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Ultrasonography for diagnosis of cirrhosis in people with alcoholic liver disease (Protocol)

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[Diagnostic Test Accuracy Protocol]

Ultrasonography for diagnosis of cirrhosis in people with alcoholic liver disease

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

To determine the diagnostic accuracy of ultrasonography for detecting the presence or absence of cirrhosis in people with alcoholic liver disease compared with liver biopsy as reference standard.

To determine the diagnostic accuracy of any of the ultrasonography tests, B-mode or Echo-colour Doppler ultrasonography, used singly or combined, or plus ultrasonography signs, or a combination of these, for detecting hepatic cirrhosis in people with alcoholic liver disease compared with liver biopsy as a reference standard, irrespective of sequence. If results differ, we will attempt to explore heterogeneity analysing:

- liver biopsy as the reference standard:
    - different grade of inflammation (amount of ongoing inflammation and necrosis) according to the liver biopsy (below two grades compared to two or greater grades of activity);
    - different lengths of liver biopsy sample (shorter than 15 mm compared to 15 mm or longer) or number of portal tracts (fewer than six compared to six or more), as reported in the studies;
    - percutaneous liver biopsy versus transvenous (transjugular) liver biopsy versus laparoscopic liver biopsy;
- different technical characteristics of the ultrasonography equipment (e.g., different transducers, different wave lengths);
- different skills of the operator as stated by the authors;
- complete abstinent (teetotallers) or non-abstinent study participants (as defined in the included studies).

- different grade of inflammation (amount of ongoing inflammation and necrosis) according to the liver biopsy (below two grades compared to two or greater grades of activity);

- different lengths of liver biopsy sample (shorter than 15 mm compared to 15 mm or longer) or number of portal tracts (fewer than six compared to six or more), as reported in the studies;

- percutaneous liver biopsy versus transvenous (transjugular) liver biopsy versus laparoscopic liver biopsy;

In addition, we will attempt to identify the most accurate ultrasonographic tests and indices for diagnosis of cirrhosis in people with alcoholic liver disease.

BACKGROUND

Alcohol consumption is a worldwide problem. Every year approximately 2.5 million people die of it; 320,000 of them are young people between 15 and 29 years of age. Based on estimates for 2004, alcohol was responsible for almost 4% of all deaths in the world (WHO 2010).

Heavy alcohol consumption causes alcoholic liver disease and is a causal factor of many types of liver injuries and concomitant diseases. It is a true systemic disease that may damage the digestive tract, the nervous system, the heart and vascular system, the bone and skeletal muscle system, and the endocrine and immune system, and can lead to cancer (WHO 2010; Rocco 2014).

Liver damage in turn, can present as multiple alcoholic liver diseases, including fatty liver, steatohepatitis, fibrosis, alcoholic cirrhosis, and hepatocellular carcinoma, with presence or absence of hepatitis B or hepatitis C virus infection (Brunt 1974; Bruha 2012; Testino 2014). There are three scarring types (fibrosis) that are most commonly found in alcoholic liver disease: centrilobular scarring, pericellular fibrosis, and periportal fibrosis. When liver fibrosis progresses, alcoholic cirrhosis occurs. Hepatocellular carcinoma occurs in 5% to 15% of people with alcoholic cirrhosis, but people in whom hepatocellular carcinoma has developed are often co-infected with hepatitis B or C virus (MacSween 1986; Jaurigue 2014).

Abstinence from alcohol may help people with alcoholic disease in improving their prognosis of survival at any stage of their disease; however, the more advanced the stage, the higher the risk of complications, co-morbidities, and mortality, and lesser the effect of abstinence (Borowsky 1981). Being abstinent one month after diagnosis of early cirrhosis will improve the chance of a seven-year life expectancy by 1.6 times (Verrill 2009). Liver transplantation is the only radical method that may change the prognosis of a person with alcoholic liver disease; however, besides the difficulties of finding a suitable liver transplant organ, there are many other factors that may influence a person's survival (Iruzubieta 2013; Singal 2013).

Cochrane systematic reviews of randomised clinical trials of pharmacological interventions used for reducing alcohol consumption such as acamprosate, benzodiazepines, naltrexone, gamma-hydroxybutyrate, baclofen (derivative of gamma-aminobutyric acid), and anticonvulsants versus placebo or another drug in alcohol-dependent people have studied the benefits and harms of these interventions for alcohol reduction or withdrawal (Amato 2010; Leone 2010; Minozzi 2010; Rösner 2010a; Rösner 2010b; Liu 2013; Pani 2014). However, the conclusions, despite showing some potential tendency of alcohol reduction or promotion of abstinence, lack the desired robustness of evidence as the performed randomised clinical trials for alcohol withdrawal with the suggested drug interventions either fail in quality, are of insufficient sample size, are too heterogeneous, or lack sufficient evidence for benefits. Without diminishing nutritional and supportive management of people with alcoholic liver disease, complete abstinence from alcohol seems still to be the only recommended form of hepatoprotection.

Ultrasound is an inexpensive method used for years in clinical practice to diagnose alcoholic cirrhosis (Rockey 2009; O'Shea 2010). Ultrasound parameters for assessing cirrhosis in people with alcoholic liver disease encompass among others liver size, bluntness of the liver edge, coarseness of the liver parenchyma, nodularity of the liver surface, size of the lymph nodes around the hepatic artery, irregularity and narrowness of the inferior vena cava, portal vein velocity, and spleen size (Nishiura 2005).

In a series of 1604 people with alcoholic liver disease diagnosed on liver biopsy or clinically confirmed diagnosis, 608 (38%) people had developed alcoholic cirrhosis (Naveau 1997). Diagnosis of cirrhosis by ultrasound, especially in people who were asymptomatic, may have its advantages for the prognosis, motivation, and treatment of these people to decrease their alcohol consumption or become abstinent (O'Shea 2010).

Timely diagnosis of alcoholic cirrhosis in people with alcoholic liver disease is the cornerstone for evaluation of prognosis or choosing treatment strategies in these people.

Target condition being diagnosed

Cirrhosis in people with alcoholic liver disease

All people with alcoholic liver disease are at risk of developing liver fibrosis and cirrhosis. This risk is considered higher in people who are binge drinkers, people with increased serum alanine aminotransferase and aspartate aminotransferase levels, or in people with severe alcohol hepatitis on liver biopsy (Bouchier 1992). Cirrhosis may have symptoms and signs of liver disease, and cirrhosis may vary from one person to another. In general, people with alcoholic liver disease see a doctor when symptoms and signs from the complications of cirrhosis have already developed (O'Shea 2010). Physicians should attempt to motivate people to stop drinking. Indirect evidence of alcohol abuse can be collected through questionnaires about drinking habits, through information received from family members, and through running laboratory tests (O'Shea 2010).

Hepatic fibrosis may develop as a result of weekly alcohol consumption of seven to 13 beverages for women (one beverage = 12 g of alcohol) and 14 to 27 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 to 40 g of ethanol in women and more than 80 g of 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).

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).

Michalak 2003 validated the reproducibility of the METAVIR score, using a slightly modified METAVIR score, that is, the portal tract/septal fibrosis score, to investigate the amount of fibrosis and study the influence of centrilobular fibrosis and portal tract/septal fibrosis in alcoholic chronic liver disease. The amount of portal tract/septal fibrosis in people with alcoholic chronic disease was greater than the amount of centrilobular fibrosis in the control group of people with viral chronic hepatitis disease, which suggested that portal tract/septal fibrosis was more frequent in alcoholic chronic liver disease than in viral chronic hepatitis. However, centrilobular fibrosis forms with the advance of fibrosis in cirrhosis. The prognostic value of the METAVIR fibrosis score in alcoholic liver disease still needs to be established (Michalak 2003).

In Table 1, we have included other widely used systems for classification of fibrosis in people with alcoholic liver disease (Knodell 1981; Desmet 1994; Ishak 1995; Brunt 1999; Kleiner 2005). However, as the focus of our review is on alcoholic cirrhosis alone, for discrepancies in classification of cirrhosis, we refer the readers to the last two rows of the table (shaded).

Index test(s)

Ultrasonography is used in clinical practice for diagnosis of cirrhosis in people with alcoholic liver disease as it allows investigation of the hepatic tissue through the generation of ultrasonic waves. B-mode and Echo-colour Doppler ultrasonography seem to be the most often used methods for diagnosis of cirrhosis.

Ultrasonic patterns obtained at ultrasonography investigation in B-mode are usually classified as positive or negative considering signs, for example parenchymal (liver surface, volume, edge, and texture), extrahepatic (spleen volume, presence of ascites), and vascular (diameter of portal and spleen veins), used in different combinations and defined as indices. Hepatic fibrosis produces abnormal echo patterns on ultrasound scanning. Much higher attenuation is observed at examination of the liver of people with steatosis compared to the liver of people with hepatic fibrosis (Bamber 1979; Saverymuttu 1986).

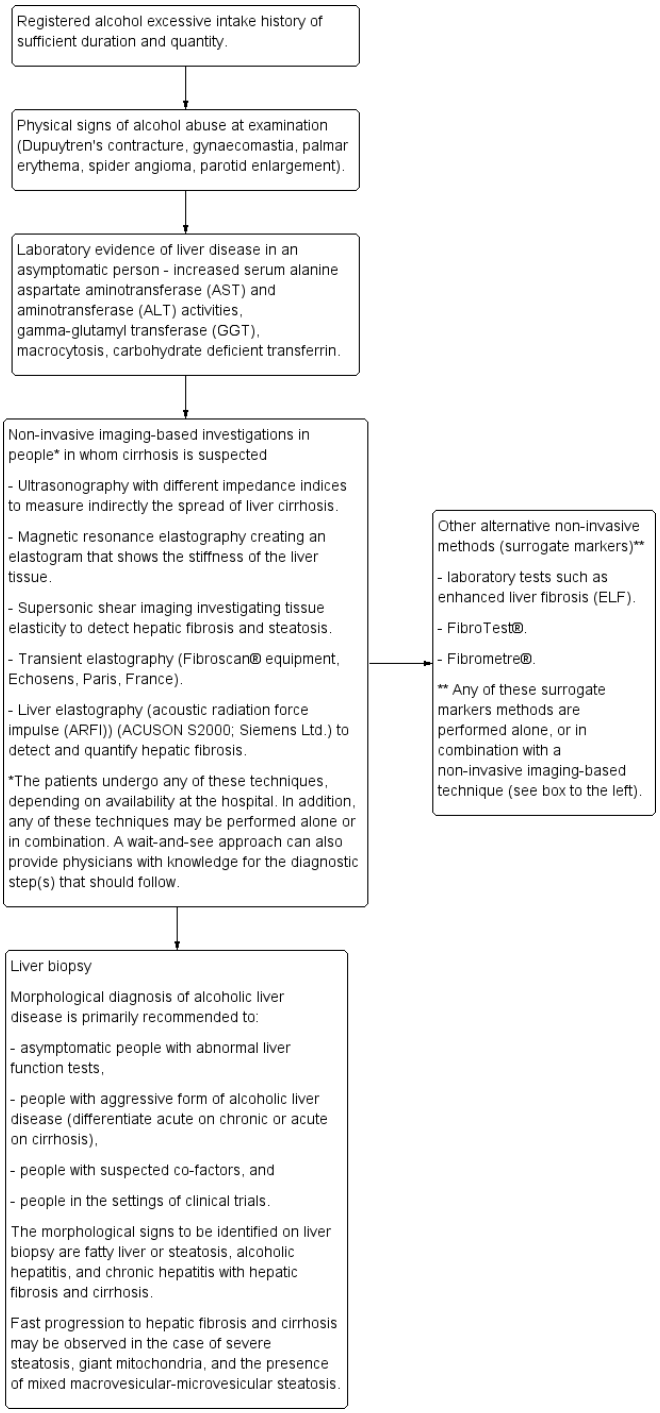
Vascular (Doppler) indices, such as Doppler perfusion index, hepatic transit time, portal vein congestive index, and various ratios analysing different blood vessels, are used indirectly for detection of portal hypertension and cirrhosis ((Ersoz 1999; Hizli 2010; Ivashkin 2011a).

The sensitivity and specificity of ultrasonography investigation for diagnosis of cirrhosis in people with alcoholic liver disease, despite their wide use, have not been established in systematic reviews yet.

Clinical pathway

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

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



Alternative test(s)

Different methods to assess liver fibrosis have been developed since 1990. Most of them 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. Acoustic radiation force impulse (ARFI) (ACUSON S2000; Siemens Ltd.) is a non-invasive imaging technique that can detect and quantify hepatic fibrosis. The ARFI technology is also called liver ultrasound elastography (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 conventional ultrasonography imagining techniques (Iyo 2009).

Supersonic shear imaging investigates 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 combines magnetic resonance imaging 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 (Yin 2007).

Transient elastography is another non-invasive method for assessment of hepatic fibrosis (Gómez-Domínguez 2006; Pavlov 2015), which measures hepatic fibrosis through the stiffness of the hepatic parenchyma. Transient elastography measures the speed of propagation of the elastic wave through the hepatic parenchyma: the stiffer the tissue, the faster the shear wave propagates the obtained hepatic stiffness, expressed as a median value in kiloPascals (kPa).

Other alternative non-invasive tests (apart from venepuncture) are laboratory tests such as aspartate aminotransferase to alanine aminotransferase ratio, platelet count, prothrombin index, hyaluronic acid, and enhanced liver fibrosis score (Crespo 2012; Liu 2012). All of these tests are used as surrogate markers for staging of hepatic fibrosis. 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 2009).

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 (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 (Seeff 2010). Transjugular liver biopsy seems a safer alternative for people with low platelet counts or clotting abnormalities. The small size of the tissue samples, either obtained transcutaneously or via the transjugular route, may also lead to sampling errors.

The technical possibilities of the ultrasonography equipment and the individual experience of the investigator performing the ultrasonography are the main factors influencing the precision of the ultrasound examination. Consensus on using ultrasonography as a non-invasive method for diagnosis of cirrhosis in people with alcoholic liver disease seems not to have been established, despite being widely used instead of, or together with, other non-invasive techniques (Shiha 2009). When a person presents with clinical symptoms (e.g., ascites, encephalopathy, oesophageal bleeding) of cirrhosis, neither liver biopsy nor ultrasonography are needed. However, in case of insufficient or unclear expression of clinical signs, a wait-and-see approach, ultrasonography, or other alternative non-invasive tests may be considered before arranging a liver biopsy investigation (Figure 1). As cirrhosis is a main prognostic variable with impact on survival of people with alcoholic liver disease, it is important to detect cirrhosis, assess the risk of complications, and encourage abstinence of drinking alcohol (Leong 2012; Singal 2013; Testino 2014).

This review aims to meta-analyse data from studies on the diagnosis of cirrhosis in people with alcoholic liver disease and to assess the diagnostic accuracy of ultrasonography in detecting the presence of cirrhosis compared with liver biopsy as reference standard, following The Cochrane Collaboration methodology (SRDTA Handbook).

We did not identify any meta-analysis or systematic review on the use of ultrasonography for defining the presence of cirrhosis in people with alcoholic liver disease. A Cochrane systematic diagnostic test accuracy review on ultrasonography in detecting cirrhosis in people with alcoholic liver disease compared with liver biopsy does not exist either. Therefore, we have planned to conduct this review.

OBJECTIVES

To determine the diagnostic accuracy of ultrasonography for detecting the presence or absence of cirrhosis in people with alcoholic liver disease compared with liver biopsy as reference standard.

Secondary objectives

To determine the diagnostic accuracy of any of the ultrasonography tests, B-mode or Echo-colour Doppler ultrasonography, used singly or combined, or plus ultrasonography signs, or a combination of these, for detecting hepatic cirrhosis in people with alcoholic liver disease compared with liver biopsy as a reference standard, irrespective of sequence. If results differ, we will attempt to explore heterogeneity analysing:

- liver biopsy as the reference standard:
    - different grade of inflammation (amount of ongoing inflammation and necrosis) according to the liver biopsy (below two grades compared to two or greater grades of activity);
    - different lengths of liver biopsy sample (shorter than 15 mm compared to 15 mm or longer) or number of portal tracts (fewer than six compared to six or more), as reported in the studies;
    - percutaneous liver biopsy versus transvenous (transjugular) liver biopsy versus laparoscopic liver biopsy;
- different technical characteristics of the ultrasonography equipment (e.g., different transducers, different wave lengths);
- different skills of the operator as stated by the authors;
- complete abstinent (teetotallers) or non-abstinent study participants (as defined in the included studies).

In addition, we will attempt to identify the most accurate ultrasonographic tests and indices for diagnosis of cirrhosis in people with alcoholic liver disease.

METHODS

Criteria for considering studies for this review

Types of studies

Diagnostic cohort study designs and diagnostic case-control study designs that had assessed cirrhosis in participants with alcoholic liver disease through ultrasonography and liver biopsy, irrespective of language or publication status, or whether data were collected prospectively or retrospectively. We may also include randomised clinical trials or controlled clinical studies if they fulfil the inclusion criteria of our review protocol.

We will include studies published as full paper articles, in the form of abstracts published in conference proceedings or presented as posters if the abstracts are identified with the searches.

We will also consider studies for inclusion if they had included participants with different aetiologies of liver disease.

Participants

Participants of any sex and ethnic origin, over 16 years old, and diagnosed with alcoholic liver disease, following study authors' statements. The participants could have been hospitalised or managed as outpatients.

The diagnosis of alcoholic liver disease in the study participants should have been established based on registered history of excessive alcohol 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 cirrhosis, both ultrasonography and liver biopsy should have been performed, irrespective of the sequence.

We will also include participants if suspected of having non-alcoholic fatty liver disease, in addition to diagnosed alcoholic liver disease.

We will not consider for inclusion participants diagnosed with alcoholic liver disease and having a concomitant liver disease such as chronic hepatitis C virus infection, chronic hepatitis B virus infection, autoimmune liver disease, or human immunodeficiency virus (HIV) infection. We will extract data on study participants with alcoholic liver disease alone whenever such data are available in the study report or whenever we can obtain the data required for the review through personal communication with study authors. In the latter case, we may disregard some of the data presented in the publication and use the data provided by the study authors through personal communication.

Index tests

Ultrasonography in any mode.

As we expect that study authors would have used different measurements, signs, and combinations of signs for assessment of cirrhosis by ultrasonography with different techniques and mode, we cannot specify these here. However, we will consider parenchymal, vascular, and extrahepatic ultrasonographic signs as different index tests.

Target conditions

There are five stages of liver fibrosis by METAVIR (Table 1):

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

The target condition is the presence of cirrhosis in people with alcoholic liver disease, defined using the METAVIR score.

Thus, we will dichotomise the fibrosis estimated by the METAVIR score as follows: we will consider people with a METAVIR score

of F4 as 'diseased' and people with a METAVIR score of F0 plus F1 plus F2 plus F3 as 'non-diseased'.

Reference standards

Liver biopsy is the reference standard that is obtained by percutaneous needle techniques with needles 1.4 to 1.6 mm (16 to 18 gauge) in diameter, transjugular method, or surgical specimens (Kuntz 2008; Ivashkin 2011b).

Liver biopsy is the only existing reference standard for diagnosing hepatic cirrhosis in people with alcoholic liver disease. Specimens of liver tissue with a length of at least 15 mm and at least six portal tracts are among the factors that can provide reliable morphological diagnosis of cirrhosis (Bedossa 2003; Colloredo 2003; Rockey 2009).

If liver biopsy samples are reported with any of the semi-quantitative scores, that is, METAVIR (Michalak 2003), Knodell (Franciscus 2007), Ishak (Franciscus 2007), Kleiner (Kleiner 2005), Scheuer (Regev 2002), Brunt (Brunt 1999), or Batts-Ludwig (Haque 2010), we will use a conversion grid for hepatic fibrosis staging adapted after Goodman 2007 to only unify results for hepatic cirrhosis on liver biopsy (Table 1). METAVIR has already been validated for staging alcoholic cirrhosis (Michalak 2003).

Search methods for identification of studies

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

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register (hbg.cochrane.org/specialised-register), *The Cochrane Library* (Wiley), MEDLINE (PubMed), EMBASE (Ovid SP), and the Science Citation Index Expanded (de Vet 2010). We will specify the time period of the listed databases that we search at the review stage (Appendix 1). We will apply no language limitations.

Searching other resources

We will also screen references of the retrieved studies to identify other potentially relevant studies for inclusion in our review. We will consider extracting data from studies presented in an abstract or poster form, or from grey literature only if data for our review can be found.

Appendix 1 shows the search strategies for the different databases with the time spans for the searches.

Data collection and analysis

We will follow the guidelines provided in the *Cochrane Diagnostic Reviewer's Handbook* (still in draft).

Selection of studies

Three review authors (CP, MP, and EL) will independently identify studies for possible inclusion in the review. While reading titles or abstracts or both of the identified studies, we will exclude references with a study design not fulfilling the inclusion criteria of our review protocol. We will retrieve the full text of the remaining references. During this second selection stage, we will group together multiple publications of one study fulfilling the inclusion criteria, and then we will screen these publications for complimentary data or we will check them for discrepancies. If in doubt, CP, GC, and DN will write e-mails to study authors.

The studies that we will include shall evaluate ultrasound in the diagnosis of hepatic cirrhosis using only liver biopsy as the reference standard.

The maximum time interval of investigation with liver biopsy and ultrasonography should not exceed six months. In addition, ultrasonography could have been performed before or after liver biopsy.

Data extraction and management

Three review authors (CP, GC, and MP) will independently extract data following the protocol. Two of the other review authors (DN and MT) will check the extraction of all study data. A sixth review author (CG) will be an arbitrator in case of disagreements between review authors.

The data needed for the conductance of this systematic review will be 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 ultrasonography, cirrhosis estimated by morphological score and ultrasonography, and information related to the QUADAS-2 items for evaluation of the risk of bias of the studies (Whiting 2011).

In order to provide data for our analyses, the studies have to provide data that could help us calculate the true positive, false positive, true negative, and false negative diagnostic values of ultrasonography for diagnosing cirrhosis.

If information on any of the true positive, false positive, true negative, and false negative diagnostic test values or results are missing, we will attempt to contact the authors of the included studies in order to obtain missing information. We will also contact authors if other types of information needed for this review are missing, especially when the publication is in the form of an abstract or poster presentation.

We will use Excel and Review Manager 5 to add data required for statistical analyses (RevMan 2012).

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, four review authors (CP, GC, MP, and DN), in pairs or independently of one another, will assess the bias risk of the included diagnostic test accuracy studies, using QUADAS-2 domains (Whiting 2011). A fifth review author (ET) will act as an arbitrator in case of disagreements between the authors assessing the bias risk of the studies. We will contact study authors if information on methodology is lacking in order to assess correctly the risk of bias of the studies.

Appendix 2 shows the adopted items that will serve the purposes of our review in addressing the participant spectrum, index test, target condition, reference standard, and flow and timing, and which answers would also reflect the general quality of the included studies.

We will classify studies at low risk of bias if all answers to the signalling questions of the four domains and applicability are positive, and, if the answers to the signalling questions of the four domains and applicability are either negative or unclear (or a combination of these), we will classify the studies at high risk of bias (Jüni 1999; Whiting 2005).

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

Statistical analysis and data synthesis

We will carry out the analyses following Chapter 10 (Analysing and Presenting Results) of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010). We will use the Review Manager 5 software for analyses and plots (RevMan 2012).

When we have assembled the majority of our studies, we will map the individual index tests or index test indices in the individual studies and on the basis thereof determine which to select for meta-analyses. We will build two-by-two tables of ultrasonography performance (true positive, true negative, false positive, false negative) for each primary study and for each index test (ultrasonography mode) and for the predefined target condition (cirrhosis). We will estimate 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 will perform a graphical descriptive analysis of the included studies: we will report forest plots (sensitivity and specificity separately, with their 95% CIs) and we will provide a graphical presentation of the studies in the receiver operating characteristic (ROC) space (sensitivity plotted against 1 - specificity). Second, if appropriate, we will perform a meta-analysis. If all studies provide dichotomised data using a common cut-off, we will use the bivariate model and we will provide the estimate of the summary operating point (the point with mean sensitivity and mean specificity). Otherwise, we will use the hierarchical summary ROC (HSROC) model and we will provide a summary ROC curve (Macaskill 2010). We will perform all analyses for each test separately.

In case of undetermined ultrasonography results, we will attempt to follow the intention-to-diagnose approach following which we will add uninterpretable test results as false positive or false negatives, depending on the liver biopsy result. In this way, we hope to avoid potential overestimation of diagnostic test accuracy of ultrasonography (Schuetz 2012).

We will use the pooled estimates obtained from the fitted models to calculate summary estimates of likelihood ratios. We will assess the probability of ultrasonography to rule in or to rule out hepatic cirrhosis by considering the estimates of likelihood ratios. A high LR+ (usually greater than 10) means that there is a large increase in post-test probability, starting from pre-test probability. A low LR- (usually lower than 0.1) means that there is a large decrease in post-test probability, starting from pre-test probability (Schoenfeld 1999). Likelihood ratio estimates can be used in clinical practice to calculate post-test probabilities for individual people, starting from patient-specific pre-test probabilities.

We will perform direct and indirect comparisons between the index tests by adding co-variates to the bi-variate or HSROC model (Macaskill 2010). In case of inconsistency of the results obtained through direct and indirect comparisons, we will report both results; otherwise, we will report one of the results, depending on the availability of comparisons.

One review author (GC) will perform all statistical analyses using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Investigations of heterogeneity

We do not expect that the ultrasonographic tests and indices used for diagnosis of cirrhosis in people with alcoholic liver disease would cause additional heterogeneity to those already mentioned in Secondary objectives.

Whenever possible, we will evaluate the effect of the pre-specified sources of heterogeneity on the accuracy estimates by adding some relevant co-variates to the bivariate model (Secondary objectives).

Sensitivity analyses

If possible, depending on number of studies with low risk of bias, we will assess the effect of risk of bias of the included studies on the diagnostic accuracy by performing a sensitivity analysis, excluding studies with high or unclear risk of bias, and perform a separate sensitivity analysis excluding unblinded studies.

We will classify 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).

We will also attempt to perform a sensitivity analysis of studies with data received from study authors.
However, we may not identify a sufficient number of studies for the planned sensitivity analyses.

Assessment of reporting bias

We will perform a funnel plot to investigate reporting bias visually, using the statistical method suggested by Deeks et al. (Deeks 2005).

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* *Indicates the major publication for the study*

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 fibrosis						
METAVIR	**Knodell**	**Ishak**	**Kleiner**	**Desmet**	**Brunt**	**Batts-Ludvig**
F0	F0	F0	F0	F0	F0	F0
F1	F1	F1	F1	F1	F1	F1
F1	F1	F2	F1	F1	F1	F1

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

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**

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.

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 greater on the METAVIR scale from F0 to F4 with F4 being cirrhosis.

Clinically significant fibrosis is defined as Ishak fibrosis stage F3 to F6, and cirrhosis defined as Ishak fibrosis F5 or F6.

APPENDICES

Appendix 1. Search strategy

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	The issue of *The Cochrane Library* will be given at review stage.	(ultrason* or ultrasound* or echograph* or echotomograph* or doppler* or B-mode or B-scan or grey*scale) AND ((hepatic or liver) and (fibrosis or cirrhosis))
Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Register	Date will be given at review stage.	(ultrason* or ultrasound* or echograph* or echotomograph* or doppler* or B-mode or B-scan or grey*scale) AND ((hepatic or liver) and (fibrosis or cirrhosis))
The Cochrane Library	Date will be given at review stage.	#1 MeSH descriptor: [Ultrasonography] explode all trees #2 (ultrason* or ultrasound* or echograph* or echotomograph* or doppler* or B-mode or B-scan or grey*scale) #3 #1 or #2 #4 MeSH descriptor: [Liver Cirrhosis] this term only

(*Continued*)

		#5 ((hepatic or liver) and (fibrosis or cirrhosis)) #6 #4 or #5 #7 #3 and #6
MEDLINE (Ovid SP)	1946 to the date of search.	1. exp Ultrasonography/ 2. (ultrason* or ultrasound* or echograph* or echotomograph* or doppler* or B-mode or B-scan or grey*scale).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] 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. 3 and 6
EMBASE (Ovid SP)	1974 to the date of search.	1. exp echography/ 2. (ultrason* or ultrasound* or echograph* or echotomograph* or doppler* or B-mode or B-scan or grey*scale).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. exp liver fibrosis/ 6. ((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] 7. 4 or 5 or 6 8. 3 and 7
Science Citation Index Expanded	1900 to the date of search.	#3 4,352 #2 AND #1 #2 76,895 TS=((hepatic or liver) and (fibrosis or cirrhosis)) #1 425,695 TS=(ultrason* or ultrasound* or echograph* or echotomograph*

(*Continued*)

		or doppler* or B-mode or B-scan or grey*scale)

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 fulfil the inclusion criteria of this review should have included participants of any sex and ethnic origin, over 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 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. We will exclude other causes of liver disease such as viral hepatitis, autoimmunity, metabolic diseases, and toxins. To ascertain	**Describe the index test and how it was conducted and interpreted:** Ultrasonography for diagnosing cirrhosis, conducted either before or after liver biopsy	**Describe the reference standard and how it was conducted and interpreted:** Liver biopsy with ≥ 6 portal tracts or length of liver biopsy specimen > 15 mm is considered adequate in establishing cirrhosis in people with alcoholic liver disease The morphological interpretation of the liver biopsy samples is reported with semi-quantitative scores such as METAVIR, Knodell, Ishak, Kleiner, Scheuer, or Brunt (see Table 1).	**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 early cirrhosis may reverse with time in abstinent people, but mild to moderate fibrosis may evolve to cirrhosis in non-abstinent people, we will exclude participants if the time interval between diagnostic liver biopsy and ultrasonography investigations is > 6 months

(*Continued*)

	the diagnosis of alcoholic liver disease and study the presence of cirrhosis, both ultrasonography and liver biopsy have to be performed, irrespective of the sequence			
Signalling questions: yes/no/unclear	**Was a consecutive or random sample of participants 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	**Were the index test results interpreted without knowledge of the results of the reference standard?** Yes: ultrasonography test results were interpreted without knowledge of the results of the liver biopsy No: ultrasonography results were interpreted with knowledge of the results of the liver biopsy Unclear: insufficient data were reported	**Is the reference standard likely to classify the target condition correctly?** Yes: if participants have undergone liver biopsy and the liver tissue specimen was deemed adequate for confident histological assessment No: the liver tissue specimen was not deemed adequate for confident histological assessment Unclear: insufficient data were reported	**Was there an appropriate interval between index test(s) and reference standard?** Yes: the interval between the ultrasonography and liver biopsy was $\leq$ 6 months No: the interval between the ultrasonography test and liver biopsy was >6 months Unclear: insufficient data were reported to permit a judgement
	Was a patient-control design avoided? Yes: patient-control design was avoided. No: patient-control design was not avoided. Unclear: insufficient information was reported to permit a judgement	**If a threshold was used, was it pre-specified?** Yes. No. Unclear: it is not reported or not clearly described.	**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 ultrasonography 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		to permit a judgement	**Did all participants receive the same reference standard?** Yes: all participants received the same refer-

(*Continued*)

	(e.g., difficult to diagnose participants, failure at liver biopsy, failure on ultrasonography) No: the study excluded participants inappropriately. Unclear: insuffi-			ence standard, i.e., liver biopsy No: not all participants received the same reference standard, i.e., liver biopsy Unclear: insufficient data were reported **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 have introduced bias Low risk of bias: no, if the selection of participants have not introduced bias Unclear risk of bias: insufficient data on participants selection were reported to permit a judge-	**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 is 'no' Low risk of bias: if the answer to the signalling questions on the conduct or interpretation of the index test is 'yes' Unclear risk of bias: if	**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 is 'no' Low risk of bias: if the answer to the signalling questions on the refer-	**Could the participant flow have introduced bias?** High risk of bias: if the answer to the signalling questions on flow and timing is 'no' Low risk of bias: if the answer to the signalling questions on flow and timing is 'yes' Unclear risk of bias: if the answers to the 4 signalling questions on

(*Continued*)

	ment on the risk of bias	the answers to the 2 signalling questions on the conduct or interpretation of the index test is either 'unclear' or any combination of 'unclear' with 'yes' or 'no'	ence standard, its conduct, or its interpretation is 'yes' Unclear risk of bias: if the answers to the three signalling questions on the reference standard, its conduct, or its interpretation is either 'unclear' or any combination of 'unclear' with 'yes' or 'no'	flow and timing is either 'unclear' or any combination of 'unclear' with 'yes' or 'no'
Concerns regarding applicability: high/low/unclear	**Are there concerns that the included participants do not match the review question?** High concern: there is high concern that the included participants do not match the review question Low concern: there is low concern that the included participants do not match the review question Unclear concern: if it is unclear.	**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** High concern: there is high concern that the conduct or interpretation of the ultrasonography test differs from the way it is likely to be used in clinical practice Low concern: there is low concern that the conduct or interpretation of the ultrasonography test differs from the way it is likely to be used in clinical practice Unclear concern: if it is unclear.	**Are there concerns that the target condition as defined by the reference standard does not match the review question?** High concern: all participants did not undergo liver biopsy for cirrhosis Low concern: all participants underwent liver biopsy for cirrhosis If it is unclear.	--

CONTRIBUTIONS OF AUTHORS

Chavdar Pavlov: generated the idea for the review protocol, drafted and revised the protocol, and serves as a guarantor of the protocol.

Giovanni Casazza: wrote the statistical part of the review protocol, and drafted and revised the protocol.

Marianna Pavlova: revised the protocol.

Dimitrinka Nikolova: revised the protocol.

Emmanuel Tsochatzis: commented on the protocol.

Ekaterina Lusina: commented on the protocol.

Christian Gluud: commented and revised the protocol.

All authors agreed on the final version of the review protocol.

DECLARATIONS OF INTEREST

Chavdar Pavlov: none known.

Giovanni Casazza: none known.

Mariana Pavlova: none known.

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Emmanuel Tsochatzis: none known.

Ekaterina Lusina: none known.

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