A systematic review to evaluate the prevalence of clinically significant liver disease, as defined by non-invasive markers of liver fibrosis, within the general population setting

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Abbreviations:

ALD= Alcoholic liver disease; ALT = alanine aminotransferase; AST = aspartame aminotransferase; APRI = AST:platelet count ratio; AUDIT = Alcohol use disorders identification test; BAAT = score of age≥50 years (1 point), body mass index≥28 kg/m^2 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L; BARD = weighted score of Body mass index ≥28kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point); BMI = body mass index; EASL = European association for the study of liver; ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide);FIB4 = combination of age, ALT, AST and platelet count; kPa = kilopascals; LFTs = Liver function tests; MeSH = Medical subject headings; NAFLD = Non-alcoholic fatty liver disease; NASH = Non-alcoholic steatohepatits; NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio); OR = Odds Ratio; TE = Transient Elastography; UK= United Kingdom

Keywords:

Chronic liver disease, risk stratification, community, non-invasive test

Summary

At present, there is no evidence based pathway to stratify risk of chronic liver disease in a general population setting. Non-invasive tests of liver fibrosis may provide a mechanism for earlier diagnosis. These tests have been extensively validated in the hospital setting but their performance in a general population setting is unclear. We performed a systematic review of non-invasive tests used to stratify patients at risk of clinically significant liver disease in a general population setting and report the prevalence of chronic liver disease as defined by these tests. We systematically searched EMBASE, MEDLINE, Web of Science, reference lists from the original studies and recent conference proceedings. All study designs were considered. Nineteen studies were identified, utilising eleven non-invasive tests. Only transient elastography and Fibrotest were compared against histological end-points. The prevalence of liver fibrosis varied between 0.7% and 25.7%. More focussed stratification for advanced liver fibrosis (0.9%-2%) or cirrhosis (0.1%-1.7%) narrowed estimates of prevalence. Studies targeting patients with liver disease risk factors such as hazardous alcohol use or type 2 diabetes reported higher prevalence of advanced liver fibrosis (0%-27.9%) and cirrhosis (2.4%-4%). Validated non-invasive tests of liver fibrosis consistently detected otherwise unrecognised liver disease in the general population. Studies targeting risk factors found cirrhosis in 2.4 to 4 % of their target populations. Reliance on abnormal liver function tests will miss the majority of patients with significant liver injury. New pathways to stratify chronic liver, using non-invasive markers of liver fibrosis, are needed in the general population setting.

Introduction

Chronic liver disease has become an increasing health burden worldwide. In 2015, cirrhosis and chronic liver diseases accounted for 2% of worldwide deaths, with a relative increase of 10.3% from 2005(1). There are significant variations in mortality among different regions of the world with Mokdad *et al*(2) reporting liver cirrhosis as a health priority in Central Asia, Central Europe, Eastern Europe and Central Latin America. Increasing mortality rates are attributable to viral hepatitis but also driven by the increasing prevalence of alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) which are now the most common causes of chronic liver disease in the Western world(3-5).

Due to the increasing morbidity and mortality of chronic liver disease there is a necessity for urgent action to be taken to prioritise the earlier identification and treatment of patients, particularly within the community(6). Commonly used diagnostic tests have poor sensitivity and specificity, are completed opportunistically or are not appropriate to be used within a community setting therefore limiting the opportunities for intervening at an earlier stage in the disease. This results in nearly 50% of patients only receiving their diagnosis of cirrhosis following an emergency admission to hospital with a decompensating event(7). A liver biochemistry panel often referred to as Liver function tests (LFTs) are inappropriately relied upon in the community setting to identify patients with asymptomatic chronic liver disease(8-10). Fracanzani *et al*(11) demonstrated that 59% of patients with a histological diagnosis of NASH had a normal serum alanine aminotransferase (ALT) level and would not have been identified by current diagnostic algorithms.

At present, an evidenced based risk stratification pathway does not exist within a community setting to screen the general or a targeted population who are at risk of chronic liver disease. Until recently a

barrier has been the absence of a robust and reproducible screening tool. Non-invasive tests of liver fibrosis represent such a tool and their utility in hospital practice has been supported by a number of international organisations including recent guidelines by EASL(12). However, the majority of evidence has been derived and validated from populations based within secondary care (13-15) and thus extrapolation of these tests to a cohort in the community may not be valid due to a reliance upon abnormal LFTs instigating referral for specialist advice, a different prevalence of disease and spectrum bias.

To facilitate the emergence of strategies which aim to risk stratify patients in a general population/community setting we have systematically reviewed the available evidence. From this, the scale of undiagnosed chronic liver disease can be estimated, the inadequacy of current referral pathways can be highlighted and an optimal risk stratification strategy potentially proposed. As the commonest causes of chronic liver disease are ALD and NAFLD we have focussed on the non-invasive tests which have been used to stratify patients at risk of these aetiologies.

Aims

The primary aim of this systematic review was to determine the proportion of the studied populations found to have clinically significant liver disease as defined by the non-invasive tests used in the individual studies.

The secondary aims of this systematic review were i) to identify the proportion of patients with liver fibrosis or cirrhosis as defined by the non-invasive test who had normal ALT results, ii) to evaluate the difference in the proportion of patients identified as having liver disease using non-invasive tests between unselected or targeted populations within a community setting and iii) to determine the patient variables which are significant in identifying patients with liver fibrosis.

Methods

This review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of interventions(16) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines(17).

Search strategy

Two reviewers (RH and DH) defined key MeSH headings and free text search terms relevant to the participants involved in the studies, the two aetiologies of chronic liver disease, the community setting and the non-invasive tests used to stratify for liver fibrosis. Subsequently, a search algorithm was derived in collaboration with a local librarian (Alison Ashmore; University of Nottingham); the final search algorithms including the MeSH terms used within the specific electronic databases are listed within the appendix. Two independent searches of EMBASE (January 1980 to January 2015), MEDLINE (January 1946 to January 2015) and Web of Science were completed. Additionally a hand search was completed of all major UK and worldwide conference proceedings dating back to 2010 including the British Society of Gastroenterology, the British Association for the study of liver disease, the European Association for the study of liver disease and the American Association for the study of liver disease. A targeted search was also completed of reference lists from the original studies and abstracts including any review articles or citations that were identified.

Identification of studies was commenced in November 2014 and completed in January 2015. The titles and abstracts of all studies identified within the literature search were screened to determine their suitability for inclusion within the review. The full texts of all studies considered to be suitable were

assessed for eligibility. Any disagreements were discussed but if these could not be resolved the advice from a third reviewer (ING) was sought.

Selection criteria

Listed below are the eligibility criteria used to screen the individual studies for inclusion within the review.

Studies were included if: i) the study was performed in adults defined as 18 years or older, ii) the study population was from a non-hospital setting e.g. community, primary care or outreach unit, iii) study participants underwent a validated non-invasive test which would stratify for liver fibrosis, iv) the prevalence of clinically significant liver disease, either liver fibrosis or cirrhosis was reported as an outcome measure by the study (validation of the result by histopathology was not an absolute requirement) and v) participants were recruited from an unselected population or based upon the participants age or a defined risk factor for ALD or NAFLD.

Studies were excluded if: i) data regarding the study population, the setting in which the non-invasive test was completed or the threshold for the non-invasive test was not adequately reported, ii) the participants were solely investigated for liver disease aetiologies other than ALD or NAFLD (e.g. viral hepatitis) or iii) they were not published in the English language

Data collection and analysis

Data extraction was completed and reviewed by the two researchers independently. This included data on study characteristics, demographics of the patient population and details of the non-invasive test which was used. The outcome measure was the reported prevalence of liver fibrosis and/or cirrhosis within the population studied as defined by the non-invasive test which was used. Due to the lack of comparable studies and substantial heterogeneity a meta-analysis could not be performed.

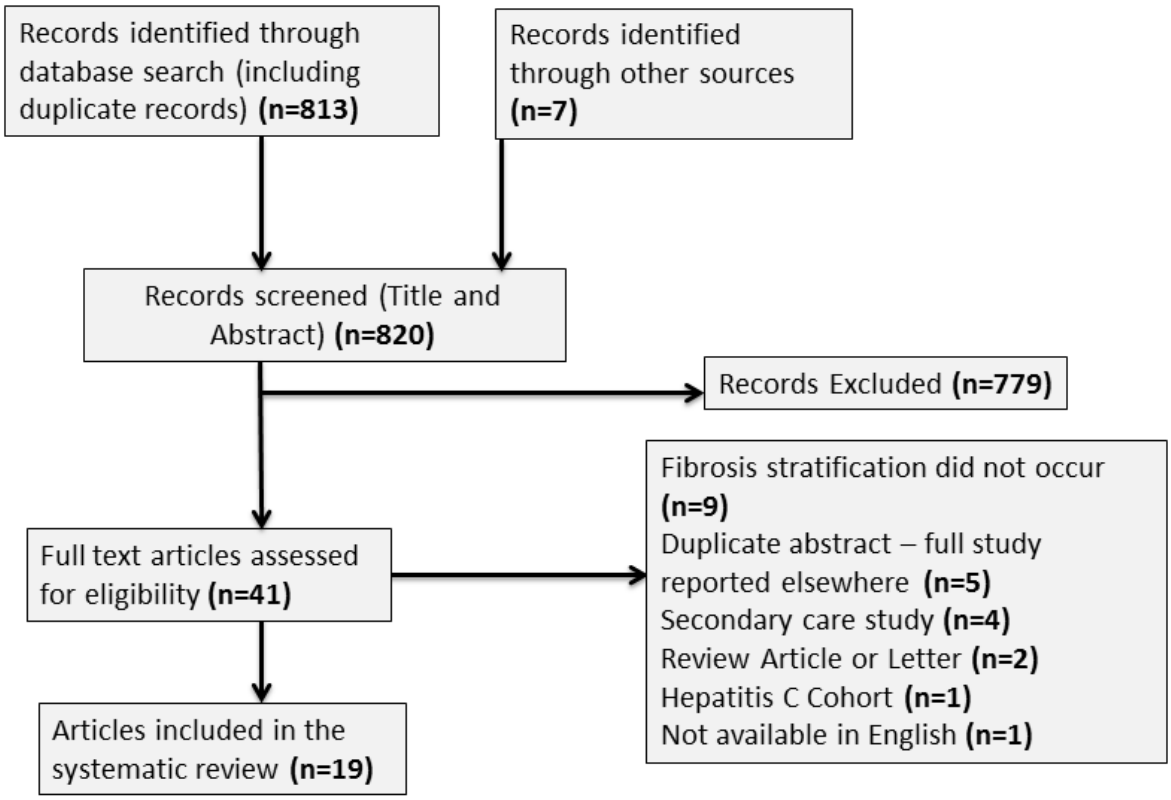

Figure 1. Flow diagram of the article search strategy and selection of studies eligible for data analysis

Results

Our systematic search of bibliographic databases identified a total of 813 citations. An additional 7 studies were identified from the grey literature. Following screening of the titles and abstracts, a total of 779 studies were excluded. The full text of 41 studies was assessed against the inclusion and exclusion criteria resulting in a further 22 studies being excluded from the final analysis. Finally, 19 studies including 17 full journal articles and 2 abstracts were included within the systematic review. The overall results of the search strategy are presented in figure 1.

Non-invasive tests used:

Eleven different non-invasive tests were utilised to stratify patients for liver fibrosis. Transient elastography (TE) was the only imaging based modality and was the most frequently used test included within 12 out of the 19 studies identified. The majority of studies reported performance using the M probe with one study reporting performance of both M and XL probes. The remaining non-invasive tests were all serum based and comprised NAFLD fibrosis score (NFS), used within 5 studies, Fibrotest, used within 3, the BARD score (BARD = weighted score of Body mass index ≥28kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point)) ; AST:ALT ratio, APRI score (APRI = AST:platelet count ratio) and the FIB4 index (FIB4 = combination of age, ALT, AST and platelet count) which were used within 2 and the BAAT score (BAAT = score of age≥50 years (1 point), body mass index≥28 kg/m^2 (1 point)) , Hyaluronic acid, the ELF score (enhanced liver fibrosis) and the Southampton traffic light test which were all used once within separate studies. The baseline characteristics of individual studies including patient demographics are reported within Table 1.

Target population:

There was significant heterogeneity in the community studies included for analysis (Table 1). The initial target population tested by the non-invasive tests varied. Five studies stratified members of the general population according to an age cut off whilst a further 5 studies stratified an unselected group of adults. The prevalence of risk factors reported within these studies would be as expected for the general population apart from the study by You et al(18) in which the prevalence of type 2 diabetes was raised at 11.9%. Ten studies stratified patients with risk factors for NAFLD including 3 studies(19-21) which completed subgroup analysis on patients initially identified from the general population. Four studies stratified patients known to be at risk of ALD including 1 study(19) which had completed further subgroup analysis. Heterogeneity also existed in the choice of non-invasive test and outcome measure, including the severity of liver fibrosis.

Screening uptake

The proportion of patients that participated in screening from the invited study population was reported in eight studies. This ranged from 20%-89% for the first study visit. In studies which had multiple steps within the algorithm(22,23) a decline in uptake was observed. In the study by Sheron et al(22) a positive AUDIT questionnaire was recorded in 24.3%, however only 34.8% of this group subsequently attended clinic for the non-invasive test to be completed.

Prevalence of fibrosis

All 19 studies reported the prevalence of liver fibrosis according to a specified threshold for the non-invasive test which was utilised.

Unselected population

In those studies reporting unselected patients from the general population the prevalence of liver fibrosis ranged from 2%-19% (Table 2). All 5 studies utilised TE but the results varied due to the different liver stiffness thresholds that were chosen and the degree of liver fibrosis that was estimated. The lowest estimate obtained in the study by Wong et al(20) used the highest threshold of 9.6kPa and estimated the prevalence of advanced liver fibrosis only. The highest estimate in the study by Malik et al(24), used a lower threshold of 7.0kPa and estimated the prevalence for any liver fibrosis. In the 5 studies which stratified members of the general population according to an age cut off, the prevalence ranged from 0.7%-25.7%. The lowest estimate obtained in the study by Poynard et al(23) used a two-step approach with only half of the patients re-attending for the second test. Overall only two studies stratified members of the general population for advanced liver fibrosis. The reported prevalence was 0.9%(25) and 2%(20) using Fibrotest ≥0.59 and TE ≥ 9.6kPa respectively.

NAFLD

In the ten studies which stratified patients identified to be at risk of NAFLD the reported prevalence of liver fibrosis ranged from 0% - 92.6% (see appendix p3). Again, the prevalence varied dependent on the non-invasive test which was used and the degree of liver fibrosis that was being estimated. In the 5 studies which estimated any liver fibrosis the prevalence ranged between 0.4%-92.6%. The studies which reported the highest estimates of prevalence were Williamson et al(26) and Morling et al(27) in which 100% of the study populations were reported to have type 2 diabetes. Four studies estimated the prevalence of advanced liver fibrosis which ranged from 0%-27.9%. The highest estimate was

obtained from Vesey et al(21) who only recruited patients aged over 65 years, therefore increasing the probability of disease being identified. The lowest estimate was obtained in the study by Wong et al(20) who utilised several non-invasive tests to demonstrate the prevalence of advanced liver fibrosis. In this cohort, use of the NAFLD fibrosis score≥0.676 and APRI≥1.5 estimated a 0% prevalence for advanced fibrosis, while using TE≥9.6kPa and AST:ALT ratio≥1.0 the prevalence increased to 3.7% and 12.1% respectively.

ALD

In the four studies which stratified patients identified to be at risk of ALD the reported prevalence ranged between 11%-20.5% (see appendix p3). In the three studies(19, 28, 29) which utilised TE the reported disease prevalence was similar despite two different thresholds being chosen and the reported outcome measures being different.

Prevalence of cirrhosis

Only seven studies reported the prevalence of cirrhosis which varied depending on the study population being stratified (Table 3). In the four studies which used subjects from the general population the reported prevalence varied between 0.1%-1.7%. The highest estimate was obtained by Malik et al(24) but they did not report the risk factor prevalence in the study population. It cannot therefore be determined why this self-selected group were at increased risk of having clinically significant liver disease. The other three studies which stratified patients due to an underlying risk factor reported a prevalence of 2.4%-4.0%; a much higher estimate of liver cirrhosis prevalence compared to studies of the general population. Interestingly, in the study by Das et al(30) which reported a cirrhosis prevalence of 2.4% in patients with NAFLD, the prevalence of cirrhosis in their

unselected cohort was calculated to be 0.2%; equivalent to the estimates reported in the other studies of the general population.

Liver biopsy results

Only six studies utilised histology on liver biopsy to confirm the diagnosis of liver fibrosis/cirrhosis as indicated by the non-invasive test (Table 4). This includes 5 studies which used TE, all of which used different thresholds of liver stiffness, and 1 study which used Fibrotest. Within no study were liver biopsies completed in all of the patients undergoing the non-invasive test.

Across the 6 studies, the acceptance rate of liver biopsies varied between 22.5%-87.5%. In the study by Roulot et al(31) the acceptance rate was 100% in the 9 patients who had a liver stiffness reading >13kPa, all of whom were confirmed to have a histological diagnosis of cirrhosis. However, in comparison, in the study by Moessner et al(28) who used a similar liver stiffness threshold of 12kPa, only 20/45 (44.4%) patients accepted a liver biopsy and only 9/20 (45%) were confirmed to have a histological diagnosis of cirrhosis. The other patients were identified to have varying degrees of liver fibrosis (4/20 = F1 fibrosis, 3/20 = F2 fibrosis, 4/20 = F3 fibrosis). Importantly, this cohort had an underlying risk factor of hazardous alcohol use for which a higher liver stiffness threshold is proposed to predict advanced fibrosis and cirrhosis compared to other aetiologies(32, 33).

ALT levels and predictors of significant liver disease

Nine studies have reported the percentage of patients with an abnormal test result who had normal ALT levels. This indicates the percentage of patients who would traditionally not have been identified though current referral algorithms which are based upon abnormal LFTs. Two studies by Wong et al(20) and Grattagliano et al(34) used conservative ALT levels of >19IU/L for women and >30IU/L for men as suggested by Prati *et al*(35) whilst the remaining studies used the more traditional cut offs.

The percentage of patients with liver fibrosis who had a normal ALT level in the studies of the general population ranged from 40%-74.6% and in those which identified patients with an underlying risk factor ranged from 26.5%-87.5% respectively. The lowest estimates reported within both ranges were seen within the two studies which utilised the more conservative cut offs. Of the three studies which used traditional cut offs in the patient populations with an underlying risk factor, 72.4%-87.5% of patients had a normal ALT level and would not have been routinely identified.

Harman et al(29) was the only study which reported the percentage of patients with a normal ALT level who were diagnosed with cirrhosis. In this study 90.9% of patients with asymptomatic compensated cirrhosis would not have been identified via traditional community based algorithms.

Predictors of clinically significant liver disease

Five studies completed a multivariate analysis to identify the variables which independently predict an outcome of elevated liver stiffness using TE or significant/confirmed fibrosis from a non-invasive test result (see appendix p4). The key variables identified include a raised BMI, an elevated waist circumference), an abnormal ALT, the age of the patient and being male.

Discussion

This review has demonstrated that a number of non-invasive tests have the ability to stratify for the severity of liver disease within a community setting. Moreover, when compared to the uptake of other screening programs, the participation of those invited suggests that as screening tests for use in the community they are acceptable to patients. The estimates of cirrhosis prevalence (0.1%-1.7%) are greater than previously reported (0.07-0.13%)(36,37) highlighting the burden of undiagnosed chronic liver disease in the general population and that the true population prevalence is still yet to be established. The presence of normal liver function tests in both significant liver disease (ranging from 41% to 75 %) and cirrhosis (90 % in one study) is a stark reminder of the limitations of these tests to detect chronic liver injury.

In this review eleven different non-invasive tests were used within heterogeneous population groups. The variation in reported disease prevalence highlights the uncertainty as to which test is most appropriate as demonstrated specifically in the studies by Morling *et al*(27) and Wong *et al*(20) who applied several non-invasive tests to the same cohort of patients resulting in widely differing estimates of prevalence for any liver fibrosis (0.4%-63.8%) and advanced liver fibrosis (0%-12.1%) respectively.

Moreover, comparing studies which used the same non-invasive test provided no further clarity as different thresholds were used for the stratification of liver fibrosis. However, as demonstrated by Roulot *et al*(31) and Moessner *et al*(28), even when similar liver stiffness thresholds for transient elastography were used a wide variation in the histological diagnoses can be observed. The variation in thresholds may be a result of using normal populations to determine thresholds. Roulot *et al*(38) defined a threshold of 8kPa, based upon the 95th centile, in a healthy population, in contrast to the study by Conti *et al* which reported the 95th centile at 6.8kPa (39). The differences observed may be

due to the younger age of participants in the study by Conti (patients in the cohort were between 30 and 60 years of age), or the separate analysis of patients with ultrasound evidence of NAFLD and hence a lower prevalence of metabolic syndrome risk factors. The normal thresholds of Fibrotest have been defined in healthy blood donors(40) and are consistent with the index validation study using the biopsy as a reference standard(41). This demonstrates that the optimal threshold for defining a specific degree of liver fibrosis is yet to be agreed. There also appears to be no concordance over which stage of liver fibrosis is clinically important with studies reporting the prevalence of any, significant or advanced liver fibrosis as their outcome measure. In NAFLD, it has been shown that patients with ≥F3 fibrosis have an increased risk of mortality predominantly from cardiovascular and liver related disease(42, 43).

It is obvious that use of a liver biopsy as a screening tool is not feasible due to the practicalities of performing an invasive procedure in a community setting, the expense and the low prevalence of disease; in combination this results in an unfavourable risk/benefit ratio. Currently all non-invasive tests continue to be validated against histological findings which have their own well documented limitations(44). From the studies within this review the true diagnostic performance could not be established as a liver biopsy was not completed on all of the patients with an abnormal test result or any patient with a negative test result. Although formal analysis of the quality of included studies was not performed as they were in essence diagnostic prevalence studies for which a relevant validated quality assessment tool was not found, one must consider all included studies to be at high risk of methodological bias due to the inherent selection bias for liver biopsy (where performed). Completion of longitudinal cohort studies would enable the true diagnostic performance of a non-invasive test to be assessed along with identifying and validating the optimum threshold that should be applied. These studies are also imperative given the emerging evidence of the additional prognostic information that

these non-invasive markers could provide(14, 42). Boursier et al(45) has recently demonstrated the value of using transient elastography in the context of NAFLD to stratify patients into specific subgroups which correlate with clinical outcomes. The clinical outcome studies that have emerged, are focused on patients presenting to hospitals with the associated limitations of both referral bias and spectrum bias. Whilst long term outcomes are awaited from biomarker studies performed specifically in a general population setting, the only feasible option is to utilise the extensively validated biomarker tests derived from specialist care. This review highlights that caution needs to be exercised in extrapolating non-invasive markers for the detection of significant liver disease but greater agreement exists in the context of detecting liver cirrhosis. Notwithstanding the limitations above, transient elastography and Fibrotest were the most frequently used tests being utilised within 3 or more studies, and had their results compared against histological findings, subsequently making these the most validated non-invasive tests in a community population.

Despite liver disease mortality in Europe being comparable to other diseases which are given a higher priority on the public health agenda(5), improved detection of early liver disease in the community continues to make slow progress and is reportedly restricted by available resources and the considerable numbers of patients at risk(46). The studies which reported the presence of any liver fibrosis in the general population have demonstrated the potential burden of disease (0.7%-25.7%) although more focussed stratification for advanced liver fibrosis (0.9%-2%) or cirrhosis (0.1%-1.7%) narrowed estimates of prevalence. To date, there has been no recommendation to screen the general population for chronic liver disease due to the concerns about cost and the unknown wider consequences of a false positive or negative result. However, with the increasing incidence of risk factors such as alcohol misuse, obesity and type 2 diabetes, targeting specific high risk populations may initially be more realistic and has recently been recommended by the European Association for the Study of Liver (EASL)(46). Studies which targeted patients with risk factors of chronic liver disease

reported a higher prevalence of advanced liver fibrosis (0%-27.9%) and cirrhosis (2.4%-4%) in comparison to the general population. Health economic evaluations to determine the cost effectiveness of targeting specific patient populations may aid decisions regarding implementation.

Finally, this review demonstrates that the longstanding reliance upon LFTs is misguided and that current strategies are ineffective and missing a large proportion of patients with asymptomatic liver disease; 26.5-87.5% of patients with an abnormal non-invasive test result had an ALT level within the normal range. Strategies which improve risk stratification are urgently required and should not be based upon abnormalities within LFTs alone. Targeting patients with known risk factors will improve the diagnostic yield and be more effective in identifying patients with asymptomatic chronic liver disease. Furthermore, employing a risk stratification algorithm which also incorporates simple patient related risk factors such as those identified through the multivariate analysis (raised BMI, elevated waist circumference, abnormal ALT, age and gender) could increase the likelihood of identifying patients with liver fibrosis.

In conclusion, this systematic review has demonstrated an appreciable burden of undetected chronic liver disease within the community setting in a diverse set of populations. Validated non-invasive tests, including transient elastography and Fibrotest, consistently detected disease which would have otherwise been missed by current referral pathways based upon abnormal liver function tests. The diagnostic yield was further enhanced if a risk factor approach was utilised rather than a general population screening programme. This review provides a starting point for creating new pathways to stratify clinically significant liver disease in a general populations setting.

Author's contributions:

Guarantor of the article: Dr Indra Neil Guha

Author contributions: RH, DJH, TRC and GPA and ING contributed to the design of the study, RH and DJH collected and analysed the data, RH wrote the paper, all authors revised the manuscript and approved the final version.

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Appendix

Search algorithms used within the electronic databases

Database: Ovid MEDLINE(R) <1946 to January Week 3 2015>

Search Strategy:

Results: **329 hits**

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1 exp Liver Cirrhosis/di [Diagnosis] (7647)

2 exp Fatty Liver/di [Diagnosis] (3112)

3 exp Liver Diseases, Alcoholic/di [Diagnosis] (1367)

4 (hepatic fibrosis or Chronic liver disease* or advanced fibrosis or non alcoholic fatty liver disease* or NAFLD or NAFL or alcoholic liver disease* or ALD or liver fibrosis* or hepatic cirrhos* or liver cirrhos* or fatty liver disease* or fatty liver or advanced fibrosis).mp. (113886)

5 exp Biological Markers/ (669858)

6 exp Elasticity Imaging Techniques/ (3985)

7 exp Diagnostic Imaging/ (1816061)

8 (non invasive biomarker* or non invasive biological marker* or non invasive marker* or fibroscan or liver stiffness or transient elastography or ultrasound abdomen or ARFI or liver function test* or LFT* or fibrotest* or fib4 or Lok or FORNS or APRI or ELF or NFS or BAAT or BARD or noninvasive biomarker* or noninvasive biological marker* or noninvasive marker* or elastogram* or sonoelastograph* or imaging tissue elastic or elasticity imaging technique*).mp.

(42847)

9 exp Family Practice/ or exp General Practice/ (65915)

10 exp Primary Health Care/ (84294)

11 exp Community Health Services/ (514681)

12 (gp or general practice* or family practice* or primary care or communit* or outreach).mp. (539188)

13 1 or 2 or 3 (10904)

14 5 or 6 or 7 or 8 (2473667)

15 4 and 14 (23298)

16 13 and 14 (4877)

17 9 or 10 or 11 or 12 (962504)

18 15 or 16 (23432)

19 17 and 18 (329)

Database: Embase <1980 to 2015 Week 03>

Search Strategy:

Results: **274 hits**

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1 exp Liver Cirrhosis/di [Diagnosis] (10375)

2 exp Fatty Liver/di [Diagnosis] (4932)

3 exp Liver Diseases, Alcoholic/di [Diagnosis] (1672)

4 (hepatic fibrosis or Chronic liver disease* or advanced fibrosis or non alcoholic fatty liver disease* or NAFLD or

NAFL or alcoholic liver disease* or ALD or liver fibrosis* or hepatic cirrhos* or liver cirrhos* or fatty liver disease* or fatty liver or advanced fibrosis).mp. (172281)

5 exp Biological Markers/ (136914)

6 exp Elasticity Imaging Techniques/ (6192)

7 exp Diagnostic Imaging/ (120239)

8 (non invasive biomarker* or non invasive biological marker* or non invasive marker* or fibroscan or liver stiffness or transient elastography or ultrasound abdomen or ARFI or liver function test* or LFT* or fibrotest* or fib4 or LOk or FORNS or APRI or ELF or NFS or BAAT or BARD or noninvasive biomarker* or noninvasive biological marker* or noninvasive marker* or elastogram* or sonoelastograph* or imaging tissue elastic or elasticity imaging technique*).mp.

(55678)

9 exp Family Practice/ or exp General Practice/ (68233)

10 exp Primary Health Care/ (110827)

11 exp Community Health Services/ (99163)

12 (gp or general practice* or family practice* or primary care or communit* or outreach).mp. (663151)

13 exp chronic liver disease/di [Diagnosis] (1122)

14 exp early diagnosis/ (72202)

15 exp liver fibrosis/ (26007)

16 exp diagnosis/ (4570720)

17 exp non invasive measurement/ (13716)

18 chronic liver disease/ (12578)

19 exp liver cirrhosis/ (109545)

20 exp fatty liver/ (39198)

21 exp nonalcoholic fatty liver/ or exp alcohol liver disease/ (31283)

22 4 or 15 or 18 or 19 or 20 or 21 (185464)

23 5 or 6 or 7 or 8 or 14 or 17 (389042)

24 (22 or 1 or 2 or 3) and 23 (17179)

25 9 or 10 or 11 or 12 (722145)

26 24 and 25 (274)

Table 1. Baseline characteristics of 19 studies included within the systematic review. Listed in order of risk factor for liver disease (unselected general population, general population selected by age, NAFLD risk factors, ALD risk factors, risk factors for both NAFLD and ALD)

Study (First Author)	Study Location/Patient Selection/Liver Disease Risk Factor	Non-invasive Test Utilised	Total Study Population	No. of Participants Screened	Mean Patient Age (years)	Male Gender (%)
Baba(19)	Japan; annual medical check-up at community health centre; unselected (alcohol and NAFLD subgroup analyses)	TE	Not Stated	423 (of whom valid TE in 416 (98.3%)); subgroups of alcohol misuse (n=151) and NAFLD (n=58)	47.4	60.1%
Wong(20)	Hong Kong; subjects invited at random aged 18-70 from census database; unselected (subgroup analysis of patients with NAFLD (MRS))	TE (all); NAFLD – AST:ALT ratio, APRI, BARD, FIB4, NAFLD fibrosis score	3000	922 (of whom valid TE in 759 (82.3%)) NAFLD subgroup - 264	48.0	42.2%
You(18)	South Korea; healthy subjects attending health check at local hospital; unselected	TE	Not Stated	164 (of whom valid TE in 159 (97%))	56.0	54.7%
Lemoine(47)	The Gambia; community screening of healthy subjects; unselected	TE	Not Stated	76 (of whom valid TE in 72 (94.7%)	49.5	43%

Malik(24)	United Kingdom; subjects recruited via advert and reviewed in private clinic; unselected	TE	Not Stated	116	Not stated	Not stated
Fabrellas(48)	Spain; subjects invited at random from state health registry; age 18-70 years	TE	Not Stated	502 (Of whom valid TE in 495 (98.6%)	47.2	41%
Zelber-Sagi(25)	Israel; random sample of participants of First Israeli National Health and Nutrition Survey; age 25-64 years	Fibrotest	799	349 (of whom 338 (96.8%) had valid Fibrotest results)	50.8	54.7%
Poynard(23)	France; free medical check-up at community health centre; age≥40 years	Fibrotest, TE	Not Stated	7,554 (of whom valid Fibrotest/absence of previous liver disease in 7,482 (99%))	56.9	55.1%
Roulot(31)	France; free medical check-up at community health centre; age>45 years	TE	Not Stated	1,358 (of whom valid TE in 1,190 (87.6%))	57.7	60.5%
Veysey(21)	Australia; general population screening of elderly patients; age ≥65 years	NAFLD Fibrosis Score	Not Stated	440; subgroup of 190 subjects with NAFLD (Fatty Liver Index)	78.0	40%

Armstrong(49)	United Kingdom; screening of subjects with raised ALT level from 8 primary care practices; NAFLD (ultrasound) and raised ALT	NAFLD Fibrosis Score (NFS)	Not Stated	295 (of whom NFS measured in 236 with available serum)	58.0	56.6%
Kim(42)	United States; subjects from NHANES III general population cohort (1988-1994); NAFLD (ultrasound)	NAFLD Fibrosis Score	Not Stated	4,083	45.5	50.4%
Grattagliano(34)	Italy; subjects from 10 primary care practices; NAFLD (ultrasound)	Fibrotest	Not Stated	259	51.0	63.7%
Williamson(26)	Scotland; subjects from Lothian Type 2 Diabetes cohort (aged 60-74); type 2 Diabetes	Hyaluronic acid, BAAT, BARD, NAFLD fibrosis Score	5,454	939 (year 1 clinic attendees); subgroup of 663 with possible NAFLD	68.9	52%
Morling(27)	Scotland; subjects from Lothian Type 2 Diabetes cohort (aged 60-74); type 2 Diabetes (subgroup analysis of patients with NAFLD (Ultrasound))	TE, ELF Score, AST:ALT ratio, APRI, FIB4	5,454	767 (year 4 clinic attendees); subgroup of 282 with NAFLD	71.4	52.8%
Das(30)	India; 1 in 3 sample of voting registry invited at random; NAFLD	TE	2,406	44 (out of 1,911 screened for NAFLD, 164 were positive and 44 also had raised ALT)	39.0	54%

	(Ultrasound and CT) and raised ALT					
Sheron(22)	United Kingdom; screening of subjects from 9 primary care practices; alcohol (AUDIT score ≥8)	Southampton Traffic Light Test	1,128	393	44.1	58.3%
Moessner(28)	Denmark; screening of subjects attending drug and alcohol outreach centre; alcohol misusers who were HCV negative	TE	759	175	Not Stated	Not Stated
Harman(29)	United Kingdom; screening of subjects from 2 primary care practices; hazardous alcohol use or type 2 Diabetes or raised ALT	TE*	920	378 (of whom valid TE in 366 (96.8%)); subgroups of hazardous alcohol misuse (n=174), Type 2 Diabetes (n=211) and raised ALT (n=54)	61.8	67.5%

ALD= Alcoholic liver disease; ALT = alanine aminotransferase; AST = aspartame aminotransferase; APRI = AST:platelet count ratio; AUDIT = Alcohol use disorders identification test; BAAT = score of age≥50 years (1 point), body mass index≥28 kg/m^2 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L; BARD = weighted score of Body mass index ≥28kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point); CT = Computer tomography; ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide);FIB4 = combination of age, ALT, AST and platelet count; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; HCV = Hepatitis C virus; MRS = Magnetic resonance spectroscopy; NAFLD = Non-alcoholic fatty liver disease; NHANES III = National health and nutrition examination survey; NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio); Southampton Traffic Light Test = combination of hyaluronic acid, Procollagen III N-Terminal Propeptide and platelet count; TE = Transient Elastography; *=study using TE where XL probe liver stiffness measurement was utilised in selected patients (failed M probe measurement or BMI≥35kg/m^2).

Table 2. Results of 10 studies reporting liver fibrosis prevalence in unselected subjects of the general population or subjects selected by age alone using a non-invasive test in a community setting					
Study (First Author)	**Risk Factor Prevalence**	**Outcome Measure**	**Non-invasive Test Threshold**	**Disease Prevalence**	**Normal ALT (%) (Diseased State)**
Baba(19)	BMI≥23 = 33.4% Alcohol consumption >20g/day = 36%	Any liver fibrosis	TE (liver stiffness) ≥5.9kPa	14.4%	55%
Wong(20)	Type 2 Diabetes = 5.2% BMI≥25 = 22.8%	Advanced Liver Fibrosis	TE (liver stiffness) ≥9.6kPa	2%	40%
You(18)	BMI>25 = 41.5% Type 2 Diabetes = 11.9% Hypertension = 25.2%	Significant Liver Fibrosis	TE (liver stiffness) ≥7kPa	6.9%	63.6%
Lemoine(47)	Not Stated	Any Liver Fibrosis	TE (liver stiffness) ≥7.2kPa	11%	Not Stated
Malik(24)	Not Stated	Any Liver Fibrosis	TE (liver stiffness) ≥7kPa	19%	Not Stated
Fabrellas(48)	Hazardous alcohol consumption = 9%	Any Liver Fibrosis	TE (liver stiffness) ≥6.8kPa	5.7%	Not stated
Zelber-Sagi(25)	Type 2 Diabetes = 6.8% Hypertension 37.3%	i) Any Liver Fibrosis ii) Significant Liver Fibrosis	i) Fibrotest ≥0.22 ii) Fibrotest ≥0.32	i) 25.7% ii) 12.8%	Not Stated

	Metabolic syndrome = 18.6%	iii) Advanced Liver Fibrosis	iii) Fibrotest ≥0.59	iii) 0.9%	
Poynard(23)	Hazardous alcohol = 22.5% BMI≥27 = 32.5% Dysglycaemia = 15.3%	i) Presumed Liver Fibrosis ii) Any Liver Fibrosis	i) Fibrotest>0.48 ii) Fibrotest>0.48 and TE (liver stiffness) ≥7.1kPa	i) 2.8% ii) 0.7%	i) 74.6% ii) 66%
Roulot(31)	Metabolic syndrome = 20.3% BMI≥30 = 17.1% BMI 25-29 = 45.8%	Any liver fibrosis	TE (liver stiffness) ≥8kPa	7.5%	43%
Veysey(21)	NAFLD (fatty liver index>60) = 43.2%	Any Liver Fibrosis	NAFLD Fibrosis Score>0.676	18.9%	Not Stated

BMI = body mass index; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio); TE = Transient Elastography

Table 3. Results of 7 studies reporting liver cirrhosis using a non-invasive test in a community setting						
Study (First Author)	**Risk Factor Prevalence**	**Outcome Measure**	**Non-invasive Test Threshold**	**Disease Prevalence (% in studied population)**	**Cirrhosis Aetiology**	**Normal ALT (%) (Diseased State)**
Malik(24)	Not Stated	Cirrhosis	TE – liver stiffness≥7kPa and liver biopsy confirmation	1.7%	Not Stated	Not Stated
Zelber-Sagi(25)	Diabetes = 6.8% Hypertension = 37.3% Metabolic syndrome = 18.6%	Cirrhosis	Fibrotest≥0.75	0.3%	Not Stated	Not Stated
Poynard(23)	Hazardous alcohol 22.5% BMI≥27 – 32.5%	Cirrhosis	Fibrotest>0.48 and TE (liver stiffness) ≥7.1kPa and liver biopsy confirmation	0.1%	NAFLD and ALD (44%), NAFLD (33%), ALD and Hepatitis C (22%)	Not Stated
Roulot(31)	Metabolic syndrome = 20.3% BMI≥30 – 17.1% BMI 25-29 = 45.8%	Cirrhosis	TE – liver stiffness>13kPa	0.76%	Alcohol (56%), Chronic viral hepatitis (44%)	Not Stated
Das(30)	**Whole population**: BMI≥25 = 7%	Cirrhosis	NAFLD (ultrasound, CT, TE –liver stiffness ≥8.0kPa)	0.2% of whole population; 2.4% of those with NAFLD	NAFLD (100%)	Not Stated

	Abdominal Obesity* =11% Dysglycaemia = 13% **NAFLD subgroup**: BMI ≥25 = 25% Abdominal obesity – 39% Dysglycaemia – 26%					
Moessner(28)	Not Stated	Cirrhosis	TE – liver stiffness≥12kPa	4%	ALD (100%)	Not Stated
Harman(29)	**Whole population:** Obesity = 34.4% Metabolic syndrome = 31.0% Type 2 Diabetes = 55.8% Hazardous alcohol use = 46.0%	Cirrhosis	TE – liver stiffness >13.0kPa	3.0%	ALD (18.2%) NAFLD (81.8%)	90.9%

ALD= Alcoholic liver disease; ALT = alanine aminotransferase; BMI = Body Mass Index; CT = Computer tomography; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; TE = Transient Elastography

Table 4. Results of 6 studies reporting liver biopsy findings in patients with an abnormal non-invasive test result				
Study (First Author)	**Non-invasive Test Threshold**	**Biopsy performed**	**Biopsy Results**	**Disease Aetiology**
Lemoine(47)	TE (Liver Stiffness)≥7.2kPa	7/8 (87.5%)	All F0-F1 fibrosis stage (individual staging not stated)	Not Stated
Malik(24)	i) TE (Liver Stiffness) 7-10kPa ii) TE (Liver Stiffness) >10kPa	i) 7/18 (38.9%) ii) 4/4 (100%)	i) No fibrosis 7/7 (100%) ii) F3 Fibrosis 2/4 (50%), Cirrhosis 2/4 (50%)	All patients ALD or NAFLD, but exact percentages not stated
Roulot(31)	i) TE (Liver Stiffness) 8-13kPa ii) TE (Liver Stiffness) >13kPa	i) 18/80 (22.5%) ii) 9/9 (100%)	i) 17/18 (94%) F1 or F2 fibrosis ii) 9/9 (100%) Cirrhosis	i) NAFLD (8), ALD (6), HBV (2), HCV (1), PBC (1) ii) ALD (5), HCV (3), HBV (1)
Grattagliano(34)	Fibrotest ≥0.58	16/34 (47.1%)	F2 Fibrosis 2/16 (12.5%) F3 Fibrosis 14/16 (87.5%),	Not Stated
Moessner(28)	TE (Liver Stiffness)≥12kPa	20/45* (44.4%)	F1 Fibrosis 4/20 (20%) F2 Fibrosis 3/20 (15%) F3 Fibrosis 4/20 (20%) Cirrhosis 9/20 (45%)	Not Stated

Harman(29)	TE (Liver stiffness)≥8kPa	25/98 (25.5%)	Hepatic fibrosis 20/25 (80%) No fibrosis 5/25 (20%)	Not stated
*Biopsy data reported in this study includes both Hepatitis C positive and negative patients. ALD = alcoholic liver disease; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; HBV = Hepatitis B Virus; HCV = Hepatitis C; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; PBC = primary biliary cirrhosis; TE = Transient Elastography				

Prisma 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3 + 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5 + 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7 + 8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	25 + 26

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9 + 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7 + 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a (see page 19)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 + 10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	27, table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	30-38 Table 2 -

			5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	39

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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