Hepatic fibrosis should be diagnosed with both transient elastography and liver biopsy and in this sequence, and transient elastography cut-off values should be pre-specified and validated. The time interval between the two investigations should not exceed three months, which is the interval mainly valid for people without cirrhosis, and assessment of results should be properly blinded. Only studies with low risk of bias, fulfilling the Standards for Reporting of Diagnostic Accuracy may answer the review question.

PLAIN LANGUAGE SUMMARY

Transient elastography for measurement of liver fibrosis and cirrhosis in people with alcoholic liver disease

Background

Liver fibrosis is a change in the microscopic structure of the liver because of liver inflammation. After many years of excessive alcohol consumption, liver fibrosis progresses to cirrhosis. Abstaining from alcohol may stop the fibrosis from further progression into significant or severe fibrosis and cirrhosis. The latter lead to complications of underlying diseases, including cancer.

Measurement of the amount of fibrosis is called staging. There are five stages (F0: no scarring (no fibrosis); F1: minimal scarring; F2: scarring has occurred and extends outside the liver area (significant fibrosis); F3: fibrosis spreading and forming bridges with other fibrotic liver areas (severe fibrosis); F4: cirrhosis or advanced scarring). Cut-off values may distinguish between the different stages of fibrosis, but in people with alcoholic liver disease, the best cut-off values have not been determined yet.

Rationale

Liver biopsy is where a sample of tissue is taken from the liver using a small needle. It is the standard method of detecting and measuring fibrosis.

Transient elastography measures stiffening of the liver caused by progressive scarring, but it has not been validated in people with alcoholic liver disease.

Aims

To find out how well transient elastography may determine the presence or absence of fibrosis and if it can stage fibrosis in people with alcoholic liver disease when compared with liver biopsy.

Methods

Using Cochrane methods and searching the literature (August 2014), the review authors obtained results from 14 studies (834 participants), out of which only seven included people with only alcoholic liver disease. Participants underwent both transient elastography (the index test) and liver biopsy (the standard test).

Findings and conclusions

The number of studies and participants was small and the participants had different severity of liver fibrosis. Only four studies were judged good quality.

Transient elastography fibrosis stage F2 or worse (significant fibrosis)

There were seven studies with 338 participants: 81% of people had significant fibrosis. Out of 1000 people, 810 will have significant fibrosis. Of these 810 people, 49 people would be missed even though they had significant fibrosis. A clinical follow-up could provide physicians with knowledge for the next diagnostic step. The remaining 190 people would not have significant fibrosis; 21 people would have unnecessary worries about their liver fibrosis stage.

Transient elastography fibrosis stage F3 or worse (severe fibrosis)

There were eight studies with 564 participants: 61% of people had severe fibrosis. Out of 1000 people, 610 would have severe fibrosis. Of these 610 people, 49 people would be missed even though they had severe fibrosis. A clinical follow-up could provide physicians with knowledge for the next diagnostic step. The remaining 390 people would not have severe fibrosis; 117 people would have unnecessary worries about their liver fibrosis stage.

Transient elastography fibrosis stage F4 (cirrhosis)

There were seven studies with 330 participants: 51% of people had cirrhosis. Out of 1000 people, 510 will have cirrhosis. Of these 510 people, 26 people would be missed even though they had cirrhosis. A clinical follow-up could provide physicians with knowledge for the next diagnostic step. The remaining 490 people would not have cirrhosis; 143 people would have unnecessary worries about their liver fibrosis stage.

Transient elastography may be used as a diagnostic tool to rule out liver cirrhosis and may also help in ruling out severe fibrosis in people with alcoholic liver disease. Liver biopsy investigation still remains an option if the certainty to rule in or rule out the stage of hepatic fibrosis or cirrhosis remains insufficient after a clinical follow-up or any other non-invasive test considered useful by the clinician.

The best cut-off values for differentiating between the five liver fibrosis stages could still not be established.

Future studies should include only people with alcoholic liver disease. Hepatic fibrosis should be diagnosed with transient elastography followed by liver biopsy and the transient elastography cut-off values of liver stiffness for the different stages of liver fibrosis should be decided before the test occurs. The time interval between the two tests should not exceed three months, an interval that is mainly valid for people without cirrhosis. Assessors of results should be unaware of the treatment given.

BACKGROUND

Transient elastography is a widely used non-invasive method for assessing and staging hepatic fibrosis (scarring of the liver tissue). Transient elastography measures stiffening of the liver, which is caused by progressive scarring. Transient elastography assessment of hepatic (liver) fibrosis has already been validated in many people with chronic liver diseases of various aetiologies (Sandrin 2003; Nahon 2008). It is important to define the cut-off values that could differentiate hepatic fibrosis stages. In fact, cut-off levels for specific stages of hepatic fibrosis vary according to the aetiology of the chronic liver disease. In people with alcoholic liver disease, such cut-off values have not been established and validated yet (Rockey 2008).

Excessive alcohol consumption may lead to alcohol-related liver disease. Every year, alcohol use kills 2.5 million people, including 320,000 young people between 15 and 29 years of age. Alcohol is the third leading risk factor for poor health globally, and harmful use of alcohol was responsible for almost 4% of all deaths in the world, according to the estimates for 2004 (WHO 2010). Alcoholism is a disease that damages the brain, liver, heart, and other organs. Heavy alcohol consumption can lead to brain shrinkage, dementia, alcoholism, cancer, and death. Negative effects of alcohol include liver damage and multiple liver diseases, including liver cirrhosis and cancer (Bruha 2012).

The presence and progression of hepatic fibrosis into cirrhosis is a main prognostic variable having impact on survival in people with alcoholic liver disease. Transient elastography may indicate the amount of hepatic fibrosis in people with alcoholic liver disease (de Lédinghen 2010). A number of clinical studies have compared liver stiffness measured by transient elastography with presence and histological staging of hepatic fibrosis by liver biopsy, reaching a conclusion that transient elastography is a reliable method for assessment of hepatic fibrosis (Foucher 2006; Gómez-Domínguez 2006; Ivashkin 2011a; Tsochatzis 2011). In addition, studies have found a correlation between the level of liver stiffness and the degree of hepatic fibrosis in people with alcoholic liver disease (Nguyen-Khac 2008; Nahon 2009; Mueller 2010). The prevalence of hepatic fibrosis in heavy drinkers is not well known. In a series of 1407 people with alcoholic liver disease diagnosed on liver biopsy, 809 (57.5%) people had developed hepatic fibrosis (Naveau 1997). Accurate detection of hepatic fibrosis stage is important for prognosis of hepatic fibrosis and choice of treatment in people with alcohol-related liver injury (O'Shea 2010).

Target condition being diagnosed

Hepatic fibrosis in people with alcoholic liver disease

All people with alcoholic liver disease are at risk of developing hepatic fibrosis. This risk is considered higher in people who are binge drinkers, people with increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, or in people with severe alcohol hepatitis on liver biopsy (Bouchier 1992).
Hepatic fibrosis may develop as a result of weekly alcohol consumption of seven to 13 alcoholic beverages for women (one beverage = 12 g alcohol) and 14 to 27 alcoholic beverages for men in the course of five or more years (Savolainen 1993; Becker 1996). The risk ratio of progression of fibrosis to cirrhosis increases significantly with a daily consumption of 20 g to 40 g ethanol in women and more than 80 g ethanol in men (Sherlock 1997; O'Shea 2010).
The liver is the main site of alcohol metabolism acting through two hepatic enzymes, alcohol dehydrogenase and cytochrome P-450 (CYP) 2E1. Increased alcohol intake disrupts the metabolic liver function, and, as a result, alcoholic liver disease develops (Stewart 2001). Histologically, alcoholic liver disease occurs in three forms: fatty liver or steatosis, alcoholic hepatitis, and chronic hepatitis with hepatic fibrosis and cirrhosis (O'Shea 2010). Morphological features that predict progression to hepatic fibrosis and cirrhosis include severe steatosis, giant mitochondria, and the presence of mixed macrovesicular-microvesicular steatosis (Teli 1995).
Early staging of hepatic fibrosis in people with alcoholic liver diseases could motivate patients and physicians in finding an optimal strategy for achieving abstinence. A single staging system for evaluating hepatic fibrosis in alcoholic liver disease does not exist. METAVIR is the most widely used scoring system for interpretation of liver biopsy results based on the stage of fibrosis where F0 indicates no fibrosis, F1 indicates portal fibrous expansion, F2 indicates thin fibrous septa emanating from portal triads, F3 indicates fibrous septa bridging portal triads and central veins, and F4 indicates cirrhosis (Table 1). Hepatic fibrosis could be consid-

ered clinically significant if defined as F2 or worse than F2, using METAVIR score (Franciscus 2007). Hepatic fibrosis could be considered clinically severe if defined as F3 or worse than F3, using METAVIR score (F3 and F4). In Table 1, we have also included other widely used systems for classification of hepatic fibrosis in people with alcoholic liver disease (Knodell 1981; Desmet 1994; Ishak 1995; Brunt 1999; Kleiner 2005), as liver pathologists have reached no universal consensus on the standardisation of scoring systems.

Index test(s)

Transient elastography is designed to measure liver stiffness, using FibroScan® equipment (Echosens, Paris, France; Echosens 2009). A probe, consisting of an ultrasound transducer located at the end of a vibrating piston, is put on the skin surface overlying the liver while the person is in the supine position. After pressing the button on the probe, a pulse wave is transmitted across the liver parenchyma. After a short interval, a second ultrasound wave is transmitted. The difference between the velocities of the two waves in the liver parenchyma is calculated using the Doppler technique (Sandrin 2003; Nahon 2008). As it is known from physical principles, the velocity of the pulse wave increases with the stiffness of the liver parenchyma, corresponding to increasing severity of fibrosis.

Liver stiffness is expressed as the median value of 10 valid measurements in kiloPascals (kPa). The findings of 'normal' liver stiffness values for apparently healthy women and men differ in different studies, lying between 3.3 kPa and 7.0 kPa, using the 5th and 95th percentiles (Roulot 2008; Kim 2012). While age is does not affect liver stiffness, men compared to women have slightly higher liver stiffness values (Roulot 2008). A pre-defined cut-off of 8.00 kPa is predictive of severe hepatic fibrosis in alcoholic liver disease, of F3 or worse by the METAVIR scoring system (Mueller 2010). The transient elastography method is non-invasive, simple, highly reproducible, and allows examination of at least 100 times larger volume of liver tissue compared to a liver sample obtained through liver biopsy (de Lédinghen 2008). This is why the sampling error of transient elastography investigation is considered less than with liver biopsy (Ingiliz 2009). Transient elastography increases its diagnostic accuracy when applied in combination with serum markers (Castera 2010). The diagnostic accuracy of transient elastography was compared with alternative tests such as acoustic radiation forced impulse (ARFI) imaging and enhanced liver fibrosis (ELF) test, concluding that transient elastography can be used for diagnosis of hepatic fibrosis alone or in combination with any of them (Crespo 2012). Janssens et al. have shown that transient elastography is more accurate than currently available serum markers for people with chronic hepatitis C (Janssens 2010). However, the diagnostic accuracy of transient elastography in people with alcoholic liver disease is not established yet.

Alternative test(s)

Different methods to perform elasticity measurements have been developed since 1990. They are aimed at quantifying the elasticity or viscoelasticity of the liver tissue. There are two common elements in every elasticity imaging method: a force or stress is applied on the liver tissue and the obtained mechanical response is measured.

Siemens Ltd. (i.e., ACUSON S2000) has developed a medical technology that can detect hepatic fibrosis, and hence, it enables the quantification of the hepatic fibrosis in its different stages. The technology is also called liver elastography, performed using ARFI imaging (Iyo 2009). ARFI imaging is faster than conventional methods as ARFI uses higher frequencies that are comparable to those used in colour Doppler imaging. The images have greater contrast and the boundary of the focal lesions are better defined compared with the conventional ultrasonography imagining techniques (Iyo 2009).

Ultrasonography measures the progression or regression of hepatic fibrosis in alcoholic liver disease (Caballeria 1998). It allows investigation of the hepatic tissue through generation of ultrasonic waves. Different ultrasonography impedance indices based on Echo-colour Doppler variables of the liver blood flow have been proposed for indirect estimation of the stage of hepatic fibrosis (Ersoz 1999; Hizli 2010; Ivashkin 2011a). We undertook this systematic review to assess the diagnostic accuracy of ultrasonography for staging hepatic fibrosis and detecting cirrhosis in people with alcoholic liver disease (Pavlov 2014a).

Supersonic shear imaging (SSI) is a technique that uses tissue elasticity to detect hepatic fibrosis and steatosis. It is based on velocity estimation of a shear wave, generated by a radiation force (Bercoff 2004).

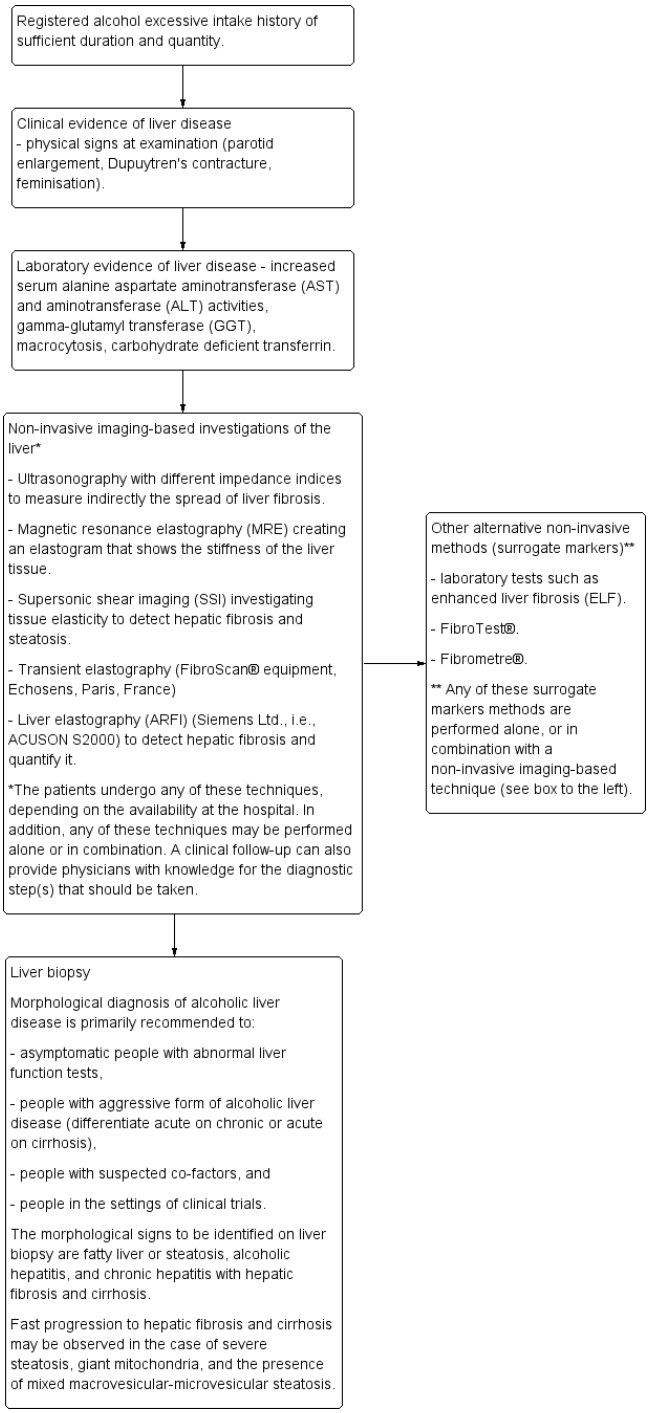
Magnetic resonance elastography (MRE) combines magnetic resonance imaging (MRI) with sound waves to create a visual map (elastogram) showing the stiffness of the liver tissue. It is used primarily to detect hardening of the liver caused by different types of liver diseases, including those of alcoholic aetiology (Jin 2007).

Other alternative non-invasive tests (apart from venepuncture) to transient elastography are laboratory tests such as AST (aspartate aminotransferase) to ALT (alanine aminotransferase) ratio, prothrombin index, hyaluronic acid, ELF, etc. (Crespo 2012; Liu 2012). All of these tests are used as surrogate markers for staging of hepatic fibrosis (Gluud 2007). In addition, different combinations of biochemical tests such as FibroTest® and Fibrometre® are used for diagnosis and staging of hepatic fibrosis in people with alcoholic liver disease (Morra 2007; Poynard 2007; Poynard 2008; Angulo 2009a). We are also undertaking a systematic review to determine the diagnostic accuracy of transient elastography plus FibroTest® versus FibroTest® alone for diagnosis of hepatic fibrosis in adults with chronic hepatitis C (Pavlov 2014b).

Clinical pathway

Figure 1 presents the clinical pathway in diagnosis of alcoholic liver disease.

Figure 1. Clinical pathway in the diagnosis of alcoholic liver disease.



Rationale

Liver biopsy has so far been considered the standard method for detection of hepatic fibrosis and its staging, using different semi-quantitative morphological scores on liver tissue samples with a size of no more than 1 to 2 cm^3 (Table 1). One advantage of liver biopsy is that it may give diagnostic information for concurrent liver diseases (Poulsen 1979; Ismail 2011). However, there are a number of disadvantages with liver biopsy. It is invasive, and it may have potential risks to the person, such as punctures of abdominal organs and haemorrhage. Liver biopsy can be painful, time-consuming, and stressful for the person and depends on the physician's experience and skills (Grant 1999; O'Shea 2010; Ivashkin 2011b). The risk of haemorrhage and death after a percutaneous liver biopsy is especially higher in people with a platelet count of 60,000 per mm^3 or less, and also in people with an international normalisation ratio greater than 1.3 (Seeff 2010). Transjugular liver biopsy seemed a safer alternative for people with low numbers of platelets or clotting abnormalities. The small size of the tissue samples, either obtained transcutaneously or via the transjugular route, may also lead to sampling errors.

Consensus on using transient elastography as a non-invasive method for diagnosis of hepatic fibrosis has not been established (Rockey 2008; Sagir 2008; Colli 2010; Yashima 2011; Yoshioka 2013). As for interventions, clinicians should request solid evidence for diagnostic tests (Colli 2014). It has been shown that confounding factors such as inflammation, cholestasis, and increased hepatic vein congestion (e.g., chronic heart failure), influence the precision of transient elastography irrespective of the aetiology of the underlying liver disease (Rockey 2008; Colli 2010). Increased body mass index, sex, and age are not considered confounding factors, but they may affect the number of reliable results (i.e., success rate).

Published meta-analyses demonstrated that cause of liver disease is the most important factor leading to heterogeneity of transient elastography results, thus indicating that the different chronic liver diseases should be analysed separately (Friedrich-Rust 2008; Poynard 2008; Stebbing 2010; Tsochatzis 2011). However, these meta-analyses obtained results for all causes of liver disease together, which may become a limitation for determining the diagnostic accuracy of the method of transient elastography when used to diagnose hepatic fibrosis in people with alcoholic liver disease. Furthermore, these meta-analyses did not examine in detail the possible confounding influences of factors such as the degree of hepatic steatosis or the level of liver inflammation activity in people with alcoholic liver disease (Savolainen 1993). This review aimed to complete present research and to study further the diagnostic accuracy of transient elastography in detecting the presence or absence of hepatic fibrosis in people with alcoholic liver disease, and to establish the optimal cut-off values for differentiating between the hepatic fibrosis stages, following The Cochrane Collaboration methodology (SRDTA Handbook). In addition, this review will help researchers working on designing interventions for people with alcoholic liver disease by knowing the grade and progression of fibrosis and cirrhosis.

OBJECTIVES

To determine the diagnostic accuracy of transient elastography for diagnosis and staging hepatic fibrosis in people with alcoholic liver disease when compared with liver biopsy. In addition, to identify the optimal cut-off values for differentiating the five stages of hepatic fibrosis.

METHODS

Criteria for considering studies for this review

Types of studies

We sought to include diagnostic cohort studies and diagnostic case-control studies that had assessed hepatic fibrosis in participants with alcoholic liver disease through transient elastography and liver biopsy, irrespective of language or publication status, or whether data were collected prospectively or retrospectively. We considered studies for inclusion also if they had included participants with different aetiologies of liver disease.

Participants

The studies had to include participants of any sex and ethnic origin, above 16 years old, and diagnosed with alcoholic liver disease. The participants could have been hospitalised or managed as outpatients. The diagnosis of alcoholic liver disease in the study participants had to be established based on registered history of excessive intake of alcohol of sufficient duration and quantity together with clinical evidence of liver disease expressed with physical signs at examination and followed by laboratory evidence of liver disease. To ascertain the diagnosis of alcoholic liver disease and study the presence or absence of hepatic fibrosis or cirrhosis, the studies had to perform both transient elastography and liver biopsy (Bouchier 1992).

For this review, we did not consider for inclusion data on participants diagnosed with alcoholic liver disease and having a concomitant liver disease such as non-alcoholic fatty liver disease, chronic hepatitis C virus infection, chronic hepatitis B virus infection, autoimmune liver disease, or human immunodeficiency virus (HIV) infection. We extracted data on study participants with alcoholic liver disease alone whenever such data were available in the study report or whenever we could obtain the data required for the review through personal communication with study authors. In the latter case, we disregarded some of the data presented in the publication and used the data provided by the study authors through personal communication.

Index tests

Transient elastography, a non-invasive test measuring liver stiffness in kiloPascals (kPa).

Following the recommended technical parameters for transient elastography and to ensure the validity of the transient elastography result for every participant in the single studies, participants should have undergone at least 10 validated stiffness measurements at the same measurement point. The measurements should have had an interquartile range of 30% or less, and the ratio of the number of successful measurements to the total number of acquisitions should have been 60% or less (Echosens 2009). We only considered data from people who provided the full set of the described data.

Transient elastography is not recommended for use in pregnant women, people with pacemakers, and people with ascites. Factors that may influence the success of transient elastography investigation are experience of the operator and body mass index of the person. Liver stiffness measurement can produce biased results depending on the grade of necro-inflammation and grade of steatosis (Myers 2010).

Target conditions

The presence of hepatic fibrosis in people with alcoholic liver disease. Based on the METAVIR histopathological score for interpreting liver biopsy, there are five stages of hepatic fibrosis (Table 1).

- F0: no fibrosis.
- F1: mild fibrosis.
- F2: significant fibrosis.
- F3: severe fibrosis.
- F4: cirrhosis.

We dichotomised the hepatic fibrosis estimated by the METAVIR score as follows:

- people with METAVIR score of F1 or worse were considered 'diseased' and people with METAVIR score of F0 are considered 'non-diseased';
- people with METAVIR score of F2 or worse were considered 'diseased' and people with METAVIR score of F0 plus F1 are considered 'non-diseased';
- people with METAVIR score of F3 or worse were considered 'diseased' and people with METAVIR score of F0 plus F1 plus F2 are considered 'non-diseased';
- people with METAVIR score of F4 were considered 'diseased' and people with METAVIR score of F0 plus F1 plus F2 plus F3 are considered 'non-diseased'.

Reference standards

Liver biopsy is the reference standard that is obtained by percutaneous needle techniques, transjugular method, ultrasound-guided fine-needle, or surgical specimens (Kuntz 2008; Ivashkin 2011b). Liver biopsy is the only existing reference standard so far for diagnosing hepatic fibrosis stages in people with alcoholic liver disease. Specimens of liver tissue with a mean length of at least 15 mm and at least seven portal tracts are among the factors that can provide reliable morphological staging of hepatic fibrosis and grading of inflammation (Rockey 2009).

If liver biopsy samples were reported with any of the semi-quantitative scores, that is, METAVIR (Franciscus 2007), Knodell (Franciscus 2007), Ishak (Franciscus 2007), Kleiner (Kleiner 2005), Scheuer (Regev 2002), Brunt (Brunt 1999), or Batts-Ludwig (Haque 2010), we used a conversion grid for hepatic fibrosis staging adapted after Goodman 2007 (Table 1) to unify results on the grade of hepatic fibrosis on liver biopsy. For grading alcoholic steatosis, we used the Nonalcoholic Steatohepatitis Clinical Research Network scoring system (Kleiner 2005) (Table 2).

Search methods for identification of studies

We combined electronic searches with reading references of identified studies of possible interest.

Electronic searches

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (August 2014), The Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register (August 2014), *The Cochrane Library* (2014, Issue 7), MEDLINE (OvidSP) (1946 to August 2014), EMBASE (OvidSP) (1974 to August 2014), and Science Citation Index Expanded (1900 to August 2014) (Royle 2003; de Vet 2008).

We also screened references of the retrieved studies to identify other potentially relevant studies for inclusion in our review.

Appendix 1 shows the search strategies for the different databases with the time spans for the searches. The given search strategies did not differ from those provided in the published protocol.

Searching other resources

Abstracts, published in conference proceedings or presented as posters, were also eligible for inclusion if retrieved with the search results or if found in the reference lists of the studies of interest to this review.

Data collection and analysis

We followed the guidelines provided in the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*, which is still in preparation (Reitsma 2005; de Vet 2008).

Selection of studies

Two review authors (CP and DN) independently identified studies for possible inclusion in the review. By reading titles or abstracts or both of the identified studies, we excluded references with a study design not fulfilling the inclusion criteria of our review protocol. Then, we retrieved the full text of the remaining references. During this second selection, we grouped multiple publications on a study fulfilling the inclusion criteria together, and then screened these publications for complimentary data or checked them for discrepancies of data. If in doubt, CP and DN wrote emails to the study authors.

The studies that we included assessed transient elastography in the diagnosis of hepatic fibrosis severity using liver biopsy as the reference standard.

The maximum time interval between liver biopsy and transient elastography investigations was not to exceed three months. However, at the time of extraction of study data for our review, we decided to also include studies with intervals of more than three months, and then perform sensitivity analyses in which we included studies with up to three months' interval between the liver biopsy and transient elastography assessments.

Data extraction and management

Two review authors (CP and DN) extracted data, using a data extraction sheet. Two other review authors (GC and ET) checked the extraction of all data. A fifth review author (CG) was an arbitrator in case of disagreements between the review authors who extracted the information.

We extracted the following data: study origin, year and language of publication, study design, participants' epidemiological and laboratory characteristics, definition of alcoholic liver disease as defined by the authors of the individual studies considered for inclusion, technical failures in undertaking liver biopsy and transient elastography, cut-off values of liver stiffness, grade of hepatic fibrosis estimated by a morphological score, and information related to the QUADAS-2 items for evaluation of the bias risk of the studies (Whiting 2011).

In order to provide data for our analyses, the studies had to provide data that could help us calculate the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) diagnostic values of the reference standard, liver biopsy, as well as the index test, transient elastography, for diagnosing the stages of hepatic fibrosis, based on semi-quantitative morphological scores and cut-off points for liver stiffness, and as described by the authors of the identified studies.

If information on any of the TP, FP, FN, and TN diagnostic test values or results were missing, we attempted to contact the authors of the included studies in order to obtain this or other missing information.

In the cases when authors sent us individual data, we extracted data on the TP, FP, FN, and TN using the most common cut-off value for each target condition.

Assessment of methodological quality

Design flaws in test accuracy studies can produce biased results (Lijmer 1999; Whiting 2004; Rutjes 2006). In addition, evaluation of study results is quite often impossible due to incomplete reporting (Smidt 2005).

To limit the influence of different biases, three review authors (CP, GC, and DN) independently assessed the bias risk of the included diagnostic test accuracy studies, using QUADAS-2 domains (Whiting 2011). A fourth review author (ET) acted as an arbitrator in case of disagreements between the review authors assessing the bias risk of the studies. To assess correctly the bias risk of the studies, we attempted to contact study authors for more information on methodology

The presented items in Appendix 2 are adopted to serve the purposes of our review in addressing the patient spectrum, index test, target condition, and reference standard, and flow and timing, and which answers would also reflect the overall quality of the included studies.

QUADAS-2 is not used to generate a summary 'quality score' because of the well-known problems associated with such scores (Jüni 1999; Whiting 2005). If a study is judged as 'low' on all domains relating to bias or applicability, then it is appropriate to have an overall judgement of 'low risk of bias' or 'low concern regarding applicability' for that study. If a study is judged as 'high' or 'unclear' on one or more domains, then it may be judged 'at risk of bias' or as having 'concerns regarding applicability'.

We used tabular and graphical displays to summarise QUADAS-2 assessments.

Statistical analysis and data synthesis

We carried out the analyses following Chapter 10 (Analysing and Presenting Results), as recommended in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010).

We used the Review Manager 5 software for analyses and plots (RevMan 2012).

We built two-by-two tables of the transient elastography performance (TP, TN, FP, FN) for each primary study and for all of the pre-defined target conditions (mild hepatic fibrosis, significant hepatic fibrosis, severe hepatic fibrosis, and cirrhosis). We estimated sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-), positive and negative predictive values (PPV and NPV) with their 95% confidence intervals (CI). First, we performed a graphical descriptive analysis of the included studies: we reported forest plots (sensitivity and specificity separately, with their 95% CIs) and we provided a graphical representation of the studies in the receiver operating characteristic (ROC) space (sensitivity against 1 - specificity). Second, where appropriate, we performed a meta-analysis. When the primary studies reported accuracy estimates of transient elastography using different cut-off points, we used the hierarchical summary ROC model (HSROC) to pool data (sensitivities and specificities) and to plot a summary ROC (SROC) curve (Rutter 2001). When considering studies with a common cut-off, we used the bivariate model and we provided the estimate of the summary operating point (the point with mean sensitivity and mean specificity). Finally, when, due to a low variability of sensitivity or specificity (or both) across studies, the bivariate model failed to converge, we fitted a bivariate model without random effects, and we estimated a summary operating point. In particular, we performed the analyses using bivariate models with random effects for only specificity (or for only sensitivity) or bivariate models without random effects, as appropriate (Macaskill 2010).

The pooled estimates obtained from the fitted models were used to calculate summary estimates of LRs. We assessed the usefulness of transient elastography to rule in or to rule out hepatic fibrosis by considering the estimates of likelihood ratios. An LR+ greater than 10 means that there is a large increase in post-test probability, starting from pre-test probability. An LR- lower than 0.1 means that there is a large decrease in post-test probability, starting from pre-test probability (Schoenfeld 1999).

For primary studies that reported accuracy results for more than one cut-off point, we reported sensitivities and specificities for all of the cut-off points, but we used a single cut-off point for each study in HSROC (or bivariate model) analysis. We planned to base the choice of the cut-off value on the maximum of the Youden's index (sensitivity + specificity - 1), but instead, we decided to use the most commonly reported cut-off value for each stage of hepatic fibrosis whenever these data were available in the published articles or retrieved through personal communication.

Finally, whenever possible, we added some relevant co-variates (see Investigations of heterogeneity) to the bivariate or HSROC model to investigate the effect of the pre-defined sources of heterogeneity. One review author (GC) did all statistical analyses performed with SAS statistical software, release 9.2 (SAS Institute Inc., Cary, NC, USA).

Investigations of heterogeneity

We attempted to investigate the sources of heterogeneity by evaluating differences of diagnostic accuracy in pre-defined subgroups, related to:

- liver biopsy as the reference standard:
  - different grade of inflammation according to the liver biopsy (below two grades compared to two or greater grades of activity);
  - different lengths of liver biopsy sample (less than 15 mm compared to 15 mm or more than 15 mm);
  - different number of portal tracts included in a liver biopsy sample (less than seven compared to seven or more than seven);
  - different grades of steatosis according to the liver biopsy (less than 5% compared to 5% or more than 5%);
  - mild fibrosis compared to significant fibrosis compared to severe fibrosis or cirrhosis as estimated by the different semi-quantitative histopathological scoring systems used (see Table 1);
- population group:
  - different body mass indices (below 25 kg/m^2 compared to 25 kg/m^2 or more than 25 kg/m^2) (WHO);
  - serum levels of AST activity (normal, i.e., 5 to 35 U/L, compared to twice the upper limit (Dufour 2000));
- definition of alcoholic liver disease.

We attempted to evaluate the effect of the above-mentioned sources of heterogeneity on the accuracy estimates by adding co-variates to the bivariate or HSROC models.

Sensitivity analyses

We attempted to assess the effect of risk of bias of the included studies on the diagnostic accuracy by performing a sensitivity analysis, excluding studies with high risk of bias. We classified a study with high risk of bias if judged as high risk of bias or unclear risk of bias in at least one of the domains of QUADAS-2 (Appendix 2).

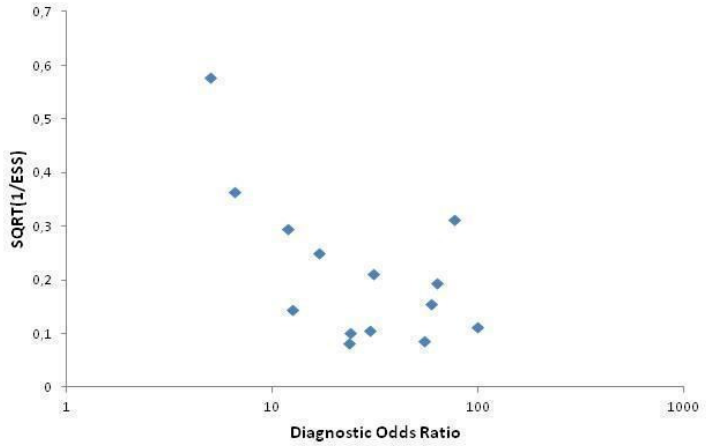
Moreover, to assess the effect of time interval between transient elastography and liver biopsy, we performed a second sensitivity analysis by considering only studies with up to three months' interval.

Due to variation of cut-off values, overlap of cut-off values, and lack of sufficient data to produce subgroup analyses, we performed one additional sensitivity analysis in which we removed studies with cut-off values different to the most common cut-off value of 9.5 kPa for severe fibrosis and cirrhosis (see Data table 5).

Assessment of reporting bias

Using the suggested method by Deeks et al. (Deeks 2005), we performed a funnel plot to investigate the reporting bias by visual inspection of the patterns drawn from study data, where lack of symmetry should denote high risk of reporting bias (Figure 2).

Figure 2. Funnel plot for reporting bias for liver fibrosis F4 in 14 included studiesEven though the Figure is not in the form of a funnel plot, it seems that there is no clear indication of reporting bias as the points were equally distributed along the x- and y-axes. There seems to be two outliers (to the right) (Bardou-Jacquet 2013; Carl 2012): both studies had a small number of participants (eight and four).



RESULTS

Results of the search

We identified 3111 references through electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (two references), Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Register (27 references), *The Cochrane Library* (38 references), MEDLINE (OvidSP) (485 references), EMBASE (OvidSP) (1671), and Science Citation Index Expanded (885 references). We identified no additional studies by searching other sources. After exclusion of duplicates, 2198 references remained. Having performed two selections, we found 2129 hits to be irrelevant references. Forty-one references seemed to fulfil the inclusion criteria. However, we had to exclude 13 of these, and thus 28 references remained for further assessment. As data for the two-by-two tables could not be extracted from seven of these study publications, 21 references remained, describing 14 studies and providing data for the meta-analysis. We added one additional reference towards the final stage of the review because we received a substantial amount of information from the study author (de Ledinghen 2013). Thus, 22 references describing 14 studies provided data for the meta-analysis of our review.

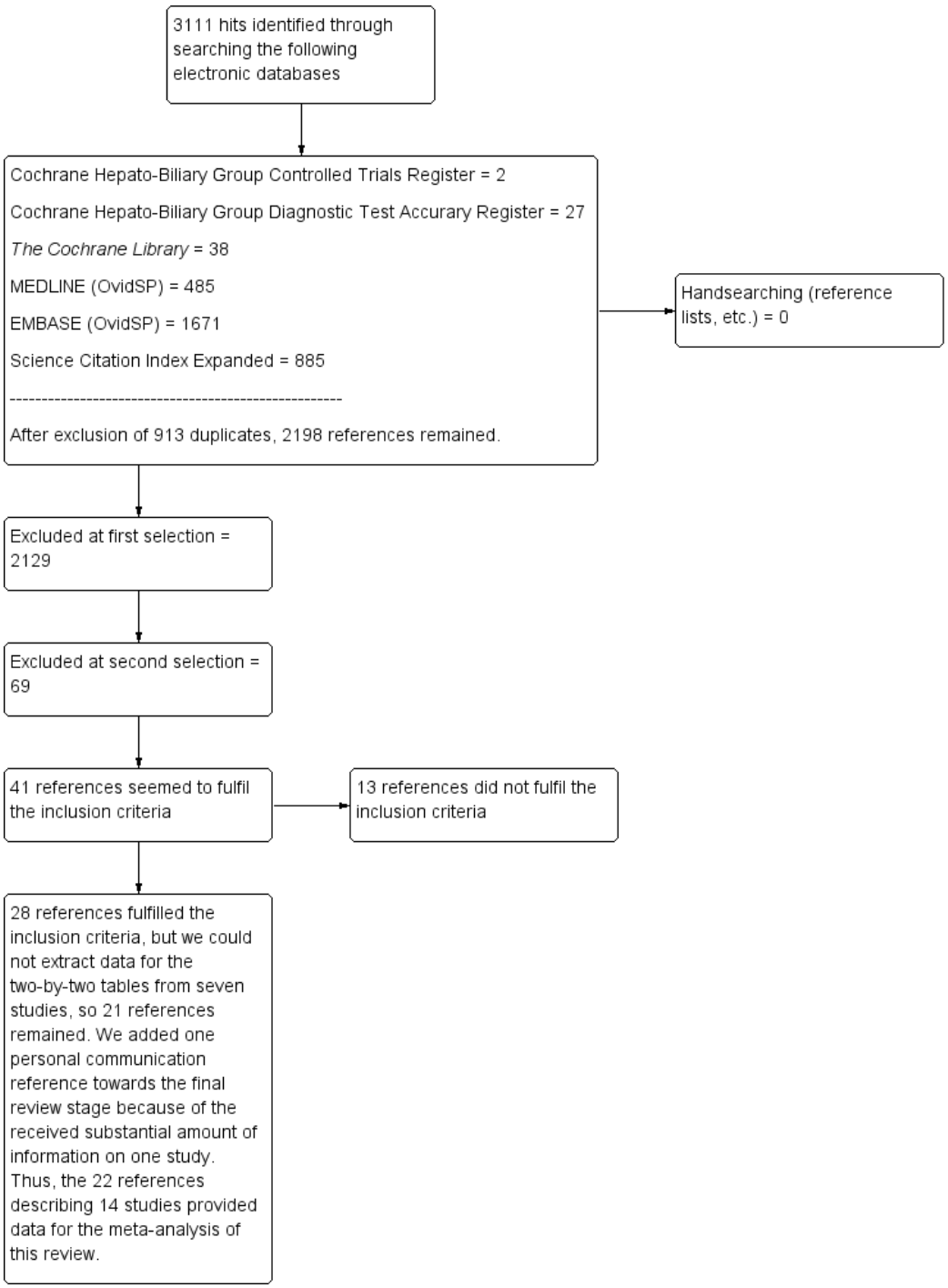
Eight of the 13 excluded studies (referred to above) could have been included in our review had the number of participants been five or more than five and had it been possible to build up a two-by-two table with the available data (Characteristics of excluded studies). An exception from the latter explanation was the included study by Carl 2012 with four participants only, as we received individual participant data from the study author, and in this way, we could use the provided data in a two-by-two table. In the remaining 13 included studies, the number of participants ranged from eight to

147. As some of the studies included participants with different liver diseases, for the purpose of our review, we extracted data only on participants diagnosed with alcoholic liver disease alone (see Included studies; Characteristics of included studies).

In total, seven study authors provided individual participant data of people with alcoholic liver disease (Boursier 2009; Kim 2009; Anastasiou 2010; Carl 2012; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013) (for details, see Characteristics of included studies). However, even after personal communication, we could not collect all missing information of relevance to our review analyses.

We found no diagnostic case-control studies that met the selection criteria. No studies are awaiting classification. Figure 3 shows the reference flow.

Figure 3. Flow chart.



Characteristics of included studies

We have summarised the characteristics of the 14 included studies in the Characteristics of included studies table.

Study design

Nine of the included studies were prospective cohort studies (Nahon 2008; Lemoine 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Janssens 2010; Mueller 2010; de Ledinghen 2013), and five were retrospective cohort studies (Carl 2012; Fernandez 2012; Bardou-Jacquet 2013; Dolman 2013; Lannerstedt 2013).

Funding

Five of the studies declared no financial interest and support by the manufacturer of transient elastography equipment (Nahon 2008; Lemoine 2008; Nguyen-Khac 2008; Janssens 2010; Dolman 2013), while this information was either missing or unclear in the remaining nine studies.

Participants

Only seven of the 14 studies included participants with alcoholic liver disease aetiology (Nahon 2008; Nguyen-Khac 2008; Kim 2009; Janssens 2010; Mueller 2010; Fernandez 2012; Bardou-Jacquet 2013); the participants in the remaining seven studies had chronic liver disease with different aetiologies, among which was alcoholic liver disease. The number of participants with alcoholic liver disease in the 14 studies was 834, and all participants underwent both the index test (transient elastography) and the reference standard (liver biopsy) and were included in our analyses. The definition of the diagnosis of alcoholic liver disease was not provided in one study (Carl 2012), was not clearly defined in two studies (Fernandez 2012; Dolman 2013), but the definition was clear in the remaining 11 studies.

Seven studies reported the body mass index of participants as 25 kg/m^2 or greater (Nahon 2008; Nguyen-Khac 2008; Boursier 2009; Janssens 2010; Mueller 2010; de Ledinghen 2013; Dolman 2013), three studies below 25 kg/m^2 (Kim 2009; Anastasiou 2010; Lannerstedt 2013), and four studies provided no information.

In 12 studies, the serum levels of AST activity was greater than 35 U/L. Bardou-Jacquet 2013 provided AST data for 13 abstinent and 24 relapsers separately; however, it was not possible to extract the data separately for the eight participants included in our analyses. There was no information provided in the study by Dolman 2013, but through personal communication with the study author, we understood that AST had not been routinely available in their centre at the time of the study.

The maximum time interval of investigation with liver biopsy and transient elastography was within six months in 11 studies (Nahon 2008; Lemoine 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Janssens 2010; Mueller 2010; Fernandez 2012; de Ledinghen 2013; Dolman 2013). The time interval in the study by Lannerstedt 2013 was less than three months in 50% of the participants and more than three months (range 1.9 to 8.6 years) in the remaining 50%. Bardou-Jacquet 2013 reported a median time interval of 32.5 weeks in six of the eight participants. The time internal in the study by Carl 2012 was unclear.

Liver biopsy morphological scoring systems

The morphological scoring systems in the 14 studies used to assess hepatic fibrosis on liver biopsy were as follows: METAVIR in nine studies (Nguyen-Khac 2008; Boursier 2009; Anastasiou 2010; Janssens 2010; Fernandez 2012; Bardou-Jacquet 2013; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013), and Ishak (Carl 2012), Batts-Ludwig (Kim 2009), Chevallier (Lemoine 2008), Kleiner (Mueller 2010), and Brunt and Chevallier (Nahon 2008), in one study each.

Length of liver biopsy specimen

Nine studies provided the length of liver biopsy specimen and it was more than 10 mm (Nahon 2008; Lemoine 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013). The remaining five studies provided no information.

Number of portal tracts

Three studies reported the number of portal tracts to be more than seven (Nguyen-Khac 2008; Dolman 2013; Lannerstedt 2013). The remaining 11 studies provided no information.

Level of inflammation

Five studies reported the level of inflammation less than two grades of activity (Nahon 2008; Nguyen-Khac 2008; Anastasiou 2010; Dolman 2013; Lannerstedt 2013). The remaining nine studies provided no information.

Grade of steatosis

Seven studies found the grade of steatosis to be more than 5% (Nahon 2008; Nguyen-Khac 2008; Kim 2009; Janssens 2010; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013). The remaining seven studies provided no information.

Study information on the index test - transient elastography

In six of the 14 studies, the authors used pre-defined cut-off values for staging hepatic fibrosis (Nahon 2008; Janssens 2010; Mueller 2010; Bardou-Jacquet 2013; Dolman 2013; Lannerstedt 2013). In the remaining eight studies, the authors used cut-off values that were established during the study.

One study with 103 participants provided data for fibrosis stages F1 or worse (Nguyen-Khac 2008); eight studies with 342 participants provided data for fibrosis stages F2 or worse (Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Carl 2012; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013); 10 studies with 760 participants provided data for fibrosis stages F3 or worse (Nahon 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Janssens 2010; Mueller 2010; Fernandez 2012; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013); and all 14 studies with 834 participants provided data for fibrosis stage F4 (i.e., cirrhosis).

Methodological quality of included studies

Figure 4 and Figure 5 summarise the methodological quality in the included studies. Only four studies were at low risk of bias in all domains (Nahon 2008; Janssens 2010; Mueller 2010; Dolman 2013).

Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

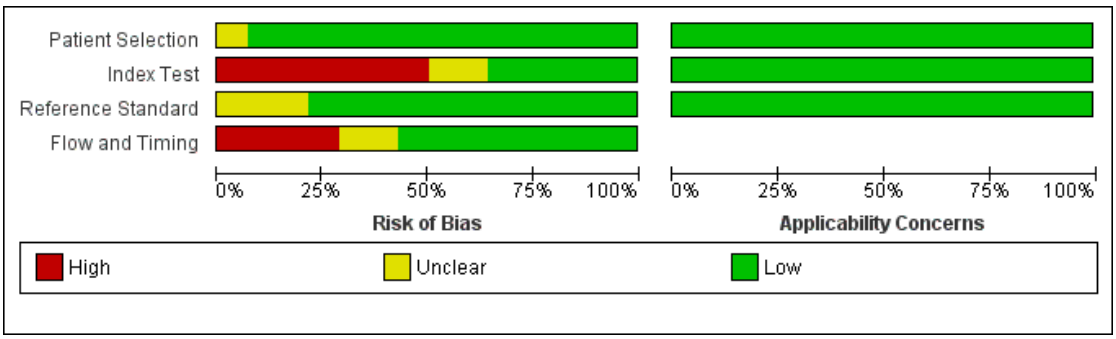
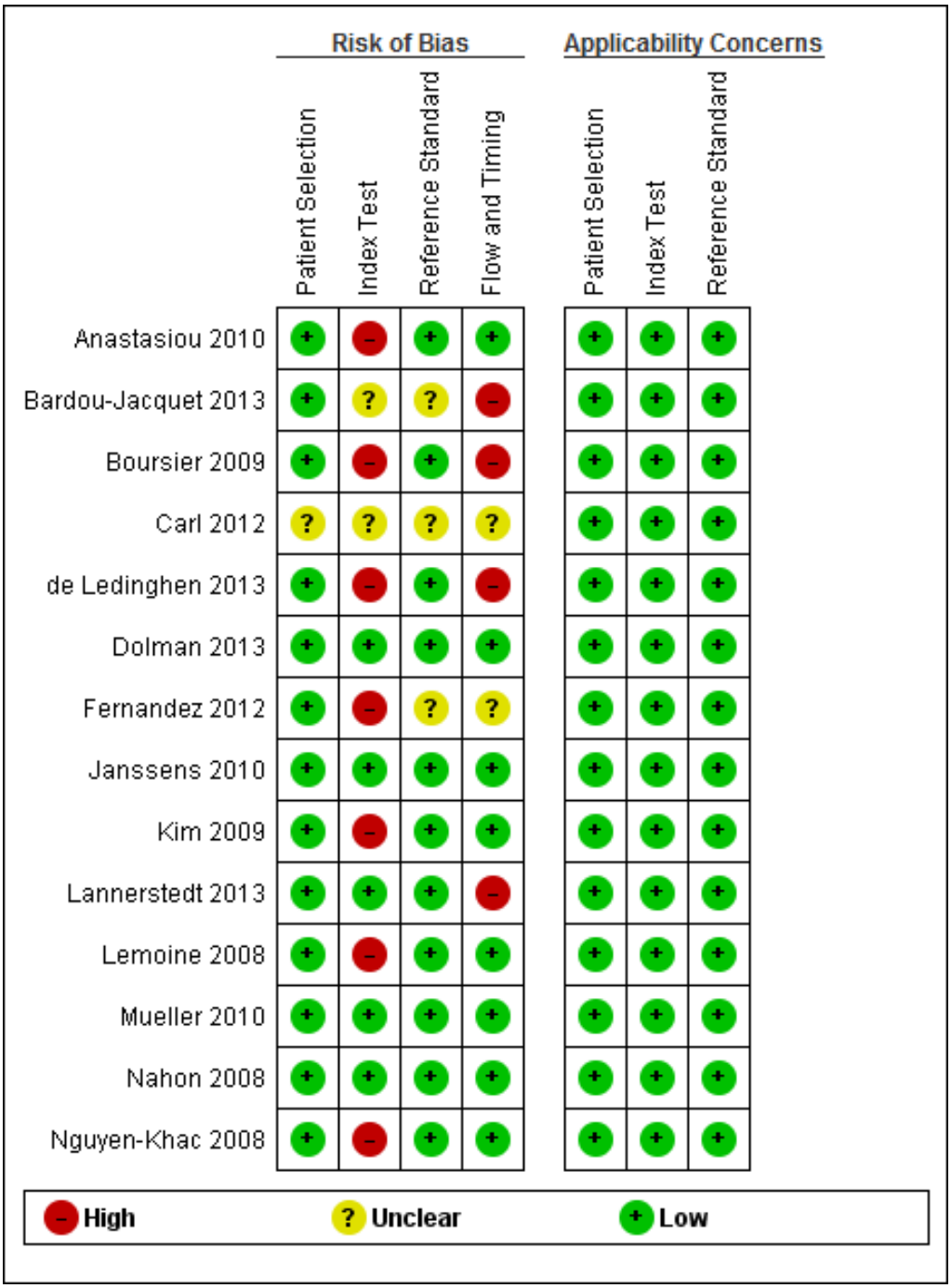


Figure 5. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



Participant selection

Thirteen studies were at low risk of bias in the 'patient selection' domain (Nahon 2008; Lemoine 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Janssens 2010; Mueller 2010; Fernandez 2012; Bardou-Jacquet 2013; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013). One study was at unclear risk of bias in the 'patient selection' domain as it was not clear if Carl et al. had avoided inappropriate exclusions (Carl 2012) (Figure 5). However, we judged that all 14 studies had low concern about applicability in this domain (Figure 5).

Index test

Five studies were at low risk of bias as they had pre-specified cut-off values and results were interpreted without the knowledge of the reference standard result (i.e., blinding) (Nahon 2008; Janssens 2010; Mueller 2010; Dolman 2013; Lannerstedt 2013), seven studies were at high risk of bias as cut-off values were not pre-specified (Lemoine 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Fernandez 2012; de Ledinghen 2013), and two studies were at unclear risk of bias in the 'index test' domain (Carl 2012 (no information about blinding or pre-specified cut-off values); Bardou-Jacquet 2013 (no information about blinding)) (Figure 5). Besides lack of pre-specified cut-off values in Fernandez 2012, it was unclear whether the index test results were interpreted without the knowledge of the reference standard result. We judged that all 14 studies had low concern about applicability in this domain (Figure 5).

Reference standard

Eleven studies were at low risk of bias (Nahon 2008; Lemoine 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Janssens 2010; Mueller 2010; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013), and three were at unclear risk of bias in the 'reference standard' domain as there was no information about blinding (Carl 2012; Fernandez 2012; Bardou-Jacquet 2013) (Figure 5). However, we judged that all 14 studies had low concern about applicability in this domain (Figure 5).

Flow and timing

Eight studies were at low risk of bias (Lemoine 2008; Nahon 2008; Nguyen-Khac 2008; Kim 2009; Anastasiou 2010; Janssens 2010; Mueller 2010; Dolman 2013), four studies were at high risk of bias (Bardou-Jacquet 2013 (due to inappropriate time interval and exclusion of participants from the analyses); Boursier 2009 (due to exclusion of participants from the analyses); de Ledinghen 2013 (due to exclusion of participants from the analyses); Lannerstedt 2013 (due to inappropriate time interval)), and two studies were at unclear risk of bias in the 'flow and timing' domain due to unclear time intervals in the studies (Carl 2012; Fernandez 2012) (Figure 5).

We made our judgements based on the following information.

Bardou-Jacquet 2013 reported that two of the eight participants had their liver biopsy within four weeks' interval and the remaining six participants had their liver biopsy performed during the follow-up period of between 15 and 85 weeks. The study included participants with excessive alcohol consumption, and at the end of follow-up all but one participant were relapsers and had advanced stage of fibrosis on liver biopsy and transient elastography (i.e., cirrhosis). In the de Ledinghen 2013 study, even though the flow and timing was within one week, not all participants were included in the analyses, which made the study of high risk of bias in this domain.

The time interval between liver biopsy and transient elastography was not clear in three studies. Carl 2012 reported that participants underwent liver biopsy and transient elastography between 1 May 2008 and 31 July 2011; Fernandez 2012 reported that transient elastography was performed within six months of liver biopsy in the 139 consecutive participants with alcoholic liver disease; and Lannerstedt 2013 reported that the time interval between liver biopsy and transient elastography was less than three months in 50% of the participants and more than three months (range 1.9 to 8.6 years) in the remaining 50%). As all of the eight participants (i.e., 50%) with the time interval of more than six months had cirrhosis, it is unlikely that the stage of fibrosis (i.e., cirrhosis) would improve.

Liver biopsy seemed to have been performed before transient elastography in six studies (Nahon 2008; Nguyen-Khac 2008; Boursier 2009; Anastasiou 2010; Fernandez 2012; Lannerstedt 2013), and after transient elastography in three studies (Lemoine 2008; Janssens 2010; Dolman 2013). In the remaining five studies, it was unclear which test was performed first.

Findings

Transient elastography for F1 or worse

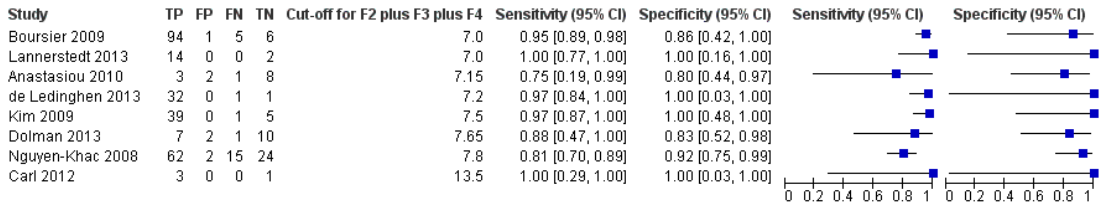
One study with 103 participants provided data for transient elastography assessing people with hepatic fibrosis stage F1 or worse (Nguyen-Khac 2008) (Data table 1). The cut-off value for F1 was 5.9 kPa.

Transient elastography for F2 or worse

Eight studies with 342 participants provided data for transient elastography assessing people with hepatic fibrosis stage F2 or worse (Nguyen-Khac 2008; Boursier 2009; Kim 2009; Anastasiou 2010;

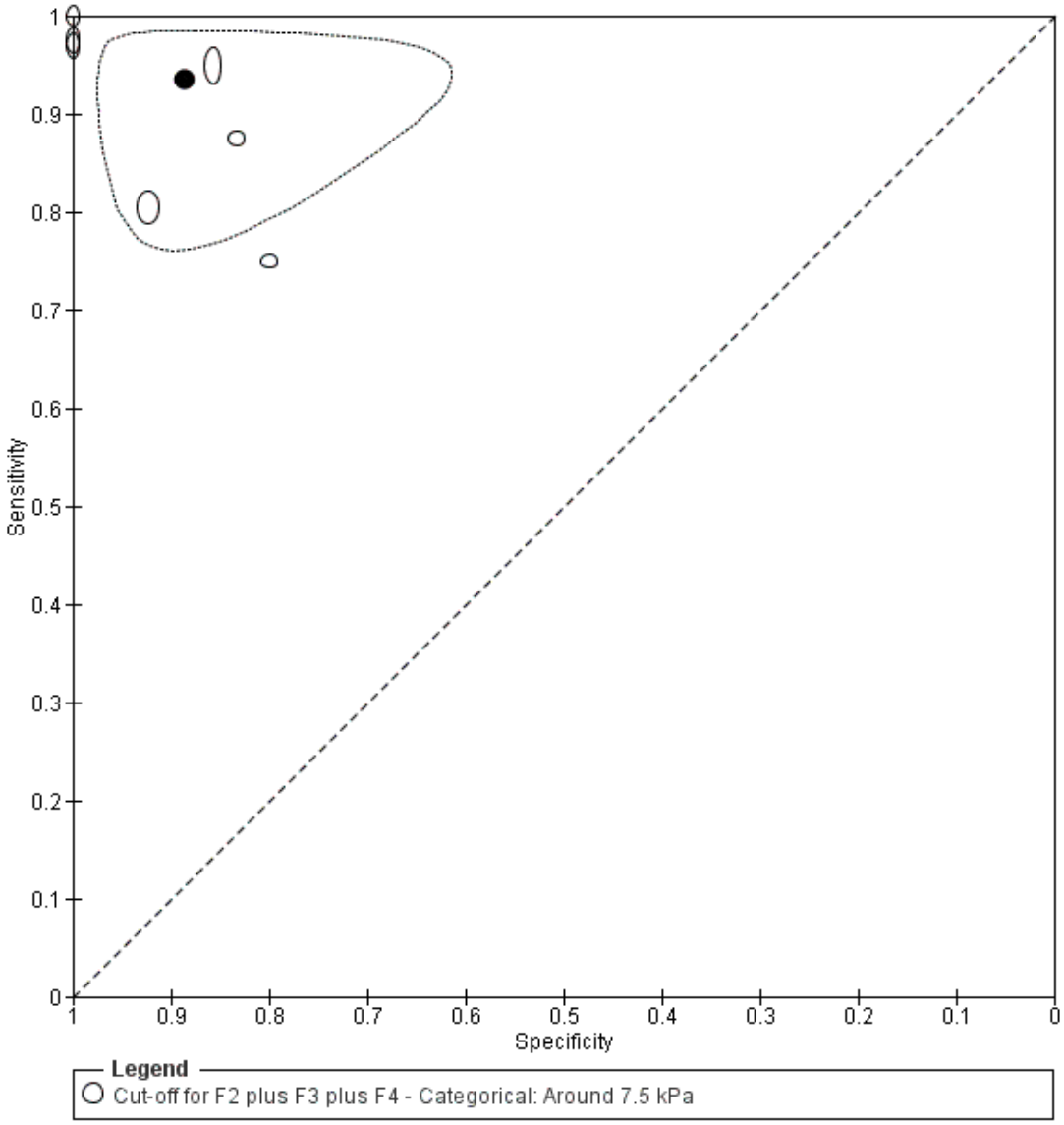
Carl 2012; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013) (Data table 2). The sensitivity of the eight studies varied from 75% to 100% and the specificity from 80% to 100% (Figure 6). The cut-off values in seven studies were around 7.5 kPa (range 7.00 to 7.8 kPa). As the cut-off value in one study with four participants was 13.5 kPa (Carl 2012), we decided to conduct a meta-analysis by including the studies with cut-off values around 7.5 kPa only.

Figure 6. Forest plot: Transient elastography for F2 or worse.



We fitted the bivariate model to the seven studies with 338 participants and estimated a summary operating point (a point with the mean sensitivity and specificity of the transient elastography test). We obtained the following results: sensitivity 0.94 (95% CI 0.86 to 0.97); specificity 0.89 (95% CI 0.76 to 0.95); positive likelihood ratio (LR+) 8.2 (95% CI 3.6 to 18.5); negative likelihood ratio (LR-) 0.07 (95% CI 0.03 to 0.17) (Figure 7).

Figure 7. Summary operating point and 95% confidence region: Transient elastography for F2 or worse with cut-offs around 7.5 kPa.



The mean prevalence of F2 or worse in the seven studies was 81%. Using this value as a pre-test probability, we obtained a post-test probability of 97% when the test was positive and a post-test probability of 23% when the test was negative (Summary of findings).

Transient elastography for F3 or worse

Ten studies with 760 participants provided data for transient elastography assessing people with hepatic fibrosis stage F3 or worse (Nahon 2008; Nguyen-Khac 2008; Boursier 2009; Kim 2009; Janssens 2010; Mueller 2010; Fernandez 2012; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013) (Data table 3). The sensitivity of the 10 studies varied from 72% to 100% and the specificity from 59% to 89% (Figure 8). The cut-off values in the 10 studies ranged from 8.0 to 17.0 kPa. We used the HSROC model and it was possible to estimate a summary receiver-operating characteristic curve (SROC) (Data and analyses; Figure 9).

Figure 8. Forest plot: Transient elastography for F3 or worse.

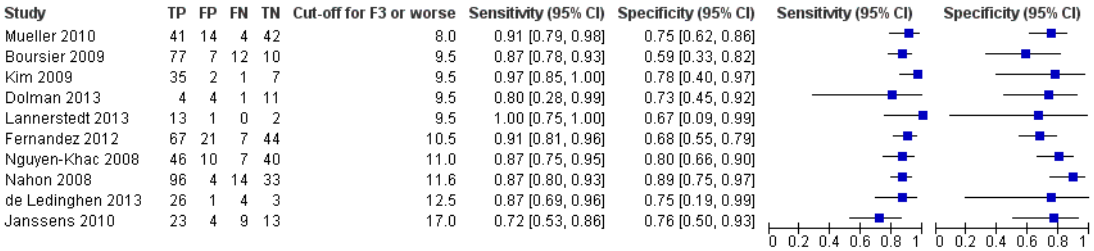
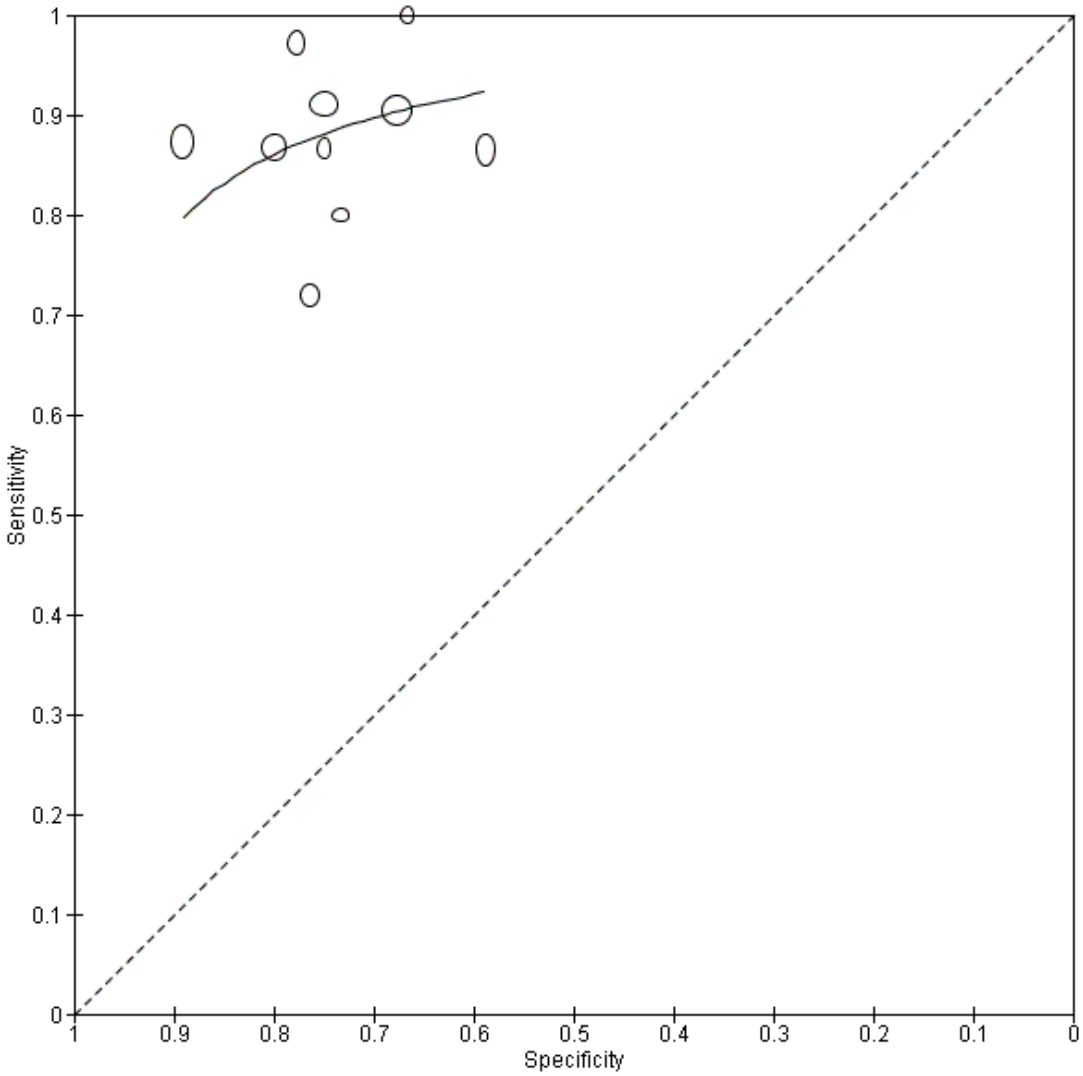


Figure 9. Hierarchical summary receiver operating characteristic (ROC) curve: Transient elastography for F3 or worse. The cut-offs in the nine studies ranged from 8.0 to 17.0 kPa.



The sensitivity analysis on studies with up to three months' interval could not provide results, due to a statistical problem (the model did not converge).

Transient elastography for F3 or worse with cut-off values around 9.5 KPa

When we considered the eight studies with 564 participants using cut-off values around 9.5 KPa (range 8 to 11 kPa), it was possible to estimate a summary operating point (a point with the mean sensitivity and specificity of the transient elastography test) (Nguyen-Khac 2008; Boursier 2009; Kim 2009; Mueller 2010; Fernandez 2012; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013) (Data table 4). The sensitivity of the eight studies varied from 80% to 100% and the specificity from 50% to 80% (Figure 10). Using a bivariate method (with random effect for only specificity), we obtained the following results: sensitivity 0.92 (95% CI 0.89 to 0.96); specificity 0.70 (95% CI 0.61 to 0.79); positive likelihood ratio (LR+) 3.1 (95% CI 2.1 to 4.1); negative likelihood ratio (LR-) 0.11 (95% CI 0.06 to 0.16) (Figure 11).

Figure 10. Forest plot: Transient elastography for F3 or worse with cut-offs around 9.5 kPa.

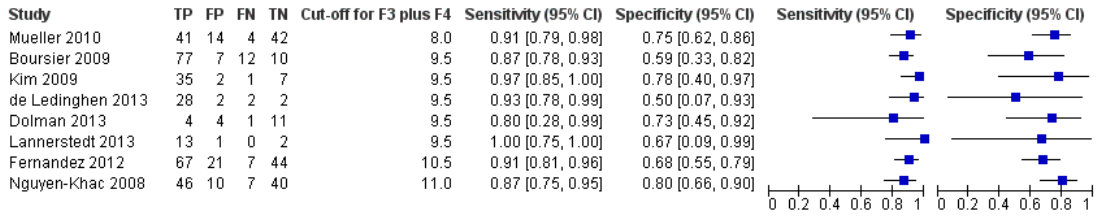
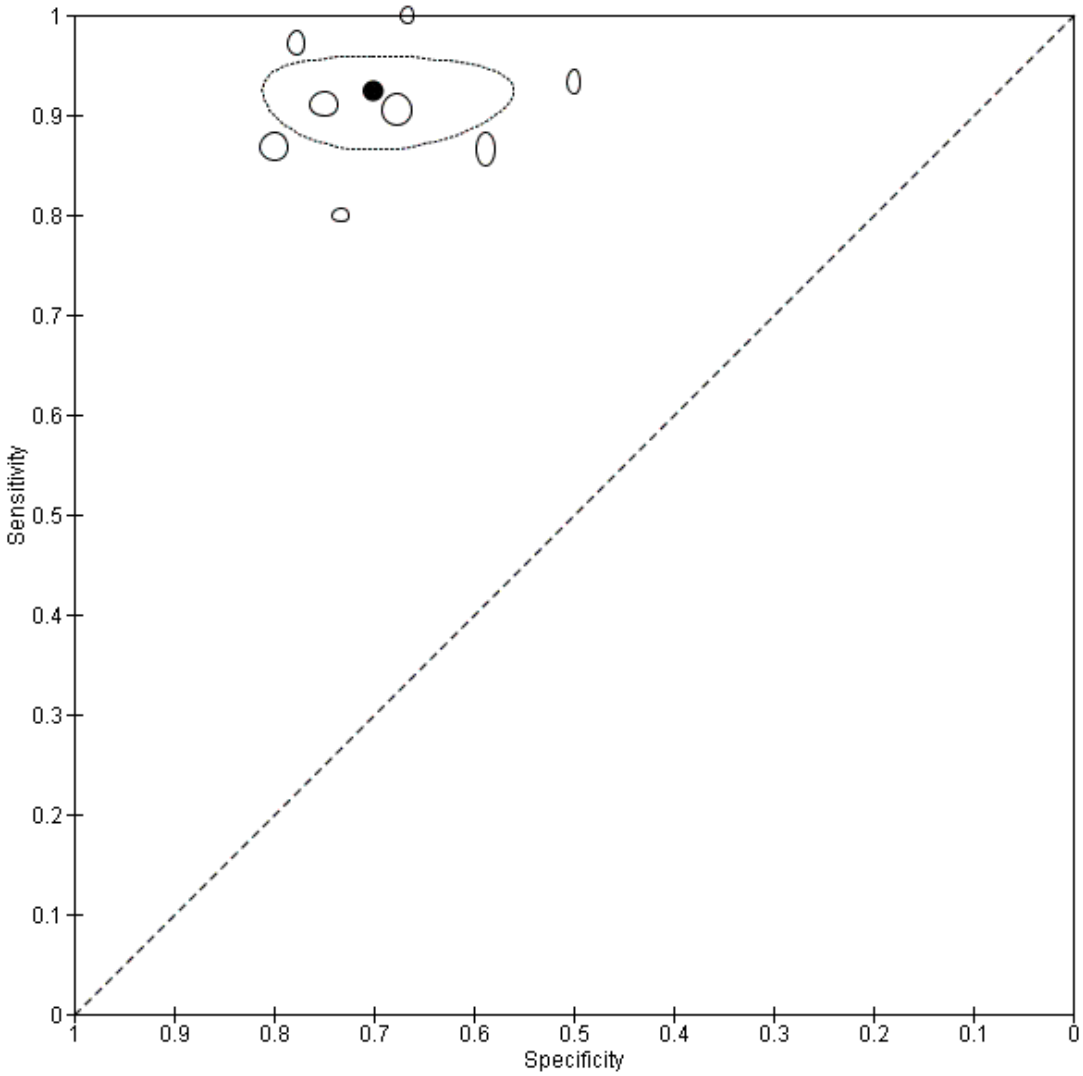


Figure 11. Summary operating point and 95% confidence region: Transient elastography for F3 or worse with cut-offs around 9.5 kPa.



The mean prevalence of F3 or worse in these eight studies was 61%. Using this value as a pre-test probability, we obtained a post-test probability of 83% when the test was positive and a post-test probability of 15% when the test was negative (Summary of findings).

Transient elastography for F3 or worse with cut-off values around 9.5 kPa and time interval within three months - sensitivity analysis

When we considered only the seven studies with 425 participants with up to three months' interval between transient elastography and liver biopsy, the pooled estimates obtained using a bivariate method (with random effect for only specificity) were as follows: sensitivity 0.90 (95% CI 0.86 to 0.95); specificity 0.69 (95% CI 0.46 to 0.92); positive likelihood ratio (LR+) 2.9 (95% CI 0.8 to 5.1); negative likelihood ratio (LR-) 0.14 (95% CI 0.06 to 0.22), showing that the pooled results were not noticeably affected when we excluded the study with a time interval longer than three months (Fernandez 2012).

Transient elastography for F3 or worse with a cut-off value of 9.5 kPa - sensitivity analysis

When we considered the five studies with 221 participants using a cut-off of 9.5 kPa, it was possible to estimate a summary operating point (a point with the mean sensitivity and specificity of the transient elastography test). Using a bivariate method, we obtained the following results: sensitivity 0.92 (95% CI 0.83 to 0.97); specificity 0.68 (95% CI 0.52 to 0.80); positive likelihood ratio (LR+) 2.9 (95% CI 1.8 to 4.5); negative likelihood ratio (LR-) 0.11 (95% CI 0.05 to 0.27).

The mean prevalence of F3 or worse in these five studies was 78%. Using this value as a pre-test probability, we obtained a post-test probability of 91% when the test was positive and a post-test probability of 28% when the test was negative (Summary of findings).

Transient elastography for F4

Fourteen studies with 834 participants using nine different cut-off values ranging from 7.15 to 34.9 kPa provided data for transient elastography assessing people with hepatic fibrosis for F4 (Nahon 2008; Nguyen-Khac 2008; Lemoine 2008; Boursier 2009; Kim 2009; Anastasiou 2010; Janssens 2010; Mueller 2010; Carl 2012; Fernandez 2012; Bardou-Jacquet 2013; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013) (Data table 6). The sensitivity of the 14 studies varied from 75% to 100% and the specificity from 33% to 94% (Figure 12). We used the HSROC model and it was possible to estimate the SROC curve (Figure 13), which showed that the variation between the different values of the cut-off values seemed to affect more specificity than the sensitivity of the index test.

Figure 12. Forest plot: Transient elastography for F4.

Study	TP	FP	FN	TN	Cut-off for F4	Cut-off for F4 as categorical value	Sensitivity (95% CI)	Specificity (95% CI)
Anastasiou 2010	3	2	1	8	7.15	below 12.5	0.75 [0.19, 0.99]	0.80 [0.44, 0.97]
Boursier 2009	62	10	7	27	12.5	equal to 12.5	0.90 [0.80, 0.96]	0.73 [0.56, 0.86]
Kim 2009	29	8	0	8	12.5	equal to 12.5	1.00 [0.88, 1.00]	0.50 [0.25, 0.75]
Mueller 2010	25	15	1	60	12.5	equal to 12.5	0.96 [0.80, 1.00]	0.80 [0.69, 0.88]
Bardou-Jacquet 2013	5	2	0	1	12.5	equal to 12.5	1.00 [0.48, 1.00]	0.33 [0.01, 0.91]
de Ledinghen 2013	25	2	2	5	12.5	equal to 12.5	0.93 [0.76, 0.99]	0.71 [0.29, 0.96]
Dolman 2013	3	1	0	16	12.5	equal to 12.5	1.00 [0.29, 1.00]	0.94 [0.71, 1.00]
Lannerstedt 2013	8	4	0	4	12.5	equal to 12.5	1.00 [0.63, 1.00]	0.50 [0.16, 0.84]
Carl 2012	1	1	0	2	15.1	above 12.5	1.00 [0.03, 1.00]	0.67 [0.09, 0.99]
Fernandez 2012	51	11	6	71	15.7	above 12.5	0.89 [0.78, 0.96]	0.87 [0.77, 0.93]
Nguyen-Khac 2008	28	11	5	59	19.5	above 12.5	0.85 [0.68, 0.95]	0.84 [0.74, 0.92]
Janssens 2010	16	7	4	22	19.6	above 12.5	0.80 [0.56, 0.94]	0.76 [0.56, 0.90]
Nahon 2008	66	12	13	56	22.7	above 12.5	0.84 [0.74, 0.91]	0.82 [0.71, 0.91]
Lemoine 2008	36	1	4	7	34.9	above 12.5	0.90 [0.76, 0.97]	0.88 [0.47, 1.00]

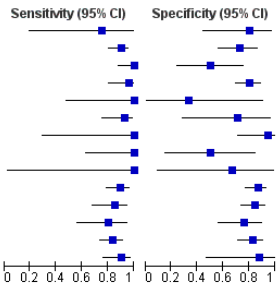
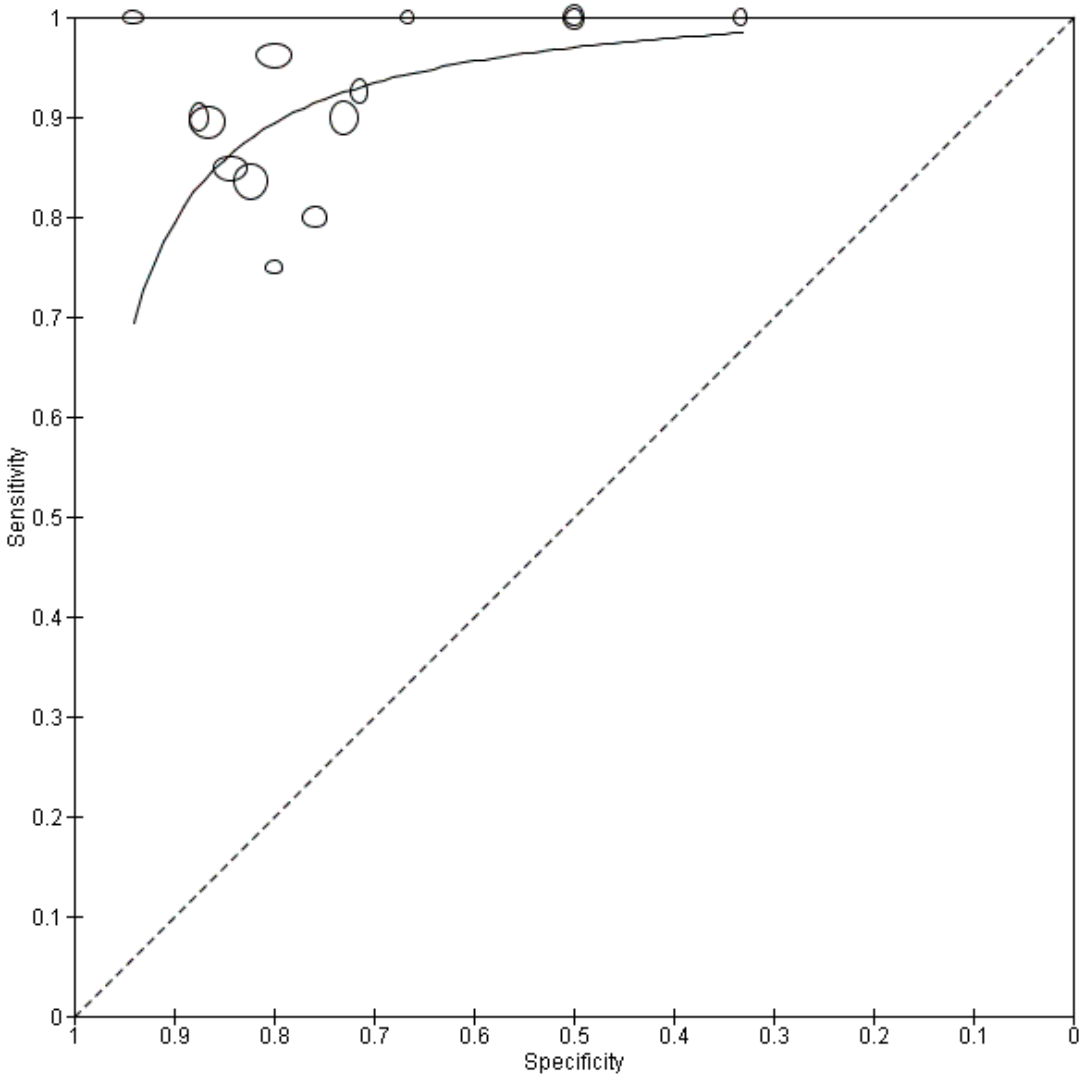


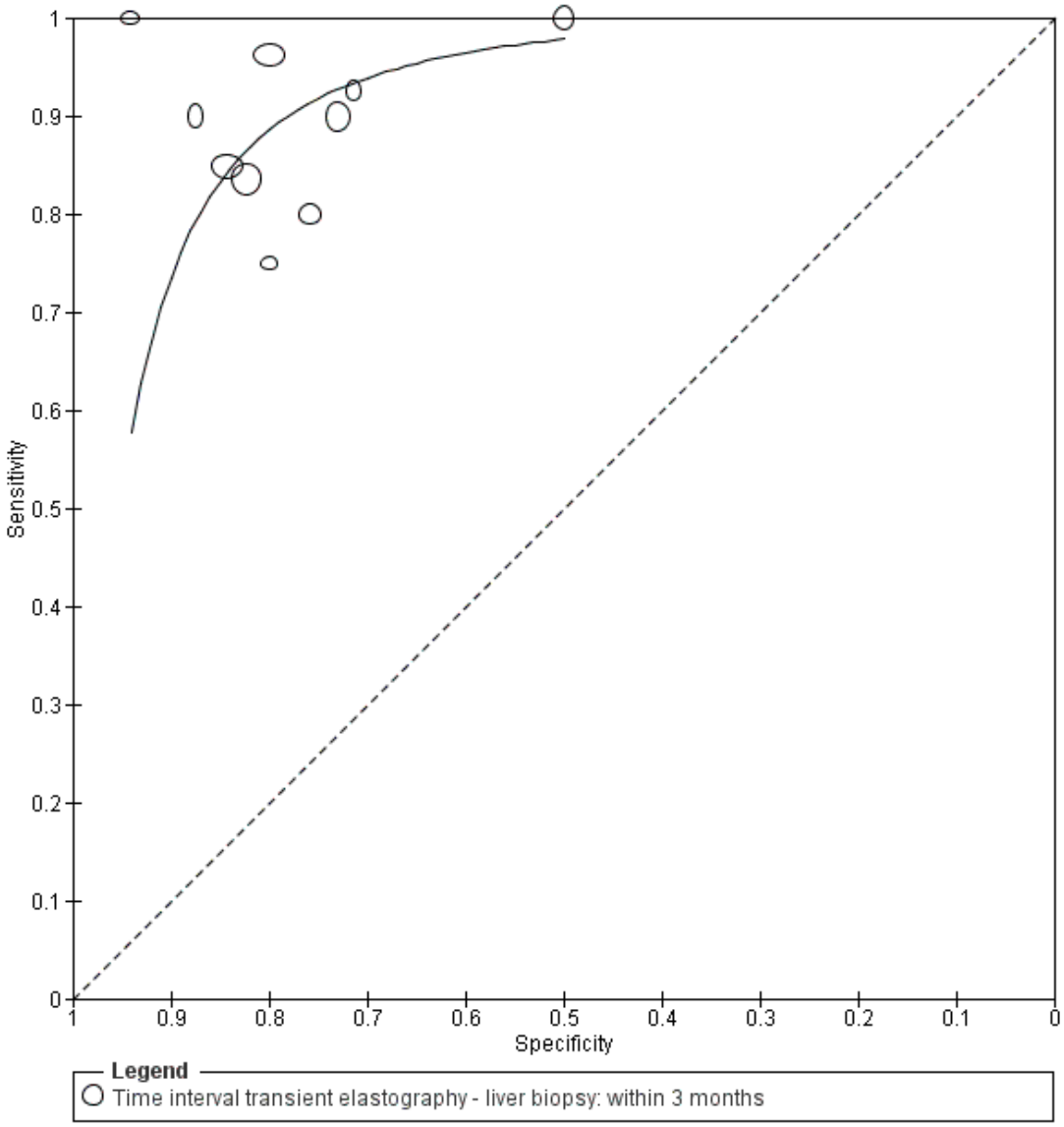
Figure 13. Hierarchical summary receiver operating characteristic (ROC) curve: Transient elastography for F4.



Transient elastography for F4 and time interval within three months - sensitivity analysis

When we considered only the 10 studies with 667 participants with up to three months' interval between transient elastography and liver biopsy, the obtained SROC curve (Figure 14) was similar to the curve obtained when considering all 14 studies; the results were not noticeably affected when we excluded the four studies with time intervals longer than three months (Carl 2012; Fernandez 2012; Bardou-Jacquet 2013; Lannerstedt 2013).

Figure 14. Hierarchical summary receiver operating characteristic (ROC) curve: Transient elastography for F4 (cirrhosis): only studies with time interval between transient elastography and liver biopsy within three months.



Transient elastography for F4 with a cut-off value 12.5 kPa - sensitivity analysis

We performed the analysis with seven studies reporting a cut-off of 12.5 kPa (the most common cut-off for F4) in which 330 participants were tested (Boursier 2009; Kim 2009; Mueller 2010; Bardou-Jacquet 2013; de Ledinghen 2013; Dolman 2013; Lannerstedt 2013) (Data table 7). The sensitivity of the seven studies varied from 90% to 100% and the specificity from 33% to 94% (Figure 15). Using a bivariate model, we obtained the following results: sensitivity 0.95 (95% CI 0.87 to 0.98); specificity 0.71 (95% CI 0.56 to 0.82); positive likelihood ratio (LR+) 3.3 (95% CI 2.1 to 5.0); negative likelihood ratio (LR-) 0.07 (95% CI 0.03 to 0.19) (Figure 16).

Figure 15. Forest plot: Transient elastography for F4 (most common cut-off = 12.5 kPa).

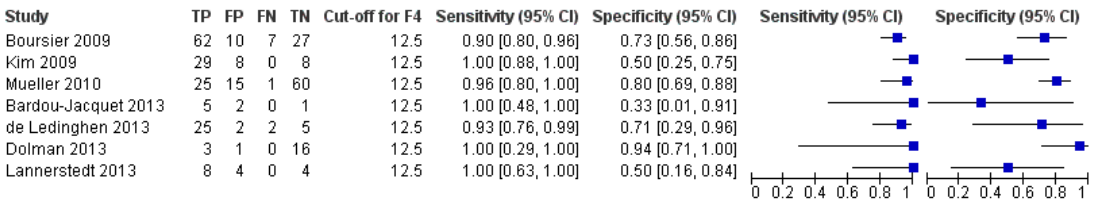
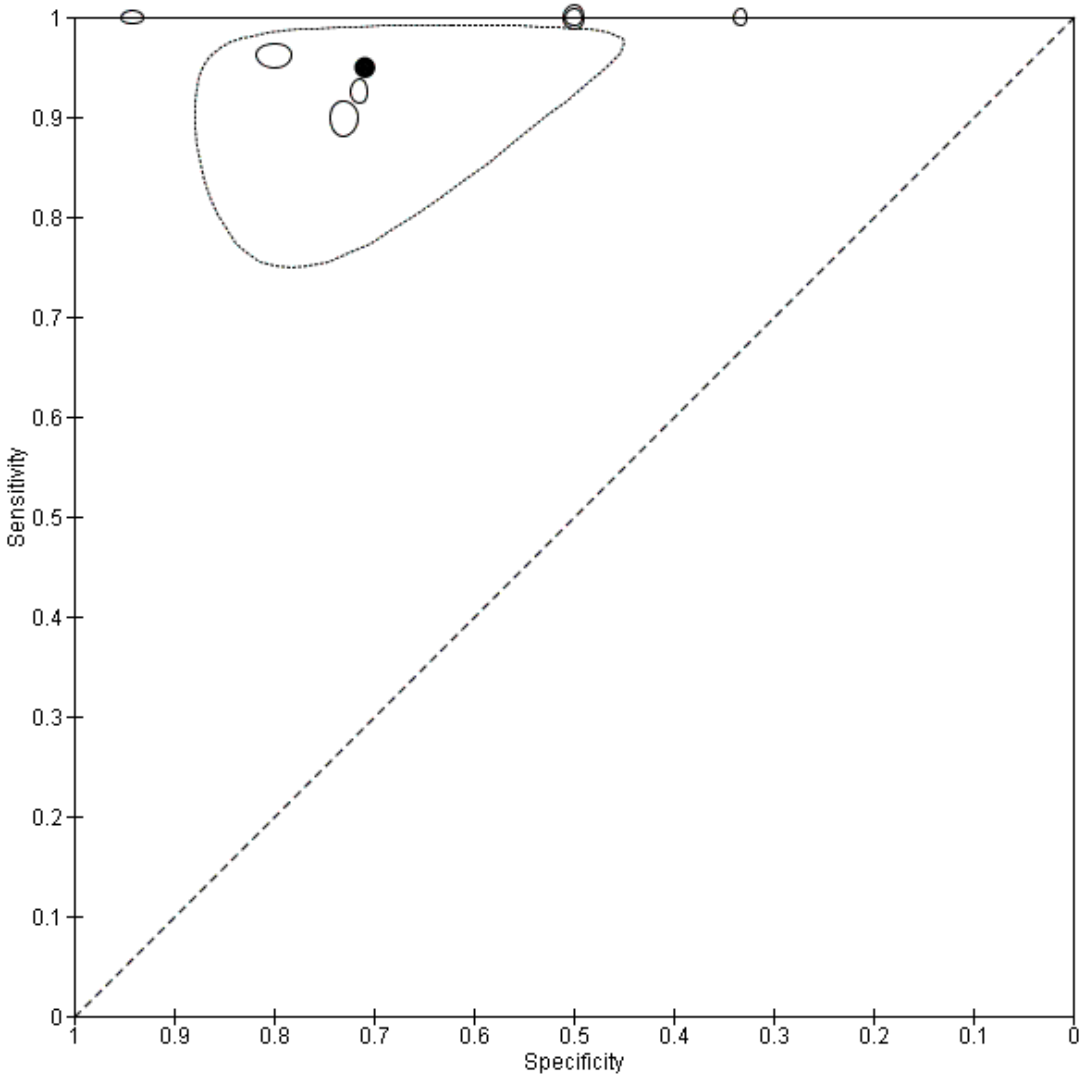


Figure 16. Summary operating point and 95% confidence region: Transient elastography for F4 (cirrhosis) with the most common cut-off = 12.5 kPa.



The mean prevalence of F4 in these seven studies was 51%. Using this value as a pre-test probability, we obtained a post-test probability of 77% when the test was positive and a post-test probability of 7% when the test was negative (Summary of findings).

Transient elastography for F4 with a cut-off value 12.5 kPa and time interval within three months - sensitivity analysis

In order to provide an estimate for accuracy with the most common cut-off of 12.5 kPa and considering only the studies with up to three months' interval between transient elastography and the liver biopsy, we performed a separate analysis in which five studies with 306 participants could be included (Boursier 2009; Kim 2009; Mueller 2010; de Ledinghen 2013; Dolman 2013). The results changed slightly: sensitivity 0.94 (95% CI 0.87 to 0.97); specificity 0.76 (95% CI 0.63 to 0.85); positive likelihood ratio (LR+) 3.8 (95% CI 2.5 to 6.0); negative likelihood ratio (LR-) 0.08 (95% CI 0.04 to 0.17), showing that the pooled results were not affected when we excluded the two studies with time interval longer than three months (Bardou-Jacquet 2013; Lannerstedt 2013).

Investigation of heterogeneity

Despite the fact that we could collect data for sources of heterogeneity, it was not possible to perform formal analyses to explore the effect as almost all studies had the same covariate values.

Reporting bias

The funnel plot for investigation of reporting bias in the 14 studies reporting on hepatic fibrosis F4 (cirrhosis) did not seem to raise concerns as the studies were equally distributed along the x- and y- axes and the two outliers were studies with a small number of participants (four participants, Carl 2012; eight participants, Bardou-Jacquet 2013) (Figure 2). For stages of fibrosis of F1 to F3, we did not attempt to construct funnel plots, as the number of studies with data were fewer than 10.

Summary of findings

What is the diagnostic accuracy of transient elastography examination for the different stages of hepatic fibrosis or cirrhosis at different cut-off values?

Patients/population: people (men and women) diagnosed with alcoholic liver disease on liver biopsy and transient elastography
Prior testing: -
Settings: outpatients and inpatients.
Index test: transient elastography.
Importance: transient elastography is a non-invasive test. The risk of the liver biopsy performance and complications is avoided
Reference standard: liver biopsy.
Studies: cross-sectional studies. No case-control studies were found
Individual patient data: obtained from 7 studies.

Stage of hepatic fibrosis	Summary accuracy (95% CI)	No. of participants (studies)	Prevalence mean (range)	Implications	Post-test probability Post-test probability when the test is positive Post-test probability when the test is negative	Quality and comments
Transient elastography fibrosis stage F2 or worse						
Cut-off around 7.5 kPa (range 7.0 to 7.8). Significant fibrosis	Sensitivity 0.94 (95% CI 0.86 to 0.97) Specificity 0.89 (95% CI 0.76 to 0.95) LR+ 8.2 (95% CI 3.6 to 18.5) LR- 0.07 (95% CI 0.03 to 0.17)	338 participants (7 studies)	81% (range 29% to 97%)	With a prevalence of 81%, 810 out of 1000 people will have significant fibrosis. Of these 810 people, 49 (6% of 810) people will be missed as having significant fibrosis. A clinical follow-up can provide physicians with knowledge for the next diagnostic step that should be taken The remaining 190 people will not have significant	Positive test 97%* Negative test 23%*	The overall quality of the studies in terms of bias risk was assessed as moderate 3 (43%) of the studies included 20 or <than 20 participants Study design (mixed aetiologies); risk of selection bias (not all participants included in the analyses)

				fibrosis. 21 people (11% of 190), i.e., the false positives, will have unnecessary worries about their liver fibrosis stage. However, as the treatment is not a pharmacological treatment, there should be no serious adverse physical outcomes for these people.**		
Transient elastography fibrosis stage F3 or worse						
Cut-off around 9.5 kPa (range 8.0 to 11.0). Severe fibrosis.	Sensitivity 0.92 (95% CI 0.89 to 0.96) Specificity 0.70 (95% CI 0.61 to 0.79) LR+ 3.1 (95% CI 2.1 to 4.1) LR- 0.11 (95% CI 0.06 to 0.16)	564 participants (8 studies)	61% (range 25% to 88%)	With a prevalence of 61%, 610 out of 1000 people will have severe fibrosis. Of these 610 people, 49 (8% of 610) people will be missed as having severe fibrosis. A clinical follow-up can provide physicians with knowledge for the next diagnostic step that should be taken The remaining 390 people will not have severe fibrosis. 117 people (30% of 390), i.e., the false positives, will have unnecessary worries about their liver fibrosis stage. However, as the treatment is not a pharmacological treatment, there should be no serious adverse physical outcomes for these people.**	Positive test 83%* Negative test 15%*	The overall quality of the studies in terms of bias risk was assessed as moderate 2 (25%) of the studies included 20 or <20 participants. Study design (mixed aetiologies); risk of selection bias (not all participants included in the analyses)

Transient elastography fibrosis stage F4					
Cut-off of 12.5 (most common). Cirrhosis.	Sensitivity 0.95 (95% CI 0.87 to 0.98) Specificity 0.71 (95% CI 0.56 to 0.82) LR+ 3.3 (95% CI 2.1 to 5.0) LR- 0.07 (95% CI 0.03 to 0.19)	330 participants (7 studies)	51% (range 15% to 79%)	With a prevalence of 51%, 510 out of 1000 people will have cirrhosis. Of these 510 people, 26 (5% of 510) people will be missed as having severe fibrosis. A clinical follow-up can provide physicians with knowledge for the next diagnostic step that should be taken The remaining 490 people will not have cirrhosis. 143 (29% of 490) people, i.e., the false positives, will have unnecessary worries about their liver fibrosis stage. However, as the treatment is not a pharmacological treatment, there should be no serious adverse physical outcomes for these people.**	Positive test 77%* Negative test 7%*	The overall quality of the studies in terms of bias risk was assessed as moderate 3 (43%) of the studies included 20 or <20 participants. Study design (mixed aetiologies); risk of selection bias (not all participants included in the analyses)

LR+: likelihood ratio positive; LR-: likelihood ratio negative.

* The post-test probability when the test is positive and when the test is negative is calculated based on the pre-test probability estimated by the prevalence of significant fibrosis.

** We considered the mean prevalence of significant or severe fibrosis for the calculations of the number reported in 'Consequences in a cohort of 1000 participants'. The number of false negatives were calculated using the pooled summary sensitivity, and the number of false positives were calculated using the summary specificity (as reported in the table).

Note: the results in this table should not be interpreted in isolation from the results of the individual included studies contributing to each summary test accuracy measure. These are reported in the main body of the text of the review.

DISCUSSION

Summary of main results

In this review, we aimed to determine the diagnostic accuracy of transient elastography for the diagnosis of hepatic fibrosis in people with alcoholic liver disease compared with the reference standard, liver biopsy. We also attempted to identify the optimal cut-off values for the five stages of hepatic fibrosis. We identified 21 studies including participants with alcoholic liver disease of which only 14 studies with 834 participants provided data for the review analyses and hence constituted the included studies of this review. In addition to published article data, we used individual participant data obtained through correspondence with authors of seven of these studies. Participants in all 14 studies had undergone both transient elastography and liver biopsy investigations. The lack of usable data from seven out of 21 studies raised the risk of outcome reporting bias.

Study authors used a variety of different cut-off values for transient elastography in an attempt to discriminate between the stages of hepatic fibrosis. Hence, our analyses using the most common cut-off values did not allow us to establish the best cut-off values for the separate stages of hepatic fibrosis that could be recommended for clinical practice.

Detection of fibrosis F0 or F1 is of no clinical relevance as these initial hepatic fibrosis stages do not influence prognosis and if the person abstains from alcohol consumption, the fibrosis will reverse.

Transient elastography for F2 or worse

For F2 or worse with a cut-off of around 7.5 kPa, summary sensitivity was 0.94 and specificity was 0.89. Prevalence of F2 or worse was 81%. Most of the participants were alcohol abusers.

Transient elastography for F3 or worse

For F3 or worse with a cut-off of around 9.5 kPa, summary sensitivity was 0.92 and specificity was 0.70. The result suggests that transient elastography may rule out the presence of severe fibrosis, considering the prevalence of 61%.

Transient elastography for F4

For F4 with a cut-off of 12.5 kPa, summary sensitivity was 0.95 and specificity was 0.71. The result suggests that transient elastography could be useful to rule out the presence of cirrhosis following the data results of LR- and considering the prevalence of 51%. As the post-test probability becomes 7%, further testing may not be needed to rule out cirrhosis. Thus, liver biopsy could be avoided. This result was consistent with the results of the analysis considering all the studies with the different cut-off values (Figure 13) and the sensitivity analysis on the studies with time interval between liver biopsy and transient elastography less than three months (Figure 14), as the point representing the summary sensitivity and specificity (summary operating point) was close to the two hierarchical SROC curves.

Out of 1000 participants, we would identify 510 with cirrhosis, but we would miss 26 people with cirrhosis and 143 participants would be wrongly diagnosed due to transient elastography error.

Strengths and weaknesses of the review

The aims of our review were to provide pooled estimates of accuracy of transient elastography and to find the best cut-off values of transient elastography for the five stages of hepatic fibrosis in people with alcoholic liver disease.

We judged only 29% of the studies at low risk of bias. Despite the fact that all included studies were published after 2003, that is, the STARD initiative was published (www.stard-statement.org), clinically relevant information was missing. We could not investigate whether grade of inflammation, lengths of liver biopsy sample, portal tracts, grades of steatosis, severity of fibrosis, and body mass index as sources of possible heterogeneity had an impact on our results because the collected data were not sufficient for analyses.

The role of transient elastography for determining the cut-off values for differentiating the five stages of hepatic fibrosis (F0 to F4) in people diagnosed with alcoholic liver disease has not been previously validated. Therefore, this is the first diagnostic test accuracy review with meta-analyses that attempted to determine the diagnostic test accuracy thresholds for distinguishing the stages of hepatic fibrosis, focusing only on people with alcoholic liver disease and using rigorous Cochrane Collaboration methodology (SRDTA Handbook). However, due to the very few number of studies assessing mild fibrosis and the huge variation of cut-off values in studies with participants with significant or severe hepatic fibrosis or cirrhosis, we could not establish the optimal cut-off values that could serve as thresholds for mild, significant, or severe fibrosis and cirrhosis.

Variation of cut-off values is the main source of heterogeneity in diagnostic studies. In addition, when studies reported accuracy estimates considering similar cut-off values, our analyses showed that some heterogeneity was still present, most probably due to differences in clinical characteristics of the participants (abstinent or not), as suggested by the variability of prevalence among the studies.

The observed heterogeneity for F4 seemed to affect mainly the specificity of transient elastography.

The small number of included studies with data for stages F2 or worse and F3 or worse, was one of the limitations of our systematic review, as we could not perform a comprehensive analysis to study the influence of potential sources of heterogeneity. Furthermore, the small number of studies might have had an effect on the reliability of the estimates obtained by the bivariate or HSROC

model, especially when some sensitivity analyses were performed. In addition, in some analyses there was no evidence of heterogeneity in sensitivity, which we believe may be the main reason for the failure of convergence of the statistical model. However, we have been able to obtain accuracy estimates by fitting a model with the random effect for only specificity. Unfortunately, in some sensitivity analyses, the reason of lack of convergence of the statistical models was not identified and we were unable to provide a summary result. Hence, our findings for stages F2 or worse and F3 or worse (analyses with no more than 10 studies) might be limited by the small number of studies. As the CIs for the obtained estimates of hepatic fibrosis stages were wide, caution is needed when interpreting the results.

A strength of our review is that we managed to obtain individual patient data of people with alcoholic liver disease through correspondence with authors of seven studies. By doing this, we decreased the amount of missing information and we were able to increase the number of the included studies. Contacting Echosens ® with a request for published and unpublished studies yielded a list with published studies only, so we failed at identification of any unpublished studies relevant to the review questions.

We cannot judge if lack of intention to diagnose in seven of the studies that included participants with various liver disease aetiology and the lack of information in another study would have affected the sensitivities and specificities of the transient elastography, as it was impossible to conduct such analyses.

Despite that liver biopsy is considered the reference standard, it may also present problems with its accuracy and reproducibility, which may reflect on the true estimates of the accuracy of transient elastography.

We could find only one systematic review that also included an economic evaluation assessing FibroScan® for the detection of hepatic fibrosis in people with suspected alcohol-related liver disease (Stevenson 2012). However, the authors identified only six studies to 2010 and the authors concluded that, as the number of people with suspected alcoholic liver disease was small in all the studies, the estimated sensitivities and specificities were not robust.

Only five studies reported results based on a pre-defined cut-off and it was the cut-off established for chronic hepatitis C. We were unable to define the optimal cut-off values for the stages of hepatic fibrosis in people with alcoholic liver disease, as the data that we obtained were not sufficient to perform the planned review analyses. In addition, the lack of pre-specified cut-off values in most of the included studies might have led to overestimation of the accuracy of transient elastography.

Clinicians and researchers alike will be helped by knowing the sensitivities and specificities of the most common cut-off values used for staging of hepatic fibrosis in people with alcoholic liver disease.

As transient elastography in our studies was not used as a screening or a triage test, we could not present any results in a population with a low prevalence of F3 or worse (significant hepatic fibrosis or cirrhosis) or for F4 (cirrhosis alone) in people with alcoholic liver disease. For clarity, we provided two tables.

Table 3 presented post-test probabilities obtained in our review from minimum, medium, and high pre-test probabilities when LR- is 0.11 (obtained in our analyses for F3 or worse). A negative test result will convert a pre-test probability of 25%, 61%, and 88% to a post-test probability of 4%, 15%, and 45%. Hence, the use of transient elastography to diagnose people with hepatic fibrosis stage 3 or worse seems reasonable and could avoid liver biopsy testing when the pre-test probability is not high.

Table 4 presented post-test probabilities obtained in our review from minimum, medium, and high pre-test probabilities for hepatic cirrhosis (F4) with most common cut-off of 12.5 kPa when the LR- is 0.07. A negative test result will convert a pre-test probability of 15%, 51%, and 79% to a post-test probability of 1%, 7%, and 21%. Hence, the use of transient elastography to diagnose people with F4 seems reasonable and could avoid liver biopsy testing when the pre-test probability is not high.

The results of our review confirm that transient elastography is an accurate test for differentiating the different stages of hepatic fibrosis, also in the subgroup of people with alcoholic liver disease. The high prevalence of significant or severe fibrosis and cirrhosis found in the included studies has some consequences on the clinical usefulness of transient elastography, as such scenarios are not often encountered in clinical practice. When the pre-test probability of cirrhosis is too high, clinicians should reconsider testing with transient elastography, as it is unlikely to add any further relevant information to the clinical diagnosis of cirrhosis. The more likely reason for the high prevalence is in the aetiology of the liver disease. People with alcoholic liver disease visit clinicians when they are at a more advanced stage of hepatic fibrosis than people diagnosed with other aetiologies of liver diseases. An advanced stage of hepatic fibrosis, severe or worse, is easily recognised by clinicians, which may limit the clinical utility of transient elastography test in people with alcoholic liver disease.

We assessed transient elastography in people who had liver index test conducted before, close to, or after the conduct of the reference standard, liver biopsy. As any post-liver biopsy intrahepatic bleeding may have affected the results of a following transient elastography, this sequence of tests may have affected our results.

Applicability of findings to the review question

The aims of our review were to provide pooled estimates of diagnostic accuracy performance of transient elastography with regard to the five stages of hepatic fibrosis in people with alcoholic liver disease and their differentiation by finding the optimal cut-off values for each stage of hepatic fibrosis.

Despite the fact that we could not establish the best cut-off values for differentiating the hepatic fibrosis stages, we judged that our review findings raise small applicability concerns defined through

judgement of the three QUADAS-2 applicability domains: participant selection, index test, and reference standard.
The included participants were people with alcoholic liver disease, from various settings, and having different stages of hepatic fibrosis. We found a large variance of prevalence of the different stages of hepatic fibrosis across the studies, but we believe that this does not affect the applicability of our findings.
Transient elastography investigations were performed as prescribed by the manufacturers and as usually performed and reported in clinical practice.
Liver biopsy was performed following the clinical guideline for liver biopsy investigation and morphological results were estimated by the most often used semi-quantitative morphological scores.

Implications for research

In order to obtain precise and reliable accuracy results of transient elastography, used for diagnosing hepatic fibrosis in people with alcoholic liver disease, prospective studies of adequate sample size, enrolling only participants with alcoholic liver disease, need to be performed. Hepatic fibrosis should be diagnosed with both transient elastography and liver biopsy (the reference standard) and in this sequence, and the optimal cut-off values of transient elastography should be identified and validated for hepatic fibrosis in people with alcoholic liver disease. The time interval between transient elastography and liver biopsy investigations in people without cirrhosis should not exceed three months, and assessment of results should be properly blinded, as only studies with low risk of bias, fulfilling the Standards for Reporting of Diagnostic Accuracy (The STARD statement) may answer the review questions.

AUTHORS' CONCLUSIONS

Implications for practice

We identified a small number of studies with a few participants each and were unable to include several studies, which raises the risk of outcome reporting bias. With these caveats in mind, transient elastography may be used as a diagnostic method to rule out liver cirrhosis (F4) in people with alcoholic liver disease when the pre-test probability is 51% (range 15% to 79%). Transient elastography may also help in ruling out severe fibrosis (F3 or worse). The use of transient elastography for severe fibrosis and cirrhosis may lead to a reduced need for liver biopsy. Liver biopsy investigation still remains an option if the certainty to rule in or rule out the stage of hepatic fibrosis or cirrhosis remains insufficient after a clinical follow-up or any other non-invasive test considered useful by the clinician.

The proposed cut-off values for the different stages of hepatic fibrosis may be used in clinical practice, but one should be very cautious, as those reported in this review were only the most common cut-off values used by the study authors. The best cut-off values for hepatic fibrosis in people with alcoholic liver disease could not be established yet.

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Contact editors from The Cochrane Hepato-Biliary Group: Mirella Fraquelli, Italy; Agostino Colli, Italy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anastasiou 2010

Study characteristics	
Patient sampling	Prospective cohort study. Consecutive participants.
Patient characteristics and setting	Number of participants: 14 participants diagnosed with alcoholic liver disease. See personal communication in 'Notes'. Otherwise, 76 participants with chronic liver disease underwent liver biopsy, transient elastography, and FibroTest/ActiTest
Index tests	Transient elastography.
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.
Flow and timing	The interval between the liver biopsy and the transient elastography measurement was on the same day following Anastasiou 2010 and 3 days, following personal communication on 27 July 2011
Comparative	
Notes	Email sent to J Anastasiou and colleagues 20 July 2011. Reply received 27 July 2011. **The following data were received through personal communication with** J Anastasiou: "Dear Dr Pavlov, Thank you for taking into consideration our article. Our alcoholic liver disease group was categorized as follows: 14 patients with liver fibrosis stage (METAVIR) F:0/1/2/3/4 of 8/2/0/0/4 respectively. (table 1). Taking into account the size of the ALD (alcoholic liver disease) subgroup, only an F (fibrosis) above or equal of 2, analysis was feasible. The results are as follows: Optimal cut-off value: 7.15 kPa Sensitivity: 0.75 Specificity: 0.80 Positive predictive value: 0.89 Negative predictive value: 0.6 AUROC: 0.83 Asymptomatic significance: 0.06 The interval between the liver biopsy and the transient elastography measurement was 3 days. Transient elastography was performed as an add on test to the liver biopsy. Kindest regards, Dr Anastasiou"

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Bardou-Jacquet 2013

Study characteristics			
Patient sampling	Retrospective cohort study.		
Patient characteristics and setting	Only participants followed by trained addictologists with definite information regarding alcohol consumption were included. People were excluded if they presented other causes of chronic liver disease 37 participants corresponded to the study criteria and were considered for analyses (7 women and 30 men). 8 participants had liver biopsy during follow-up		
Index tests	Transient elastography.		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	2 biopsies within 4 weeks, and 6 biopsies within the median of follow-up 32.5 weeks (15 weeks to 85 weeks)		
Comparative			
Notes	No letter sent to the study authors. Unclear when liver biopsy was performed in the 8 participants, but 8 participants had liver biopsy during follow-up. Transient elastography was performed at an interval of more than 1 week apart by a senior operator		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			

Bardou-Jacquet 2013 (*Continued*)

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		

Boursier 2009

Study characteristics	
Patient sampling	Prospective cross-sectional cohort study.
Patient characteristics and setting	From personal communication, we obtained the information that "out of 390 patients, 106 had alcoholic liver disease..." "Liver steatosis evaluation on liver biopsy was not available in our study." Hospitalised.
Index tests	Transient elastography.

Boursier 2009 (*Continued*)

Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	1 week.		
Comparative			
Notes	Email sent to Jerome Boursier and colleagues 26 February 2013. Replies received 19 February 2013 and 21 May 2013. Individual participant data, sent by the study author, were used for our review analyses. The impression is that liver biopsy was performed first and then transient elastography		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge	Yes		

Boursier 2009 (*Continued*)

of the results of the index tests?			
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		

Carl 2012

Study characteristics			
Patient sampling	Retrospective cohort study.		
Patient characteristics and setting	4 people with alcoholic liver disease were included in the analyses (see personal communication in 'Notes'.). In total, 266 participants underwent FibroScan®.		
Index tests	Transient elastography.		
Target condition and reference standard(s)	People with alcoholic liver disease and liver biopsy.		
Flow and timing	Participants who were included between 1 May 2008 and 31 July 2011		
Comparative			
Notes	Email sent 1 March 2013. Reply received 15 April 2013. Individual participant data, sent by the study author, were used for our review analyses Unclear of the sequence, but reported "All patients who underwent liver biopsy and FibroScan® between 1 May 2008 and 31 July 2011".		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

de Ledinghen 2013

Study characteristics			
Patient sampling	Prospective cohort study.		
Patient characteristics and setting	In our review analysis, we could include 34 participants as we received individual data		
Index tests	Transient elastography.		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	Within 1 week.		
Comparative			
Notes	Email request sent about additional data to Victor De-Ledinghen on 22 July 2011. Received an Excel sheet with data on 25 July 2011 In summary, retrieved data from 51 people with liver biopsy and transient elastography. After removing duplicate entries of participants, 34 participants remained It is not clear which test/investigation was performed first		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		

			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		

Dolman 2013

Study characteristics	
Patient sampling	Retrospective study using data from a consecutive cohort of participants; among the people with chronic liver disease with different aetiologies, 20 had alcoholic liver disease
Patient characteristics and setting	There were 20 participants with alcoholic liver disease. See personal communication in 'Notes'
Index tests	Transient elastography.
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.
Flow and timing	2 months.
Comparative	

Notes	Email sent to Grace Dolman on 26 May 2013. Replies received 18 June 2013, 9 April 2013, and 22 October 2013. Received individual data of interest to our review protocol on 20 participants "There were 20 patients in our study with alcoholic liver disease. This was defined as the presence of steatohepatitis with or without fibrosis, with alcohol as the most likely aetiology (and parenchymal chronic liver screen negative). All patients had transient elastography and biopsy AST was not routinely available in our centre at the time of the study, but I have included ALT as requested. BMI was missing from the notes when we reviewed them for the study for all (BMI in 2 categories a) < 25 b) ≥25 kg/m2) but one patient. Steatosis was divided into 2 categories a) < 5% steatosis; b) ≥ 5% steatosis We did not calculate sensitivity/specificity by aetiology in the study due to the small numbers in the cohort Grace Dolman" Participants were included if they had a liver biopsy within 2 months of a validated transient elastography measurement

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Fernandez 2012

Study characteristics			
Patient sampling	Retrospective cohort study.		
Patient characteristics and setting	139 people with alcoholic liver disease.		
Index tests	Transient elastography.		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	Within 6 months.		
Comparative			
Notes	No email sent. Liver biopsy was performed first and then within the 6 months, participants underwent transient elastography testing (among other tests)		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Janssens 2010

Study characteristics			
Patient sampling	Prospective cohort study.		
Patient characteristics and setting	"Two hundred fifty-five patients admitted between January 1, 2006 and February 29, 2008 to our unit for alcohol detoxification and rehabilitation Final analysis was performed on a total of 49 patients (34 men and 15 women). Median age was 53 years (range: 29 to 73 y) and median body mass index was 25 (range: 17 to 38) Number of patients: 49. Sex: male/female: 34 men/15 women. Age (years): 53 (29 to 73). BMI = 25 (17 to 38). AST = 87IU/l (25 to 311). ALT = 51IU/l (17 to 168)."		
Index tests	Transient elastography.		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	Liver biopsy performed after transient elastography investigation in 1 week		
Comparative			
Notes	No mail sent. The impression was that transient elastography was performed before liver biopsy. See also p. 581 of the primary publication		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference stan-	Yes		

Janssens 2010 (*Continued*)

dard?			
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Kim 2009

Study characteristics	
Patient sampling	Prospective cohort study.
Patient characteristics and setting	45 people with alcoholic liver disease enrolled. Fibrosis stage assessed using the Batts-Ludwig scoring system Aim of study was to determine the diagnostic accuracy of the FibroScan® in the detection of cirrhosis in people with alcoholic liver disease **Clinical data for 29 people with cirrhosis** Sex: male/female: 24 men/5 women. Age (years): 47.9 ± 7.8. BMI = 23.1 ± 3.8. AST = 114.9 IU/L ± 71.4.

	ALT = 62.6 U/L ± 92.2. **Clinical data for 16 people without cirrhosis** Sex: male/female: 13 men/3 women. Age (years): 44.9 ± 7.5. BMI = 23.1 ± 4.0. AST = 81.8 IU/L ± 63.1. ALT = 69.1 U/L ± 48.4.
Index tests	Transient elastography.
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.
Flow and timing	Liver biopsy and transient elastography performed with the interval of 11.2 ± 22 days (0 to about 92 days)
Comparative	
Notes	Mail sent 26 March 2013 and replies received on the same day. Unclear, but FibroScan® was mentioned before liver biopsy testing.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
			Low

Kim 2009 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Lannerstedt 2013

Study characteristics	
Patient sampling	Retrospective, cohort study. Participants with different chronic liver diseases
Patient characteristics and setting	16 people with alcoholic liver disease. 418 participants in total
Index tests	Transient elastography.
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.
Flow and timing	8 participants (50%) had transient elastography at < 2 months, and 8 participants (50%) had transient elastography at > 1.9 years to 8.6 years
Comparative	

Notes	Emails sent 28 February 2013. Replies received 21 May 2013 and 23 May 2013. We received individual participant data (relevant to our review information) for 16 people with alcoholic liver disease. It seems that liver biopsy was performed before transient elastography (it was also a retrospective study). However, the time interval was most likely not an issue in terms of haematoma should liver biopsy have been performed before transient elastography

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			

Was there an appropriate interval between index test and reference standard?	No		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Lemoine 2008

Study characteristics			
Patient sampling	Prospective cohort study.		
Patient characteristics and setting	Alcoholic participants. 48 people had alcohol-related cirrhosis. (Another 44 had hepatitis C virus-related cirrhosis.)		
Index tests	Transient elastography. "Liver stiffness measurement was performed using FibroScan® (Echosens) by two experienced operators who were not aware of the haemodynamic results. Briefly, FibroScan® was performed as previously described on the right lobe of the liver, in the intercostal space with the patient lying in dorsal decubitus with the right arm in maximal abduction. Only procedures with 10 validated acquisitions, interquartile range $\leq$ 30% of the median value and a success rate of at least 70% were considered reliable. The median value of all validated acquisitions was considered as LSM and the results were expressed in kilopascal (kPa)."		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	Transient elastography and liver biopsy were performed on the same day		
Comparative			
Notes	No mail sent. Transient elastography and liver biopsy (transjugular route) were performed on the same day, and it seems that transient elastography was performed first		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Mueller 2010

Study characteristics			
Patient sampling	Prospective cohort study of 101 people with alcoholic liver disease		
Patient characteristics and setting	Validation cohort: in the second part of the study, the study authors included 101 (73 men and 28 women) people with histologically staged alcoholic liver disease. (In the first part of the study, sequential analyses of liver stiffness was performed in 50 people presenting at a university medical centre for alcohol detoxification.)		
Index tests	Transient elastography.		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	A mean observation interval of 5.3 days. Range 3 to 10 days.		
Comparative			
Notes	No mail sent. Unclear. The FibroScan® examination (with M probe) was performed at the time of liver biopsy, i.e., at the same time in 100 participants		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low

Mueller 2010 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Nahon 2008

Study characteristics	
Patient sampling	Prospective blinded cohort study that included consecutive participants with suspected alcoholic liver disease
Patient characteristics and setting	Out of 174 participants fulfilling the study inclusion criteria, 147 participants remained to be included
Index tests	Transient elastography.
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.
Flow and timing	Transient elastography and liver biopsy on the same day.
Comparative	
Notes	No mail sent. Liver biopsy seems to have been performed first, followed by transient elastography on the same day

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Nguyen-Khac 2008

Study characteristics			
Patient sampling	Prospective cohort study.		
Patient characteristics and setting	The number of participants included in the final analyses was 103. Otherwise, 160 participants met the inclusion criteria. Rehabilitation outpatients and inpatients with alcohol abuse, prospectively included from April 2005 to January 2007		
Index tests	Transient elastography.		
Target condition and reference standard(s)	Participants with alcoholic liver disease and liver biopsy.		
Flow and timing	Transient elastography and liver biopsy on the same day.		
Comparative			
Notes	No mail sent. It seemed that liver biopsy (percutaneously) was performed before transient elastography. Both on the same day		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low

Nguyen-Khac 2008 (*Continued*)

DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

AST: aspartate aminotransferase; BMI: body mass index; F: fibrosis; FT/AT = FibroTest (ActiTest); LSM: liver stiffness measurement; TE (FS): transient elastography (FibroScan®).

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angulo 2009b	Review article (serum markers).
Baba 2011	No reference standard.
Bureau 2008	Aim was to assess the correlation between liver stiffness and hepatic venous pressure gradient and to investigate the performance of transient elastography for the diagnosis of significant portal hypertension in participants with liver diseases (however, the cause of liver abnormalities in 51 (34%) out of 150 participants was alcohol)
Crespo 2010	Preliminary abstract published in 2010 of a study published later by Crespo 2012.
Crespo 2012	Only 4 participants with alcoholic liver disease. This information was received through email on 13 March 2014 "....Please find attached the individual data of the patients included. There were only 15 patients with alcoholic disease, and among them 11 had been transplanted (so no alcohol-related liver disease at all was present at the moment of biopsy and TE [transient elastography]). So in the end, there were only 4 "pure" immunocompetent patients with alcohol-related chronic liver disease. I have anyway included the data required of all patients just in case you decide to use them. I regret the low number of patients with which we can contribute to the review, and I understand you may decide not to use them Thanks. Gonzalo Crespo"
Ebinuma 2011	Aim was to evaluate the clinical utility of transient elastography with acoustic radiation force impulse and to compare the results with this method and those of the FibroScan® procedure.
Fraquelli 2007	No data for the 5 people with alcoholic liver disease.
Ganne-Carrié 2006	Data on 75 people with alcoholic liver disease were expected to be received from Celine Fournier working at Echosens. We understood that the data are the property of the firm. In addition, it is written in the publication that there is participant overlap with another study by Ziol et al. published in Ziol 2005 that had included people with chronic hepatitis C. Reading the 3 publications under the main reference of the included study by de Ledinghen 2013, its seemed that data on the 75 participants that we were interested in were a consistent part of the Excel sheet with individual participant data obtained through personal communication with de Ledinghen on 8 March 2013. As we cannot be completely sure, we refer to the Ganne-Carrié publication twice, i.e., under included and excluded studies
Gómez-Dominguez 2006	No data for the 3 people with alcoholic liver disease.
Ingiliz 2009	Aim was to investigate the liver stiffness measurement applicability and variability with reference to 3 probe positions according to the region of liver biopsy
Kircheis 2012	Reference standard was transient elastography.
Klibansky 2012	Aim of the study was to determine whether transient elastography could identify people with chronic liver disease at risk of clinical decompensation

(*Continued*)

Krawczyk 2011	Aim was to investigate variant adiponutrin as genetic determinant of liver fibrosis
Marinho 2007	Participants were with concomitant liver diseases.
McCorry 2012	Participants were suspected of having a chronic liver disease; however, aetiology was not reported
Nudo 2008	During the time of liver biopsy or FibroScan® measurements, people with alcoholic liver disease were abstinent
Rath 2011	Only 2 people with alcoholic liver disease, i.e., the number of participants with alcoholic liver disease was too low and the data were not given separately
Roulot 2011	Data on people with alcoholic liver disease alone could not be obtained separately
Stål 2009	Only 2 people with alcoholic liver disease. Some information on these 2 people was received from P Stål on 20 June 2013
Trabut 2012	Only 1 person (too low number) with alcoholic liver disease. The information below was received through email on 26 May 2013 " ..... We only had 1 patient with alcoholic liver disease. The majority of the subjects in our study had chronic hepatitis C. There were individuals biopsied for elevated liver enzymes of unknown etiology, but alcohol consumption was not significant in these individuals and the biopsy histology was not consistent with alcoholic liver disease The one subject was male and 44 years old. BMI 25.9, FibroScan® = 48 kPa, Biopsy showed grade 3 and stage 4 on both left and right liver lobes. (2 biopsies per lobe) The biopsy and FibroScan® were performed 21 days apart. Unfortunately that is all the data I have. Please do not hesitate to contact me if you have any further question Thank-you, Carmine Nudo, MD CM, FRCPC"

BMI: body mass index.

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

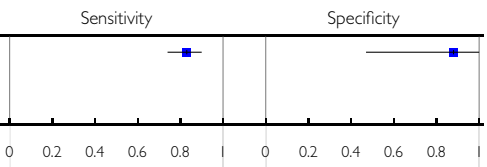
Test	No. of studies	No. of participants
1 Transient elastography for F1 or worse	1	103
2 Transient elastography for F2 or worse	8	342
3 Transient elastography for F3 or worse	10	760
4 Transient elastography for F3 or worse with cut-off values around 9.5	8	564
5 Transient elastography for F3 or worse with a cut-off value equal to 9.5	5	221
6 Transient elastography for F4	14	834
7 Transient elastography for F4 (most common cut-off value = 12.5)	7	330

Test 1. Transient elastography for F1 or worse.

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 1 Transient elastography for F1 or worse

Study	TP	FP	FN	TN	Sensitivity	Specificity
Nguyen-Khac 2008	79	1	16	7	0.83 [0.74, 0.90]	0.88 [0.47, 1.00]

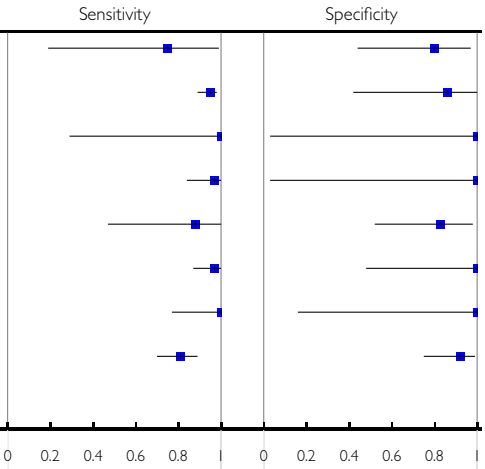


Test 2. Transient elastography for F2 or worse.

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 2 Transient elastography for F2 or worse

Study	TP	FP	FN	TN	Sensitivity	Specificity
Anastasiou 2010	3	2	1	8	0.75 [0.19, 0.99]	0.80 [0.44, 0.97]
Boursier 2009	94	1	5	6	0.95 [0.89, 0.98]	0.86 [0.42, 1.00]
Carl 2012	3	0	0	1	1.00 [0.29, 1.00]	1.00 [0.03, 1.00]
de Ledinghen 2013	32	0	1	1	0.97 [0.84, 1.00]	1.00 [0.03, 1.00]
Dolman 2013	7	2	1	10	0.88 [0.47, 1.00]	0.83 [0.52, 0.98]
Kim 2009	39	0	1	5	0.98 [0.87, 1.00]	1.00 [0.48, 1.00]
Lannerstedt 2013	14	0	0	2	1.00 [0.77, 1.00]	1.00 [0.16, 1.00]
Nguyen-Khac 2008	62	2	15	24	0.81 [0.70, 0.89]	0.92 [0.75, 0.99]

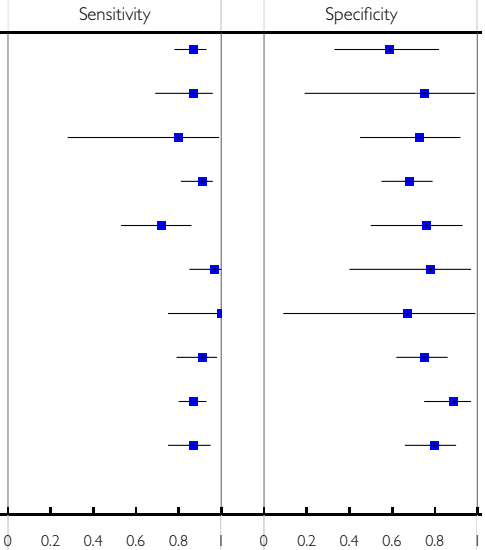


Test 3. Transient elastography for F3 or worse.

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 3 Transient elastography for F3 or worse

Study	TP	FP	FN	TN	Sensitivity	Specificity
Boursier 2009	77	7	12	10	0.87 [0.78, 0.93]	0.59 [0.33, 0.82]
de Ledinghen 2013	26	1	4	3	0.87 [0.69, 0.96]	0.75 [0.19, 0.99]
Dolman 2013	4	4	1	11	0.80 [0.28, 0.99]	0.73 [0.45, 0.92]
Fernandez 2012	67	21	7	44	0.91 [0.81, 0.96]	0.68 [0.55, 0.79]
Janssens 2010	23	4	9	13	0.72 [0.53, 0.86]	0.76 [0.50, 0.93]
Kim 2009	35	2	1	7	0.97 [0.85, 1.00]	0.78 [0.40, 0.97]
Lannerstedt 2013	13	1	0	2	1.00 [0.75, 1.00]	0.67 [0.09, 0.99]
Mueller 2010	41	14	4	42	0.91 [0.79, 0.98]	0.75 [0.62, 0.86]
Nahon 2008	96	4	14	33	0.87 [0.80, 0.93]	0.89 [0.75, 0.97]
Nguyen-Khac 2008	46	10	7	40	0.87 [0.75, 0.95]	0.80 [0.66, 0.90]

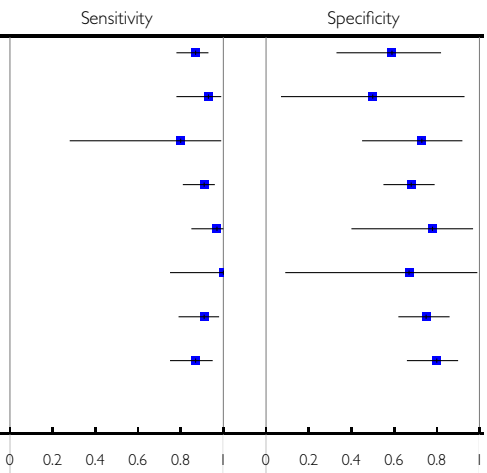


Test 4. Transient elastography for F3 or worse with cut-off values around 9.5.

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 4 Transient elastography for F3 or worse with cut-off values around 9.5

Study	TP	FP	FN	TN	Sensitivity	Specificity
Boursier 2009	77	7	12	10	0.87 [0.78, 0.93]	0.59 [0.33, 0.82]
de Ledinghen 2013	28	2	2	2	0.93 [0.78, 0.99]	0.50 [0.07, 0.93]
Dolman 2013	4	4	1	11	0.80 [0.28, 0.99]	0.73 [0.45, 0.92]
Fernandez 2012	67	21	7	44	0.91 [0.81, 0.96]	0.68 [0.55, 0.79]
Kim 2009	35	2	1	7	0.97 [0.85, 1.00]	0.78 [0.40, 0.97]
Lannerstedt 2013	13	1	0	2	1.00 [0.75, 1.00]	0.67 [0.09, 0.99]
Mueller 2010	41	14	4	42	0.91 [0.79, 0.98]	0.75 [0.62, 0.86]
Nguyen-Khac 2008	46	10	7	40	0.87 [0.75, 0.95]	0.80 [0.66, 0.90]

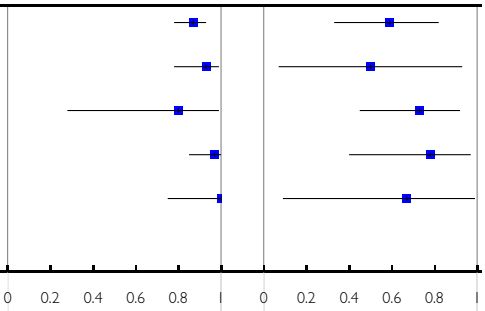


Test 5. Transient elastography for F3 or worse with a cut-off value equal to 9.5.

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 5 Transient elastography for F3 or worse with a cut-off value equal to 9.5

Study	TP	FP	FN	TN	Sensitivity	Specificity
Boursier 2009	77	7	12	10	0.87 [0.78, 0.93]	0.59 [0.33, 0.82]
de Ledinghen 2013	28	2	2	2	0.93 [0.78, 0.99]	0.50 [0.07, 0.93]
Dolman 2013	4	4	1	11	0.80 [0.28, 0.99]	0.73 [0.45, 0.92]
Kim 2009	35	2	1	7	0.97 [0.85, 1.00]	0.78 [0.40, 0.97]
Lannerstedt 2013	13	1	0	2	1.00 [0.75, 1.00]	0.67 [0.09, 0.99]

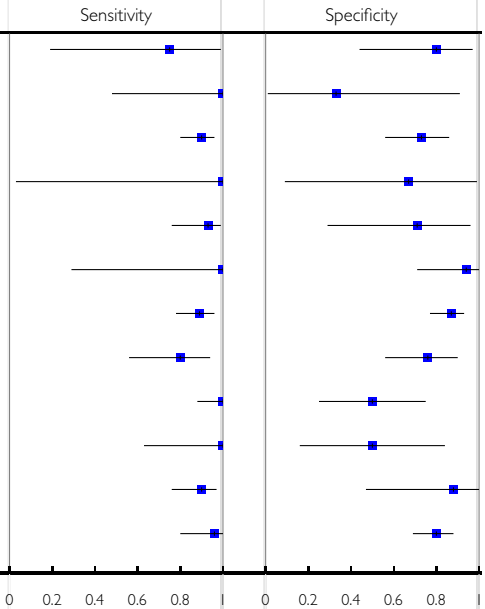


Test 6. Transient elastography for F4.

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 6 Transient elastography for F4

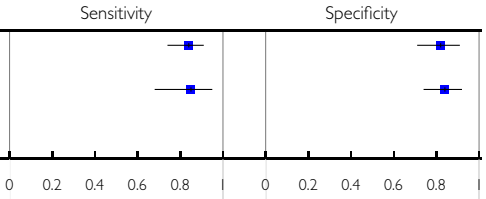
Study	TP	FP	FN	TN	Sensitivity	Specificity
Anastasiou 2010	3	2	1	8	0.75 [0.19, 0.99]	0.80 [0.44, 0.97]
Bardou-Jacquet 2013	5	2	0	1	1.00 [0.48, 1.00]	0.33 [0.01, 0.91]
Boursier 2009	62	10	7	27	0.90 [0.80, 0.96]	0.73 [0.56, 0.86]
Carl 2012	1	1	0	2	1.00 [0.03, 1.00]	0.67 [0.09, 0.99]
de Ledinghen 2013	25	2	2	5	0.93 [0.76, 0.99]	0.71 [0.29, 0.96]
Dolman 2013	3	1	0	16	1.00 [0.29, 1.00]	0.94 [0.71, 1.00]
Fernandez 2012	51	11	6	71	0.89 [0.78, 0.96]	0.87 [0.77, 0.93]
Janssens 2010	16	7	4	22	0.80 [0.56, 0.94]	0.76 [0.56, 0.90]
Kim 2009	29	8	0	8	1.00 [0.88, 1.00]	0.50 [0.25, 0.75]
Lannerstedt 2013	8	4	0	4	1.00 [0.63, 1.00]	0.50 [0.16, 0.84]
Lemoine 2008	36	1	4	7	0.90 [0.76, 0.97]	0.88 [0.47, 1.00]
Mueller 2010	25	15	1	60	0.96 [0.80, 1.00]	0.80 [0.69, 0.88]



(*Continued . . .*)

(. . . *Continued*)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Nahon 2008	66	12	13	56	0.84 [0.74, 0.91]	0.82 [0.71, 0.91]
Nguyen-Khac 2008	28	11	5	59	0.85 [0.68, 0.95]	0.84 [0.74, 0.92]

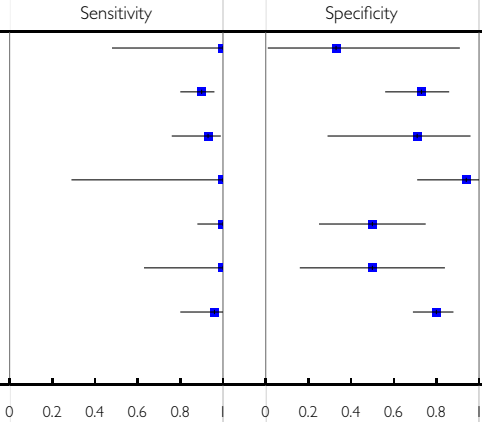


Test 7. Transient elastography for F4 (most common cut-off value = 12.5).

Review: Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Test: 7 Transient elastography for F4 (most common cut-off value = 12.5)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bardou-Jacquet 2013	5	2	0	1	1.00 [0.48, 1.00]	0.33 [0.01, 0.91]
Boursier 2009	62	10	7	27	0.90 [0.80, 0.96]	0.73 [0.56, 0.86]
de Ledinghen 2013	25	2	2	5	0.93 [0.76, 0.99]	0.71 [0.29, 0.96]
Dolman 2013	3	1	0	16	1.00 [0.29, 1.00]	0.94 [0.71, 1.00]
Kim 2009	29	8	0	8	1.00 [0.88, 1.00]	0.50 [0.25, 0.75]
Lannerstedt 2013	8	4	0	4	1.00 [0.63, 1.00]	0.50 [0.16, 0.84]
Mueller 2010	25	15	1	60	0.96 [0.80, 1.00]	0.80 [0.69, 0.88]



ADDITIONAL TABLES

Table 1. Semi-quantitative histopathological scoring systems for progression of fibrosis to cirrhosis. Conversion grid for the stages of hepatic fibrosis*

Stage of estimated fibrosis						
METAVIR	**Knodell**	**Ishak**	**Kleiner**	**Desmet**	**Brunt**	**Batts-Ludwig**

Table 1. Semi-quantitative histopathological scoring systems for progression of fibrosis to cirrhosis. Conversion grid for the stages of hepatic fibrosis* (*Continued*)

F0	F0	F0	F0	F0	F0	F0
F1	F1	F1	F1	F1	F1	F1
F1	F1	F2	F1	F1	F1	F1
F2	F3	F3	F2	F2	F2	F2
F3	F3	F4	F2	F3	F3	F3
F4	F4	F5	F3	F4	F4	F4
F4	F4	F6	F4	F4	F4	F4

F: stage of hepatic fibrosis
F0: no fibrosis; F1: portal fibrous expansion; F2: thin fibrous septa emanating from portal triads; F3: fibrous septa bridging portal triads and central veins; F4: cirrhosis. Clinically significant fibrosis is generally defined as F2 or worse (on the METAVIR scale from F0 to F4 with F4 being cirrhosis).
METAVIR, Knodell, Ishak, Kleiner, Desmet, and Brunt scoring systems are used to classify fibrosis (and steatosis) due to alcoholic liver disease. For references, please see review text.
*Adapted from Goodman 2007.

Table 2. Nonalcoholic Steatohepatitis Clinical Research Network scoring system for grade of hepatic steatosis

Evaluation of parenchymal involvement by steatosis	*Steatosis grade*
< 5%	0
5% to 33%	1
34% to 66%	2
> 66%	3

Table 3. Post-test probabilities (calculated in case of negative test results), starting from three pre-test probabilities for F3 or worse with a cut-off around 9.5 kPa

Pre-test probability	**LR-**	**Post-test probability**
25% (minimum)*	0.11	4%
61% (mean)*	0.11	15%
88% (maximum)*	0.11	45%

F3 or F4: significant hepatic fibrosis or cirrhosis (or both) in participants with alcoholic liver disease.
* as it is reported in this review.

Table 4. Post-test probabilities (calculated in case of negative test results), starting from three pre-test probabilities for F4 with most common cut-off of 12.5 kPa

Pre-test probability	LR-	Post-test probability
15% (minimum)*	0.07	1%
51% (mean)*	0.07	7%
79% (maximum)*	0.07	21%

F4: cirrhosis.
* as it is reported in this review.

APPENDICES

Appendix 1. Search strategy

Database	date of search	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	August 2014	(transient elastograph* OR fibroscan) AND ((hepatic OR liver) AND (fibrosis OR cirrhosis)) AND liver biops*
Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Register	August 2014	(transient elastograph* OR fibroscan) AND ((hepatic OR liver) AND (fibrosis OR cirrhosis)) AND liver biops*
The Cochrane Library	Issue 7 of 12, 2014	#1 MeSH descriptor: [Elasticity Imaging Techniques] explode all trees #2 transient elastograph* or fibroscan #3 #1 or #2 #4 MeSH descriptor: [Liver Cirrhosis] explode all trees #5 (hepatic or liver) and (fibrosis or cirrhosis) #6 #4 or #5 #7 MeSH descriptor: [Biopsy, Needle] explode all trees #8 liver biops* #9 #7 or #8 #10 #3 and #6 and #9
MEDLINE (OvidSP)	1946 to August 2014	1. exp Elasticity Imaging Techniques/ 2. (transient elastograph* or fibroscan).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word,

(*Continued*)

		rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. exp liver cirrhosis/ 5. ((hepatic or liver) and (fibrosis or cirrhosis)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 4 or 5 7. exp Biopsy, Needle/ 8. liver biops*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 7 or 8 10. 3 and 6 and 9
EMBASE (OvidSP)	1974 to August 2014	1. exp elastography/ 2. (transient elastograph* or fibroscan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2 4. exp liver cirrhosis/ 5. ((hepatic or liver) and (fibrosis or cirrhosis)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. exp liver biopsy/ 8. liver biops*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 7 or 8 10. 3 and 6 and 9
Science Citation Index Expanded	1900 to August 2014	#4 #3 AND #2 AND #1 #3 TS=(liver biops*) #2 TS=((hepatic or liver) and (fibrosis or cirrhosis)) #1 TS=(transient elastograph* or fibroscan)

Appendix 2. QUADAS-2

DOMAIN	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	**Describe methods of participant selection: describe included participants (prior testing, presentation, intended use of index test and setting):** The studies that fulfilled the inclusion criteria of this review should have included participants of any sex and ethnic origin, above 16 years old, and who were diagnosed with alcoholic liver disease. The participants could have been hospitalised or outpatients The diagnosis of alcoholic liver disease should have been established in the study participants based on registered history of alcohol excessive intake of sufficient duration and quantity together with clinical evidence of liver disease expressed with physical signs at examination and followed by laboratory evidence of liver disease. To ascertain the diagnosis of alcoholic liver disease and study the presence or absence of liver fibrosis or cirrhosis or both in each of the study participants, both transient elastography and liver biopsy should have been performed	**Describe the index test and how it was conducted and interpreted:** Transient elastography for grading hepatic fibrosis conducted either before or after liver biopsy The recommended technical parameters of transient elastography investigation are at least 10 validated stiffness measurements at the same measurement point, an interquartile range of no more than 30%, and the ratio of the number of successful measurements to the total investigational number of acquisitions should be no less than 60% (www.echosens.com/pdf/FS402˙WEB.pdf).	**Describe the reference standard and how it was conducted and interpreted:** Liver biopsy is useful in establishing the grade of hepatic fibrosis in people with alcoholic liver disease The morphological interpretation of the liver biopsy samples is reported with semiquantitative scores, such as METAVIR, Knodell, Ishak, Kleiner, Scheuer, or Brunt (see Table 1). The Nonalcoholic Steatohepatitis Clinical Research Network scoring system is used for grading steatosis (Kleiner 2005) (Table 2) .	**Describe any people who did not receive the index test(s) or reference standard (or both) or who were excluded from the 2 x 2 table (refer to flow diagram) : describe the time interval and any interventions between index test(s) and reference standard:** As fibrosis may develop rapidly with time, we excluded participants if the time interval between diagnostic liver biopsy and transient elastography investigations was longer than 6 months, an arbitrary chosen time interval
Signalling questions: yes/no/unclear	**Was a consecutive or random sample of par-**	**Were the index test results interpreted with-**	**Is the reference standard likely to clas-**	**Was there an appropriate interval between in-**

(*Continued*)

	ticipants enrolled? Yes: all consecutive participants or random sample of people with diagnosed alcoholic liver disease were enrolled in the study No: selected participants were not included. Unclear: insufficient data were reported to permit a judgement	**out knowledge of the results of the reference standard?** Yes: transient elastography test results were interpreted without knowledge of the results of the liver biopsy No: transient elastography results were interpreted with knowledge of the results of the liver biopsy Unclear: insufficient data were reported to permit a judgement	**sify the target condition correctly?** Yes: if all participants had undergone liver biopsy and the morphological results were correctly reported No: if all participants had not undergone liver biopsy or morphological results were not correctly reported Unclear: insufficient data were reported to permit a judgement	**dex test(s) and reference standard?** Yes: the interval between the transient elastography and liver biopsy was $\leq$ 6 months No: the interval between the transient elastography test and liver biopsy was > 6 months Unclear: insufficient data were reported to permit a judgement
	Was a case-control design avoided? Yes: case-control design was avoided. No: case-control design was not avoided. Unclear: insufficient information was reported to permit a judgement	**If a threshold was used, was it pre-specified?** Yes: if the threshold for a positive test was pre-specified. No: if the threshold for a positive test was not pre-specified Unclear: insufficient data were reported to permit a judgement	**Were the reference standard results interpreted without knowledge of the results of the index test?** Yes: liver biopsy results were interpreted without knowledge of the results of the transient elastography test No: liver biopsy results	**Did all participants receive the reference standard?** Yes: all participants underwent the reference standard, liver biopsy No: not all participants underwent liver biopsy. Unclear: insufficient data were reported to permit a judgement
	Did the study avoid inappropriate exclusions? Yes: the study avoided inappropriate exclusions (i.e., difficult to diagnose participants) No: the study excluded patients inappropriately. Unclear: insufficient data were reported to permit a judgement			**Did all participants receive the same reference standard?** Yes: all participants received the same reference standard, i.e., liver biopsy No: not all participants received the same reference standard, i.e., liver biopsy Unclear: insuffi-

(*Continued*)

				cient data were reported to permit a judgement **Were all participants included in the analysis?** Yes: all participants meeting the selection criteria (selected participants) were included in the analysis, or data on all the selected participants were available so that a 2 x 2 table including all selected participants could be constructed No: not all participants meeting the selection criteria were included in the analysis or the 2 x 2 table could not be constructed using data on all selected participants Unclear: insufficient data were reported to permit a judgement
Risk of bias: high/low/ unclear	**Could the selection of participants have introduced bias?** High risk of bias: yes, if the selection of participants introduced bias Low risk of bias: no, if the selection of participants not introduced bias Unclear risk of bias: insufficient data on participants selection were reported to permit a judgement on the risk of bias	**Could the conduct or interpretation of the index test have introduced bias?** High risk of bias: if the answer to the signalling questions on the conduct or interpretation of the index test was "no" Low risk of bias: if the answer to the signalling questions on the conduct or interpretation of the index test was "yes" Unclear risk of bias: if the answers to the 2 signalling questions on the conduct or interpretation of the index test was either "unclear" or	**Could the reference standard, its conduct, or its interpretation have introduced bias?** High risk of bias: if the answer to the signalling questions on the reference standard, its conduct, or its interpretation was "no" Low risk of bias: if the answer to the signalling questions on the reference standard, its conduct, or its interpretation was "yes" Unclear risk of bias: if the answers to the 3 signalling questions on	**Could the participant flow have introduced bias?** High risk of bias: if the answer to the signalling questions on flow and timing was "no" Low risk of bias: if the answer to the signalling questions on flow and timing was "yes" Unclear risk of bias: if the answers to the 4 signalling questions on flow and timing was either "unclear" or any combination of "unclear" with "yes" or "no"

(*Continued*)

		any combination of "unclear" with "yes" or "no"	the reference standard, its conduct, or its interpretation was either "unclear" or any combination of "unclear" with "yes" or "no"	
Concerns regarding applicability: high/low/unclear	**Were there concerns that the included participants did not match the review question?** High concern: there was high concern that the included participants do not match the review question Low concern: there was low concern that the included participants did not match the review question Unclear concern: if it was unclear.	**Were there concerns that the index test, its conduct, or interpretation differed from the review question?** High concern: there was high concern that the conduct or interpretation of the transient elastography test differs from the way it is likely to be used in clinical practice Low concern: there was low concern that the conduct or interpretation of the transient elastography test differed from the way it is likely to be used in clinical practice Unclear concern: if it was unclear.	**Were there concerns that the target condition as defined by the reference standard did not match the review question?** High concern: all participants did not undergo liver biopsy for grading hepatic fibrosis Low concern: all participants underwent liver biopsy for grading hepatic fibrosis Unclear concern: if it was unclear.	-

CONTRIBUTIONS OF AUTHORS

Chavdar Pavlov (CP): selected studies for inclusion, extracted study data and performed bias risk assessment, drafted the review, and is a guarantor of the review.

Giovanni Casazza (GC): checked and analysed study data, performed statistical analyses, drafted the review, commented and advised on the review during the review preparation.

Dimitrinka Nikolova (DN): selected studies for inclusion, extracted study data, and performed bias risk assessment.

Vladimir T Ivashkin: revised the review.

Emmanuel Tsochatzis (ET): checked data extraction and suggested comments for improvement of the review.

Andrew K Burroughs had contributed to the draft text of the review before Andrew passed away 15 March 15 2014.

Christian Gluud (CG): discussed review results and revised the review.

All authors agreed on the final version of the review.

DECLARATIONS OF INTEREST

Chavdar Pavlov: none known.

Giovanni Casazza: none known.

Dimitrinka Nikolova: none known.

Emmanuel Tsochatzis: none known.

Andrew K Burroughs: none known.

Vladimir T Ivashkin: none known.

Christian Gluud: none known.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We added a second objective: "In addition, to identify the optimal cut-off values for differentiating the five stages of hepatic fibrosis."

- We excluded study design (diagnostic cohort study designs compared to case-control study designs) from investigation of heterogeneity, as it is a QUADAS-2 item. In addition, in our review, all included studies were cohort studies.