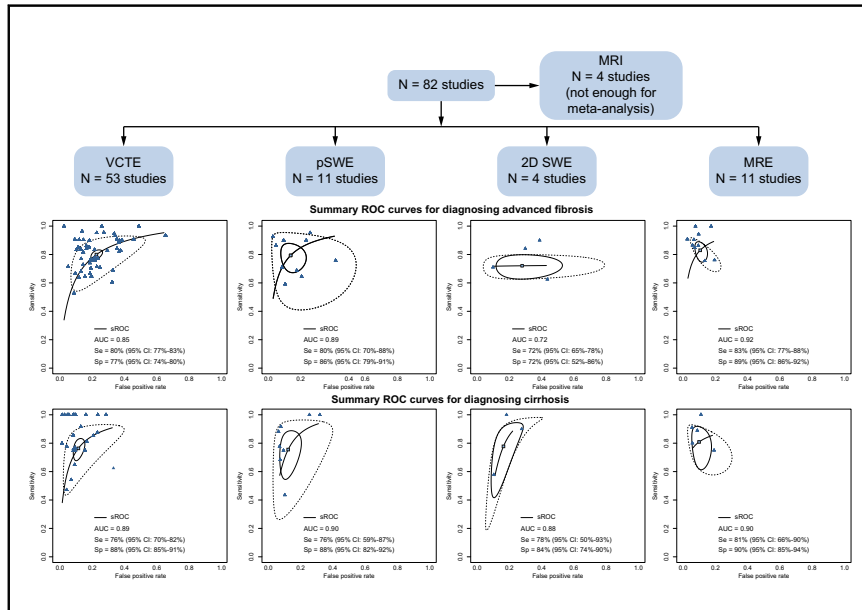


# Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: A systematic review and meta-analysis

## Graphical abstract



## Authors

Emmanuel Anandraj Selvaraj, Ferenc Emil Mózes, Arjun Narayan Ajmer Jayaswal, ..., Stephen A. Harrison, Patrick M. Bossuyt, Michael Pavlides

## Correspondence

michael.pavlides@cardiov.ox.ac.uk  
(M. Pavlides).

## Lay summary

Non-invasive tests that measure liver stiffness or use magnetic resonance imaging (MRI) have been suggested as alternatives to liver biopsy for assessing the severity of liver scarring (fibrosis) and fatty inflammation (steatohepatitis) in patients with non-alcoholic fatty liver disease (NAFLD). In this study, we summarise the results of previously published studies on how accurately these non-invasive tests can diagnose liver fibrosis and inflammation, using liver biopsy as the reference. We found that some techniques that measure liver stiffness had a good performance for the diagnosis of severe liver scarring.

## Highlights

- This is the largest systematic review of imaging/elastography biomarkers in NAFLD.
- Meta-analysis of 1 MR elastography and 3 ultrasound techniques.
- Elastography may help in fibrosis evaluation in those with NAFLD and valid readings.
- Clinical utility of these tests cannot be assessed fully as intention-to-diagnose analyses and validation of pre-specified cut-offs are lacking.



# Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: A systematic review and meta-analysis

Emmanuel Anandraj Selvaraj<sup>1,2,3,†</sup>, Ferenc Emil Mózes<sup>1,†</sup>, Arjun Narayan Ajmer Jayaswal<sup>1,†</sup>,  
Mohammad Hadi Zafarmand<sup>4</sup>, Yasaman Vali<sup>4</sup>, Jenny A. Lee<sup>4</sup>, Christina Kim Levick<sup>1</sup>,  
Liam Arnold Joseph Young<sup>1</sup>, Naaventhan Palaniyappan<sup>5</sup>, Chang-Hai Liu<sup>6,7</sup>,  
Guruprasad Padur Aithal<sup>5</sup>, Manuel Romero-Gómez<sup>6</sup>, M. Julia Brosnan<sup>8</sup>, Theresa A. Tuthill<sup>8</sup>,  
Quentin M. Anstee<sup>9,10</sup>, Stefan Neubauer<sup>1</sup>, Stephen A. Harrison<sup>1</sup>, Patrick M. Bossuyt<sup>4</sup>,  
Michael Pavlides<sup>1,2,3,\*</sup>, on behalf of the LITMUS Investigators<sup>#</sup>

<sup>1</sup>Oxford Centre for Clinical Magnetic Resonance Research, Radcliffe Department of Medicine, University of Oxford, Oxford, UK; <sup>2</sup>Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK; <sup>3</sup>NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and the University of Oxford, Oxford, UK; <sup>4</sup>Department of Epidemiology and Data Science, Amsterdam UMC, University of Amsterdam, The Netherlands; <sup>5</sup>NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK; <sup>6</sup>UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain; <sup>7</sup>Center for Infectious Diseases, West China Hospital of Sichuan University; Division of Infectious Diseases, State Key Laboratory of Biotherapy and Center of Infectious Disease, West China Hospital, Sichuan University, Chengdu, China; <sup>8</sup>Internal Medicine Research Unit, Pfizer Inc, Cambridge, MA, USA; <sup>9</sup>Liver Research Group, Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK; <sup>10</sup>NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals, NHS Foundation Trust, Newcastle upon Tyne, UK

**Background and Aims:** Vibration-controlled transient elastography (VCTE), point shear wave elastography (pSWE), 2-dimensional shear wave elastography (2DSWE), magnetic resonance elastography (MRE), and magnetic resonance imaging (MRI) have been proposed as non-invasive tests for patients with non-alcoholic fatty liver disease (NAFLD). This study evaluated their diagnostic accuracy for liver fibrosis and non-alcoholic steatohepatitis (NASH).

**Methods:** PubMed/MEDLINE, EMBASE and the Cochrane Library were searched for studies examining the diagnostic accuracy of these index tests, against histology as the reference standard, in adult patients with NAFLD. Two authors independently screened and assessed methodological quality of studies and extracted data. Summary estimates of sensitivity, specificity and area under the curve (sAUC) were calculated for fibrosis stages and NASH, using a random effects bivariate logit-normal model.

**Results:** We included 82 studies (14,609 patients). Meta-analysis for diagnosing fibrosis stages was possible in 53 VCTE, 11 MRE, 12 pSWE and 4 2DSWE studies, and for diagnosing NASH in 4 MRE studies. sAUC for diagnosis of significant fibrosis were: 0.83 for

VCTE, 0.91 for MRE, 0.86 for pSWE and 0.75 for 2DSWE. sAUC for diagnosis of advanced fibrosis were: 0.85 for VCTE, 0.92 for MRE, 0.89 for pSWE and 0.72 for 2DSWE. sAUC for diagnosis of cirrhosis were: 0.89 for VCTE, 0.90 for MRE, 0.90 for pSWE and 0.88 for 2DSWE. MRE had sAUC of 0.83 for diagnosis of NASH. Three (4%) studies reported intention-to-diagnose analyses and 15 (18%) studies reported diagnostic accuracy against pre-specified cut-offs.

**Conclusions:** When elastography index tests are acquired successfully, they have acceptable diagnostic accuracy for advanced fibrosis and cirrhosis. The potential clinical impact of these index tests cannot be assessed fully as intention-to-diagnose analyses and validation of pre-specified thresholds are lacking.

**Lay summary:** Non-invasive tests that measure liver stiffness or use magnetic resonance imaging (MRI) have been suggested as alternatives to liver biopsy for assessing the severity of liver scarring (fibrosis) and fatty inflammation (steatohepatitis) in patients with non-alcoholic fatty liver disease (NAFLD). In this study, we summarise the results of previously published studies on how accurately these non-invasive tests can diagnose liver fibrosis and inflammation, using liver biopsy as the reference. We found that some techniques that measure liver stiffness had a good performance for the diagnosis of severe liver scarring.

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) is becoming the most common cause of end-stage liver disease worldwide, and is

Keywords: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Biomarkers; Liver fibrosis; Transient elastography; Shear wave elastography; Magnetic resonance elastography; Iron-corrected T1; Diffusion-weighted imaging; deMILL; fibro-MRI; NASH-MRI.

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\* Corresponding author. Address: Oxford Centre for Clinical Magnetic Resonance Research (OCMR), Radcliffe Department of Medicine, University of Oxford, Level 0, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, United Kingdom.

E-mail address: [michael.pavlides@cardiov.ox.ac.uk](mailto:michael.pavlides@cardiov.ox.ac.uk) (M. Pavlides).

<sup>†</sup> Joint first authors

<sup>#</sup> See [supplementary information](#) for full list of investigators.  
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strongly associated with metabolic syndrome (obesity, type 2 diabetes mellitus, dyslipidaemia and hypertension).<sup>1</sup> NAFLD encompasses a spectrum of conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with or without liver fibrosis and cirrhosis.<sup>2</sup>

At the population level, most patients with NAFLD have simple steatosis and will not progress to more advanced stages of the disease. Even in patients who are identified as high risk and undergo liver biopsies, only a minority of patients will develop progressive fibrosis.<sup>3</sup> However, those with advanced fibrosis have poorer long-term outcomes.<sup>4–6</sup> Identifying this subgroup of high risk patients is one of the key issues in clinical care and drug trials. In the absence of any approved drug treatment, those at higher risk could benefit from lifestyle interventions and follow-up in secondary care. Furthermore, identifying patients with cirrhosis is important in order to enter them into surveillance for oesophageal varices and hepatocellular carcinoma. In clinical trials, diagnosis of NASH and histological staging of fibrosis are also important as these parameters define eligibility criteria and endpoints.

Histological classification of fibrosis and NASH remains the standard of practice, but the increasing burden of NAFLD renders its use unrealistic and inefficient. Liver biopsy is invasive, expensive, exhibits sampling variability, and is unacceptable to patients as a means of long-term dynamic monitoring of liver fibrosis stages.<sup>7</sup> Therefore, there has been much recent interest in developing robust, accurate and cost-effective non-invasive biomarkers to replace liver biopsy in severity assessment and risk stratification of patients with NAFLD.

Several non-invasive tests have emerged as promising alternatives for staging liver fibrosis and diagnosing NASH. Elastography-based techniques include vibration-controlled transient elastography (VCTE), point shear wave elastography (pSWE), 2-dimensional shear wave elastography (2DSWE), and magnetic resonance elastography (MRE). Magnetic resonance imaging (MRI) techniques include LiverMultiScan™ (LMS) to measure iron-corrected T1 (cT1), diffusion-weighted imaging (DWI), and detection of metabolic and liver injury (deMILI). Despite extensive experience with some of these index tests, significant questions remain about how best to use them in practice. None of these technologies have undergone sufficient validation to be granted regulatory approval for use in the context of clinical trials, while there remains a lack of consensus on thresholds for disease risk stratification in relation to histology.

In order to better understand the evolution of these tests and to summarise the literature to date, the aim of this study was to conduct a systematic review and meta-analysis evaluating the diagnostic performances of elastography and MRI index tests for the assessment of liver fibrosis and NASH in patients with NAFLD.

## Materials and methods

The protocol for this systematic review is available on PROSPERO: CRD42018116522. This study is being reported according to the PRISMA-DTA guidelines (Table S1).

### Target conditions

Liver fibrosis and NASH were the target conditions. Liver fibrosis was defined according to the NASH Clinical Research Network (CRN) histological classification.<sup>8</sup> The diagnostic accuracy of

index tests was assessed in the following dichotomised groups: F0 vs. F1–4, F0–1 vs. F2–4, F0–2 vs. F3–4, F0–3 vs. F4, and NASH vs. simple steatosis. For the purpose of this review, any definition of NASH was accepted.

### Index tests

The following index tests were assessed in this review: VCTE (FibroScan®, Echosens, Paris, France), pSWE (Virtual Touch Quantification (VTQ); Siemens Healthineers, Erlangen, Germany), 2DSWE (Aixplorer®, SuperSonic Imagine, Aix-en-Provence, France), MRE (Resoundant, Rochester, USA), cT1 measured using LMS (Perspectum, Oxford, UK), DWI, and deMILI. Each technique is summarised in Table S2.

We defined the technical failure as either unsuccessful valid measurements of an index test, unreliable measurement according to pre-defined quality criteria or poor-quality image acquisition such that analysis of data was not possible.

### Inclusion criteria

Studies in all languages reported in peer-reviewed journals or conference abstracts were included if they fulfilled the following criteria: i) reporting on adults ( $\geq 18$  years) with biopsy-proven NAFLD (data available on at least 10 patients); ii) index test performed within 6 months of biopsy; iii) liver histology according to the NASH CRN scoring system was used as the reference standard; iv) discrete data for NAFLD population could be extracted from mixed liver disease study cohort; v) estimates of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) or receiver operating characteristic curves (ROCs) for diagnosing fibrosis stages and distinguishing NASH from simple steatosis were reported.

### Exclusion criteria

Studies were excluded if they: i) included patients with coexisting liver disease (e.g. NAFLD and viral hepatitis in the same patient), ii) addressed a different context of use; iii) used an alternative histological classification system (e.g. METAVIR); iv) reported on using a pSWE or 2DSWE test other than what we specified in the index text section above; v) had insufficient data to calculate diagnostic accuracy estimates. For studies with missing data or where diagnostic performance was not reported separately for patients with NAFLD in a mixed liver disease cohort of patients, the corresponding or senior author was contacted by email to request the relevant data or results. The study was excluded if no reply was received within 28 calendar days.

### Literature search

A systematic web-based literature search of all publications in PubMed/MEDLINE, EMBASE and CENTRAL (Cochrane Library) was conducted in March 2018, January 2019 and July 2020 (see Table S3 for details of the search terms). Reference lists of related systematic reviews and included studies were searched manually to identify additional studies.

### Study selection

Search results were imported into an online platform for systematic review management (Covidence, Veritas Health Innovation, Melbourne, Australia. [www.covidence.org](http://www.covidence.org)) and duplicates were removed automatically. Titles and abstracts were screened first to identify potentially relevant papers, which were then assessed in full for eligibility. At least 2 researchers

conducted the screening of titles, abstracts, and full papers independently. Disagreements were resolved by reaching consensus between the researchers and if this was not possible, then a senior member of the team adjudicated. If multiple reports of the same study were identified, the most comprehensive and suitable publication related to our study was selected based on reaching a consensus among reviewers.

### Data extraction

Two researchers independently extracted data using a standardised data extraction sheet. Disagreements were resolved by consensus or, where not possible, by arbitration from a senior member of the review team. Data was collected on the study characteristics (country, affiliation, year of publication, type of study), patient characteristics (age, sex, ethnicity, BMI, presence of metabolic syndrome, laboratory parameters), details of index test, performance indices of index test (cut-off values, failure rates, sensitivity, specificity, PPV, NPV, AUROC), and quality of liver biopsy and histological fibrosis stages. Necessary data to calculate the number of true positives, false positives, true negatives and false negatives were extracted. If this was not reported, they were calculated from diagnostic test sensitivity, specificity, and prevalence provided in the study.

### Methodological quality assessment

Risk of bias and concerns about the applicability of study findings to the review question were assessed by 2 reviewers, independent of one another, using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.<sup>9</sup> Disagreements were resolved by consensus, if possible, and adjudicated by a third member of the review team otherwise.

### Evaluation of diagnostic accuracy

Classification tables were extracted and re-constructed for the performance of the index test for each of the pre-defined target conditions. For dichotomous classifications, study-specific estimates of sensitivity, specificity, PPV, NPV, positive likelihood ratio and negative likelihood ratio and their 95% CIs were calculated. Minimum acceptable performance of diagnostic accuracy was defined as sensitivity and specificity of at least 80%.<sup>10</sup> Graphical descriptive analysis of the included studies was performed using forest plots.

A meta-analysis was conducted whenever  $\geq 3$  studies with sufficient information for generating classification tables were available, within the same index test and target condition. In index tests without sufficient studies to conduct meta-analysis a narrative synthesis was conducted. When more than 1 cut-off value was presented, the cut-off value closest to the median value of all studies in the same group was selected for inclusion in the meta-analysis. We used a bivariate logit-normal random effects model to estimate the mean sensitivity, mean specificity and the respective variances and covariance. Summary receiver operator characteristic curves (sROC) were generated with 95% confidence regions and 95% prediction regions. The 95% confidence region is based on the confidence interval around the summary point and indicates that, based on the available data, we would expect the 'real value' to be within that region 95% of the time. The prediction region around the summary point indicates the region where we would expect results from a new study in the future to lie and is therefore wider than the confidence region as it goes beyond the uncertainty in the available

data. 95% CIs corresponding to summary AUC (sAUC) values were estimated via 500 bootstrap iterations.

A linear mixed effects model was used for modeling the multiple thresholds data of individual studies reporting more than 2 cut-offs.<sup>11,12</sup> The multiple thresholds model is a multi-level random effects model that enables the calculation of summary sensitivities and specificities of different cut-offs, and the calculation of the PPV and NPV, given the prevalence of the target condition. Sensitivity and specificity were combined at every recommended cut-off to produce a multiple-threshold sROC curve. In addition, PPV and NPV were also obtained, and cut-offs required to achieve minimum acceptable criteria were determined.

We did not attempt to construct funnel plots as it is well known that statistical tests based on funnel plot asymmetry cannot discriminate between publication bias and other sources of asymmetry, e.g. the effect of including multiple thresholds, in systematic reviews of diagnostic test accuracy studies.<sup>13</sup>

The statistical software R with the mada<sup>14</sup> and diagmeta<sup>15</sup> packages (Version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) was used in all analyses. *Post hoc* covariate meta-regression was performed for VCTE studies to explore potential sources of heterogeneity. The time interval between biopsy and VCTE, probe type and origin of study were examined as potential covariates. Reitsma-models were built using the mada R package with and without these covariates for each fibrosis stage group and compared using the likelihood ratio test statistic.

## Results

### Search results

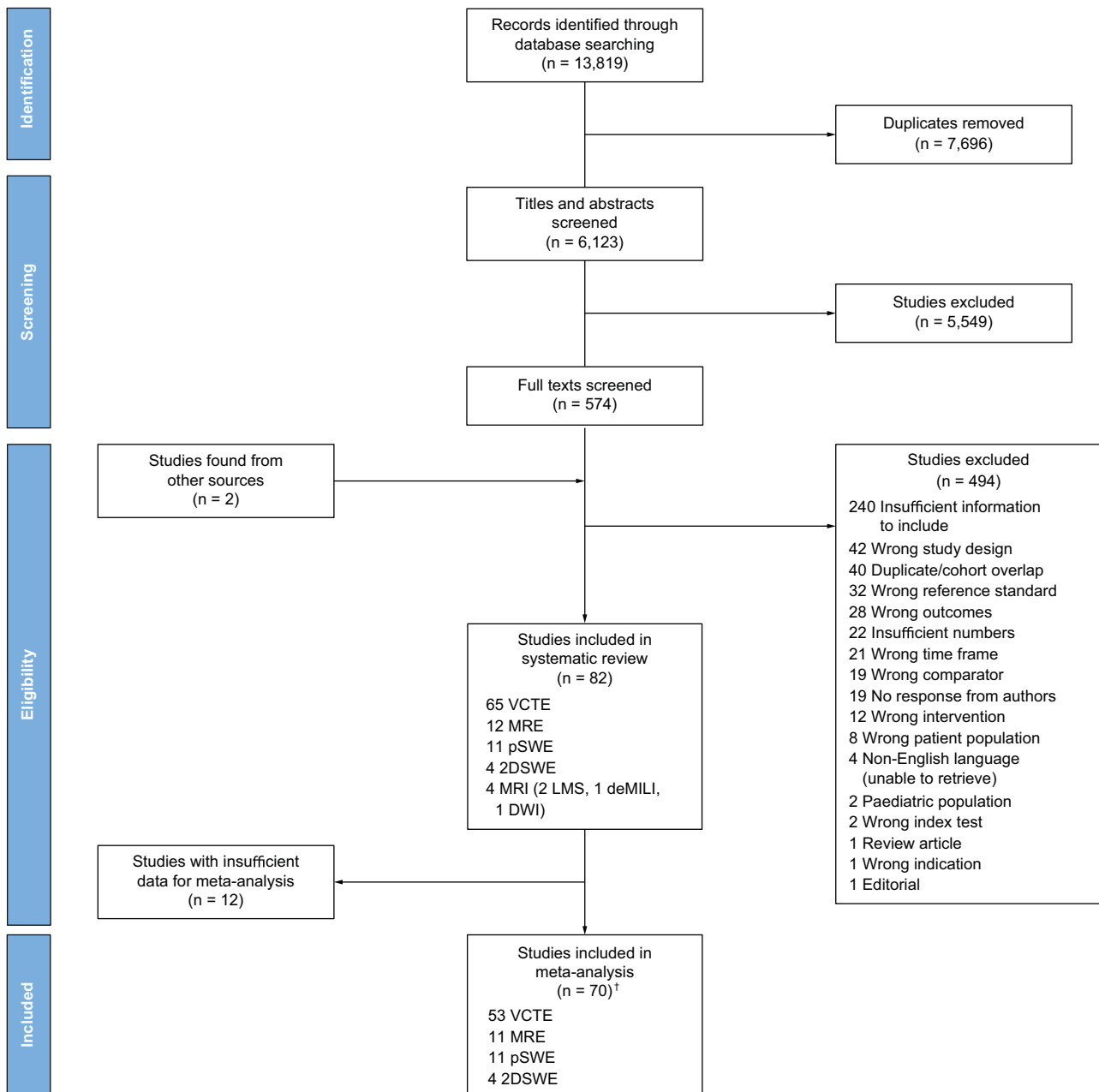
A total of 13,819 articles were identified and imported into Covidence from the electronic databases searches. After removing duplicates, we screened 6,123 articles. We found 574 articles for full-text review from the electronic searches and 2 from hand-search of reference list. We were able to include 82 studies (75 full-text reports and 7 conference abstracts) in the systematic review. After excluding 12 studies with insufficient data, 70 studies were included in the meta-analysis as shown in Fig. 1.

### Study characteristics

The characteristics of the VCTE,<sup>16–80</sup> MRE,<sup>39,49,62,81–89</sup> pSWE,<sup>19,24,25,42,47,50,84,90–94</sup> 2DSWE,<sup>25,47,95,96</sup> and MRI<sup>30,36,63,97</sup> studies included in the systematic review are summarised in Table 1. There were 73 prospective studies and 9 retrospective studies. Eleven studies compared 2 index tests and 2 studies compared 3 index tests. There were 55 single-centre and 27 multi-centre studies. Studies were from Europe (38%), Asia (38%), North America (18%), South America (4%) and Australia (2%). All studies were performed in a hospital setting.

### Study quality

The methodological quality of the studies assessed with the QUADAS-2 tool is summarised in Figs. S1–S5. There were only 2 studies with no risk of bias or applicability concerns.<sup>68,83</sup> Studies that did not report pre-defined cut-off values were judged as having high risk of bias in the index test domain of QUADAS-2. This included 80% of VCTE, 86% of MRE, 92% of pSWE, 100% of 2DSWE and 76% of MRI studies. The flow and timing domain was judged to have high risk or unclear risk of bias in 80% of VCTE,



**Fig. 1. PRISMA flow diagram of primary studies included in both the present systematic review and meta-analysis.** 2DSWE, 2-dimensional shear wave elastography; deMILI, detection of metabolic and liver injury; DWI, diffusion-weighted imaging; LMS, LiverMultiScan™; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; pSWE, point shear wave elastography; VCTE, vibration-controlled transient elastography.

33% of MRE, 91% of pSWE, 100% of 2DSWE, and 75% of MRI studies as these studies either excluded technical failures from their final diagnostic performance analysis or did not report them.

### Patient characteristics

In total, 14,609 patients with NAFLD were included in this review. There was a slight female preponderance (54%) with a mean or median age range of 35–63 years, mean or median BMI range of 27–48 kg/m<sup>2</sup>, and 35% mean prevalence of diabetes in studies that reported this metric. The study populations included patients with biopsy-proven NAFLD (83%), biopsy-proven NAFLD

reported in a mixed liver disease aetiology cohort (9%), and patients from bariatric clinics or surgery (8%).

### Index test characteristics

The range of technical failure of the index tests, when reported, were VCTE: 2–49%; MRE: 0–1%, pSWE: 0–43%; 2DSWE: 3–27%, and MRI: 5–18% (Table S4). Failure rates were not reported in 30% of VCTE, 39% of MRE, and 9% of pSWE studies. Cut-off values were pre-defined in only 20% of VCTE, 8% of MRE, 9% of pSWE, none of the 2DSWE and 25% of MRI studies (Table S5). Only 3 studies reported their intention-to-diagnose analyses.<sup>60,73,76</sup>



**Table 1. Characteristics of studies included in the systematic review.**

| Ref.        | Design     | Population  | Patients (n)                        | Age (years)        | Male (%) | BMI (kg/m <sup>2</sup> ) | T2DM (%) | HR (n; exp)  | ITR (n;exp)  |
|-------------|------------|---|-------------------------------------|--------------------|----------|--------------------------|----------|--------------|--|
| <b>VCTE</b> |            |   |                                     |                    |          |                          |          |              |  |
| 16          | MC, P, CS  | Chronic liver disease: Suspected NAFLD                  | 25                                  | —                  | —        | —                        | —        | 1            | —  |
| 17 ‡        | SC, P, UC  | Bariatric clinic  | 60                                  | —                  | —        | 48 ± 7                   | —        | 1            | —  |
| 18          | MC, P, RCT | Biopsy-proven NASH                                      | F0-2: 284<br>F3-4: 1,323            | —                  | —        | —                        | —        | 1            | —  |
| 19          | SC, P, CS  | Suspected NAFLD   | Overweight: 61<br>Obese: 26         | 51 ± 13<br>53 ± 10 | 51<br>58 | 28 ± 2<br>36 ± 5         | 18<br>42 | 1            | 1  |
| 20          | SC, P, CS  | Suspected NAFLD   | 88                                  | 46 ± 9             | 57       | 30 ± 5                   | 19       | 1            | —  |
| 21          | MC, P, CS  | Biopsy-proven NAFLD                                     | 452                                 | 56 ± 12            | 60       | 31 ± 5                   | 47       | 1            | 1 (>500 examinations)  |
| 22          | MC, P, CS  | Biopsy-proven NAFLD                                     | Training: 625<br>Validation: 313    | 56 ± 12<br>57 ± 12 | 60<br>55 | 32 ± 6<br>32 ± 6         | 51<br>52 | >1           | >1 (>500 examinations)   |
| 23          | SC, P, CS  | Suspected NAFLD   | 81                                  | 54 ± 10            | 26       | 33 ± 5                   | 61       | 1            | 1  |
| 24          | SC, P, CS  | Chronic liver disease: Suspected NAFLD                  | M-probe: 48<br>XL-probe: 49         | 55 ± 14<br>55 ± 13 | 67<br>63 | 30 ± 5<br>30 ± 5         | 48<br>43 | 1 (26 years) | >1 (>5,000 examinations)   |
| 25          | MC, P, CS  | Biopsy-proven NAFLD                                     | 223                                 | 57 ± 12            | 59       | 32 ± 6                   | 69       | >1           | >1 (>5,000 examinations)   |
| 26          | SC, P, CS  | Biopsy-proven NAFLD                                     | Training: 101<br>Validation: 46     | 50 ± 11<br>51 ± 13 | 52<br>61 | 30 ± 4<br>29 ± 6         | 53<br>52 | 1            | >1   |
| 27          | MC, P, CC  | Biopsy-proven NAFLD                                     | 57                                  | 50 ± 10            | 49       | 30 ± 5                   | —        | 1            | —  |
| 28 ‡        | MC, P, CS  | Suspected NAFLD   | 176                                 | —                  | 56       | 36                       | —        | 1            | —  |
| 29          | SC, P, CS  | Chronic liver disease: Suspected NAFLD                  | 25                                  | 46 ± 47            | 59       | 26 ± 4                   | —        | 1            | —  |
| 30          | MC, P, CS  | Biopsy-proven NAFLD                                     | 47                                  | —                  | 50       | 34 ± 5                   | 47       | >1           | >1   |
| 31          | MC, P, CS  | Suspected NAFLD   | 373                                 | 54 (19-77)†        | 55       | 34(9)†                   | 52       | 2            | >1   |
| 32          | SC, P, CS  | Biopsy-proven NASH                                      | 63                                  | 47 ± 8             | 62       | —                        | —        | 1            | 1  |
| 33 ‡        | SC, R, CS  | Biopsy-proven NAFLD                                     | 238                                 | —                  | —        | 31(5)†                   | —        | —            | —  |
| 34          | SC, P, CS  | Chronic liver disease: Suspected NAFLD                  | 72                                  | —                  | 72       | 28                       | —        | 1            | >1   |
| 35          | SC, P, CS  | Chronic liver disease: Suspected NAFLD                  | 58                                  | —                  | 76       | 28                       | —        | 1            | >1   |
| 36          | MC, P, CS  | Biopsy-proven NAFLD                                     | 126                                 | 51 ± 12            | 62       | 31 ± 5                   | 37       | —            | —  |
| 37          | SC, P, CS  | Bariatric surgery                                       | 76                                  | 38 ± 10            | 21       | 45 ± 7                   | —        | 1            | 1  |
| 38 ‡        | MC, R, UC  | Biopsy-proven NAFLD                                     | 98                                  | 52 ± 11            | 43       | 37 ± 7                   | —        | —            | —  |
| 39          | SC, P, CS  | Biopsy-proven NAFLD                                     | 142                                 | 58 ± 15            | 57       | 28 ± 5                   | 50       | 2            | 1  |
| 40          | MC, P, CS  | Biopsy-proven NAFLD                                     | 224                                 | 59 (17-85)†        | 46       | 28(17-44)†               | 55       | 2            | >1 (>500 examinations)   |
| 41          | SC, P, CS  | Bariatric surgery                                       | Training: 73<br>Validation: 50      | 35 ± 8<br>36 ± 9   | 32<br>26 | 41 ± 6<br>40 ± 5         | 16<br>26 | 2            | —  |
| 42          | SC, P, CS  | Bariatric surgery and non-bariatric biopsy-proven NAFLD | Bariatric: 41<br>Non-bariatric: 45  | 46 ± 10<br>55 ± 11 | 32<br>50 | 47<br>28 ± 4             | —        | 1            | —  |
| 43          | SC, P, CS  | Biopsy-proven NAFLD                                     | Non-cirrhotic: 120<br>Cirrhotic: 85 | 39 ± 13<br>53 ± 9  | 75<br>65 | 26 ± 4<br>27 ± 4         | 17<br>48 | 2            | —  |
| 44          | SC, P, CS  | Suspected NAFLD in diabetes                             | 94                                  | —                  | —        | —                        | 100      | 1            | >1 (>2,000 examinations, > 5 years)  |
| 45          | SC, P, CS  | Biopsy-proven NAFLD                                     | 126                                 | —                  | —        | —                        | —        | 1            | >1   |
| 46          | MC, P, CS  | Suspected NAFLD   | 183                                 | 41 ± 14            | 61       | 28 ± 4                   | 14       | 1            | 1  |
| 47          | SC, P, CS  | Biopsy-proven NAFLD                                     | 94                                  | 56 ± 13            | 44       | 27 ± 4                   | 39       | 1            | 1 (>1,000 examinations)  |
| 48          | SC, R, CS  | Biopsy-proven NASH                                      | 184                                 | 45 ± 15            | 69       | 29†                      | 38       | 1            | —  |
| 49          | SC, P, CS  | Biopsy-proven NAFLD                                     | 130                                 | 51(41-62)†         | 41       | 30(26-33)†               | 42       | 2            | 2  |
| 50          | SC, P, CS  | Biopsy-proven NAFLD                                     | 100                                 | —                  | —        | —                        | —        | 1            | 2 (>200 examinations)  |
| 51          | SC, R, CS  | Suspected NAFLD   | 215                                 | —                  | 55       | 27(25-29)†               | 55       | 2            | >1 (>50 examinations)  |
| 52          | SC, P, CS  | Biopsy-proven NASH                                      | 72                                  | —                  | 71       | 29†                      | —        | 1            | —  |
| 53          | SC, P, CS  | Biopsy-proven NAFLD                                     | 131                                 | 50 ± 12            | 53       | —                        | 47       | 1            | —  |
| 54 ‡        | MC, P, CS  | Biopsy-proven NAFLD                                     | 162                                 | —                  | —        | —                        | —        | —            | —  |
| 55          | MC, P, CS  | Chronic liver disease: Suspected NAFLD                  | 75                                  | —                  | —        | —                        | 56       | 2            | 9, (4 >500 examinations; 1 >200 examinations; 3 >100 examinations; and 1 >50 examinations) |

(continued on next page)

Table 1. (continued)

| Ref.            | Design    | Population                             | Patients (n)         | Age (years)            | Male (%) | BMI (kg/m <sup>2</sup> ) | T2DM (%) | HR (n; exp)   | ITR (n;exp)                                       |
|-----------------|-----------|--|----------------------|------------------------|----------|--------------------------|----------|---------------|---|
| 56              | SC, P, CS | Bariatric surgery                      | 100                  | 43 ± 1                 | 19       | 42 ± 1                   | 15       | 1             | >1  |
| 57              | SC, P, CS | Bariatric surgery                      | Retrospective: 194   | 41 ± 1                 | 22       | 44                       | 18       | 1             | >1  |
|                 |           |  | Prospective: 123     | 40 ± 1                 | 26       | 44 ± 1                   | 22       |               |   |
| 58              | MC, P, CS | Suspected NAFLD                        | Training: 96         | 61(20-84)              | 43       | 28 <sup>†</sup>          | 60       | 2             | 1 (>500 examinations)                             |
|                 |           |  | Validation: 103      | 63(23-90)              | 45       | 28 <sup>†</sup>          | 65       |               |   |
|                 |           |  |                      |                        |          |                          |          |               |   |
| 59              | SC, P, CS | Biopsy-proven NAFLD                    | 163                  | 56 ± 14                | 49       | 27 ± 4                   | —        | 1             | >1  |
| 60              | MC, P, CS | Bariatric surgery                      | 66                   | 46 ± 12                | 32       | 45 ± 9                   | —        | 1             | 2 (>2,000 examinations)                           |
| 61 <sup>‡</sup> | SC, P, CS | Biopsy-proven NAFLD                    | 208                  | 53 ± 12                | 67       | —                        | 30       | —             | —   |
| 62              | SC, P, CS | Biopsy-proven NAFLD                    | 97                   | 51 ± 15                | 43       | 30 ± 5                   | 30       | 1             | 1   |
| 63              | SC, P, CS | Suspected NAFLD                        | 71                   | 53 ± 12                | 61       | 33(28-38) <sup>†</sup>   | 35       | 2             | >1  |
| 64              | SC, P, CS | Biopsy-proven NAFLD                    | 146                  | 44 ± 13                | 71       | 29 ± 4                   | 14       | 1             | 1 (>100 examinations)                             |
| 65              | MC, R, CS | Biopsy-proven NAFLD                    | Training: 179        | 45 ± 13                | 68       | 29 ± 4                   | 20       | 1             | 1 (>100 examinations)                             |
|                 |           |  | Validation: 142      | 44 ± 12                | 72       | 27 ± 3                   | 16       |               |   |
| 66              | SC, P, CS | Biopsy-proven NAFLD                    | 253                  | 45 ± 13                | 70       | 29 ± 4                   | 20       | 1             | 1 (>300 examinations)                             |
| 67              | MC, P, CS | Biopsy-proven NAFLD                    | 761                  | 51 ± 13                | 60       | 30 ± 5                   | 55       | 1             | 1 (>300 examinations)                             |
| 68              | MC, P, CS | Biopsy-proven NAFLD                    | 324                  | 54 ± 13                | 44       | —                        | 46       | 1             | 1 (>300 examinations)                             |
| 69              | SC, P, CS | Chronic liver disease: Suspected NAFLD | 105                  | 45 ± 12                | 72       | 28 ± 4                   | —        | 1             | —   |
| 70              | SC, P, CS | Biopsy-proven NAFLD                    | 171                  | 57 ± 14                | 50       | 28 ± 5                   | —        | 1             | —   |
| 71              | MC, P, CS | Biopsy-proven NAFLD                    | 101                  | —                      | —        | —                        | —        | 3             | >1, >300 examinations                             |
| 72              | SC, P, CS | Biopsy-proven NAFLD                    | 249                  | 58 ± 15                | 48       | 27 ± 4                   | 57       | 1             | 1   |
| 73              | MC, P, CS | Suspected NAFLD                        | 140                  | —                      | —        | —                        | —        | 2             | —   |
| 74              | SC, P, CS | Biopsy-proven NAFLD                    | 120                  | 50 ± 13                | 63       | 31(29-35) <sup>†</sup>   | 23       | >1            | 2 (>500 examinations)                             |
| 75              | MC, P, CS | Biopsy-proven NAFLD                    | 246                  | 51 ± 11                | 55       | 28 ± 5                   | 36       | 2             | >1  |
| 76              | MC, P, CS | Biopsy-proven NAFLD                    | 193                  | 52 ± 11                | 57       | 29 ± 5                   | 51       | 2             | >1 (>50 examinations)                             |
| 77              | MC, P, CS | Biopsy-proven NAFLD                    | 496                  | —                      | —        | —                        | —        | 2             | >1 (>50 examinations)                             |
| 78              | MC, P, CS | Biopsy-proven NAFLD                    | 97                   | 52 ± 14                | 41       | 29 ± 4                   | —        | 2             | 1   |
| 79              | MC, P, CS | Biopsy-proven NAFLD                    | 292                  | 45 ± 13                | 46       | 32 ± 7                   | 11       | >1            | 1   |
| 80              | SC, P, CS | Chronic liver disease: Suspected NAFLD | 13                   | —                      | 77       | 31                       | —        | —             | —   |
| <b>MRE</b>      |           |  |                      |                        |          |                          |          |               |   |
| 81              | SC, R, CS | Biopsy-proven NAFLD                    | 58                   | 52                     | 17       | 38                       | —        | 1 (6 years)   | 1 (4 years)                                       |
| 82              | SC, P, CS | Biopsy-proven NAFLD                    | 49                   | 54 ± 13                | 14       | 32 ± 5                   | —        | —             | 1 (15 years)                                      |
| 83              | SC, P, CS | Biopsy-proven NAFLD                    | 102                  | 51 ± 14                | 59       | 32 ± 6                   | 26       | 1             | 1 (≥6 months)                                     |
| 84              | SC, P, CS | Biopsy-proven NAFLD                    | 125                  | 49 ± 15                | 46       | 32 ± 7                   | 26       | 1             | 1 (≥6 months)                                     |
| 39              | SC, P, CC | Biopsy-proven NAFLD                    | 142                  | 58 ± 15                | 57       | 28 ± 5                   | 50       | 2             | >1  |
| 85              | SC, R, CS | Suspected NAFLD                        | 142                  | 53 ± 13                | 27       | 36 ± 7                   | 28       | >1            | >2  |
| 86              | SC, P, CS | Suspected NASH                         | 47                   | 51 ± 13                | 34       | 28 ± 6                   | —        | 1 (>15 years) | 2 (>25 and >6 years)                              |
| 49              | SC, P, CS | Biopsy-proven NAFLD                    | 130                  | 51(41-62) <sup>†</sup> | 41       | 30(26-33) <sup>†</sup>   | 42       | 2             | 1   |
| 87 <sup>‡</sup> | SC, P, CS | Biopsy-proven NAFLD                    | 52                   | 50 ± 13                | 52       | 32 ± 5                   | —        | 1             | 1 (≥6 months)                                     |
| 88              | SC, P, CS | Biopsy-proven NAFLD                    | 117                  | 50 ± 13                | 44       | 32 ± 5                   | 34       | 1             | 1 (≥6 months)                                     |
| 89              | SC, P, CS | Biopsy-proven NAFLD                    | 99                   | 50 ± 14                | 44       | 32 ± 5                   | 33       | 1             | 1 (≥6 months)                                     |
| 62              | SC, P, CS | Suspected NAFLD                        | 104                  | 51 ± 15                | 43       | 30 ± 5                   | 28       | 1             | 1 (≥6 months)                                     |
| <b>pSWE</b>     |           |  |                      |                        |          |                          |          |               |   |
| 19              | SC, P, CS | Suspected NAFLD                        | Overweight: 61       | 51 ± 13                | 51       | 28 ± 2                   | 18       | 1             | 1   |
|                 |           |  | Obese: 26            | 53 ± 10                | 58       | 36 ± 5                   | 42       |               |   |
| 24              | SC, P, CS | Chronic liver disease: Suspected NAFLD | 60                   | 56 ± 13                | 67       | 30 ± 5                   | 43       | 1 (26 years)  | 4 (9-11 years, >6 months ARFI, >100 examinations) |
| 25              | MC, P, CS | Biopsy-proven NAFLD                    | 236                  | 57 ± 12                | 59       | 32 ± 6                   | 65       | >1            | 6 (>2 years)                                      |
| 84              | SC, P, CS | Biopsy-proven NAFLD                    | 125                  | 49 ± 15                | 46       | 32 ± 7                   | 26       | 1             | 1   |
| 90              | SC, P, CS | Biopsy-proven NAFLD                    | Simple steatosis: 21 | 47                     | 40       | 29                       | —        | 1 (25 years)  | —   |
|                 |           |  | NASH: 43             | 51                     | 47       | 30                       |          |               |   |
| 91              | SC, P, CS | Biopsy-proven NAFLD                    | 315                  | 55                     | 51       | 27 <sup>†</sup>          | 38       | 1             | >1  |

(continued on next page)

Table 1. (continued)

| Ref.         | Design    | Population                        | Patients (n)                       | Age (years)            | Male (%) | BMI (kg/m <sup>2</sup> ) | T2DM (%) | HR (n; exp)  | ITR (n;exp)                           |
|--------------|-----------|-----------------------------------|------------------------------------|------------------------|----------|--------------------------|----------|--------------|---------------------------------------|
| 42           | SC, P, CS | Bariatric surgery                 | Bariatric: 41<br>Non-bariatric: 48 | 46 ± 10<br>55 ± 11     | 32<br>50 | 47<br>28 ± 4             | —        | 1            | >1                                    |
| 47           | SC, P, CS | Suspected NAFLD                   | 83                                 | 56 ± 13                | 44       | 27 ± 4                   | 45       | 1            | 2 (10 and 13 years)                   |
| 92           | SC, P, CS | Suspected and biopsy-proven NAFLD | 51                                 | —                      | —        | —                        | —        | >1           | >1 (3-20 years)                       |
| 93           | SC, P, CS | Biopsy-proven NAFLD               | 135                                | —                      | 38       | —                        | —        | 1            | 5                                     |
| 94           | SC, R, CS | Biopsy-proven NAFLD               | 67                                 | 35 ± 13                | 69       | —                        | —        | 1            | —                                     |
| <b>2DSWE</b> |           |                                   |                                    |                        |          |                          |          |              |                                       |
| 25           | MC, P, CS | Biopsy-proven NAFLD               | 232                                | 57 ± 12                | 59       | 32 ± 6                   | 66       | 1            | >1                                    |
| 47           | SC, P, CS | Suspected NAFLD                   | 83                                 | 56 ± 13                | 44       | 27 ± 4                   | 45       | 1            | 1 (12 years)                          |
| 95           | SC, R, CS | Suspected and biopsy-proven NAFLD | 116                                | 51 ± 12                | 47       | 31 ± 5                   | 33       | 1 (30 years) | 6                                     |
| 96           | SC, P, CS | Biopsy-proven NAFLD               | 71                                 | 51 ± 16                | 65       | 29 ± 5                   | —        | 1            | 1 (>10 years ultrasound, >1 year SWE) |
| <b>MRI</b>   |           |                                   |                                    |                        |          |                          |          |              |                                       |
| 30           | MC, P, CS | Biopsy-proven NAFLD               | 50                                 | 54(18-73) <sup>†</sup> | 56       | 34 ± 5                   | 44       | >1           | —                                     |
| 36           | MC, P, CS | Biopsy-proven NAFLD               | 126                                | 51 ± 12                | 62       | 31 ± 5                   | 37       | 1            | 2                                     |
| 97           | SC, P, CS | Suspected NAFLD                   | 59                                 | 54 ± 9                 | 17       | 32                       | 100      | 1 (28 years) | 1 (10 years)                          |
| 63           | SC, P, CS | Suspected NAFLD                   | 71                                 | 53 ± 12                | 60       | 33 (28-38) <sup>†</sup>  | 35       | 2            | 2                                     |

— Not reported or unable to derive. CC, case-control; CS, cross-sectional; exp, experience; HR, histology readers; ITR, index test readers; MC, multi-centre; P, prospective; R, retrospective; SC, single-centre; T2DM, type 2 diabetes mellitus. <sup>†</sup>Reported as median (range). <sup>‡</sup>Abstracts.

**Liver biopsy characteristics**

Biopsy samples were evaluated by more than 1 pathologist in 29% of studies and a single pathologist in 62% of studies. It was not clear how the biopsies were reported in the remaining 9% of studies (Table 1). Consensus was sought between pathologists in 5% of studies. The size of the biopsy needle was reported in 43% of studies, length of biopsy specimen (or minimum acceptable quality criteria) in 67% of studies and number of portal tracts (or minimum acceptable quality criteria) in 39% of studies (Table S6).

**Results of meta-analysis**

*Diagnosis of any fibrosis (F0 vs. F1-4)*

The diagnostic accuracy in detecting any degree of fibrosis (≥F1) was investigated by the fewest studies (14 VCTE (n = 1,064), 6 MRE (n = 391), and 4 pSWE (n = 276); Table 2; Figs. S6-S8 for forest plots). These studies reported the poorest classification performance and no index test met the minimum acceptable performance for diagnostic accuracy. The respective sAUC, sensitivity and specificity for diagnosing stage ≥F1 were VCTE: 0.82, 78%, 72%; MRE: 0.87, 71%, 85%; and pSWE: 0.77, 64%, 76%. The summary point estimate of the mean with a 95% confidence region and 95% prediction region for each index test is shown in Fig. 2.

*Diagnosis of significant fibrosis (F0-1 vs. F2-4)*

The diagnostic accuracy in detecting significant fibrosis (≥F2) was investigated in 37 VCTE (n = 2,763), 6 MRE (n = 209), 9 pSWE (n = 805), and 4 2DSWE (n = 488) studies (Table 2; Figs. S9-S12 for forest plots). None of the index tests met the minimum acceptable performance for diagnostic accuracy. The respective sAUC, sensitivity and specificity for diagnosing stage ≥F2 were VCTE: 0.83, 80%, 73%; MRE: 0.91, 78%, 89%; pSWE: 0.86, 69%, 85%; and 2DSWE: 0.75, 71%, 67%. The summary point estimate of the mean, with a 95% confidence region and 95% prediction region for each index test is shown in Fig. 3.

*Diagnosis of advanced fibrosis (F0-2 vs. F3-4)*

The diagnostic accuracy in detecting advanced fibrosis (≥F3) was investigated by most studies (44 VCTE (n = 4,219), 10 MRE (n = 214), 11 pSWE (n = 1,209), and 4 2DSWE (n = 488); Table 2; Figs. S13-S16 for forest plots). The respective sAUC, sensitivity and specificity for diagnosing stage ≥F3 were VCTE: 0.85, 80%, 77%; MRE: 0.92, 83%, 89%; pSWE: 0.89, 80%, 86%; and 2DSWE: 0.72, 72%, 72%. MRE and pSWE met the minimum acceptable criteria for diagnostic accuracy. The summary point estimate of the mean with a 95% confidence region and 95% prediction region for each index test is shown in Fig. 4.

A multiple-threshold meta-analysis was performed in 6 primary studies (n = 1,278) reporting more than 2 cut-offs for VCTE. The sAUC was 0.85, and the Youden-index was maximised by an 8.7 kPa cut-off with 80% sensitivity and 76% specificity (Fig. S17). Predictive values for various cut-offs and prevalences are presented in Table S7. No cut-off met the minimum acceptance criteria of providing a sensitivity and specificity of 80%. However, a cut-off of 8.9 kPa was associated with 80% sensitivity and 77% specificity and a cut-off of 9.5 kPa was associated with 76% sensitivity and 80% specificity.

*Diagnosis of cirrhosis (F0-3 vs. F4)*

The diagnostic accuracy in detecting cirrhosis (F4) was investigated in 22 VCTE (n = 337), 5 MRE (n = 41), 8 pSWE (n = 759), and



**Table 2. Summary diagnostic performance of VCTE, MRE, pSWE and 2DSWE for the detection of fibrosis stages in NAFLD, and diagnostic performance of MRE for the diagnosis of NASH.**

|                    | Studies, n (patients; n) | Prevalence, % (95% CI) | Cut-off range | sAUC (95%CI)     | sSe, % (95% CI)   | sSp, % (95% CI)   |
|--------------------|--------------------------|------------------------|---------------|------------------|-------------------|-------------------|
| <b>VCTE (kPa)</b>  |                          |                        |               |                  |                   |                   |
| F≥1                | 14 (1,064)               | 67 (23–94)             | 5.3–8.2       | 0.82 (0.78–0.85) | 78 (73–82)        | 72 (65–79)        |
| F≥2                | 37 (2,763)               | 45 (5–77)              | 3.8–10.2      | 0.83 (0.80–0.87) | 80 (76–83)        | 73 (68–77)        |
| F≥3                | 44 (4,219)               | 25 (5–54)              | 6.8–12.9      | 0.85 (0.83–0.87) | 80 (77–83)        | 77 (74–80)        |
| F=4                | 22 (337)                 | 9 (3–31)               | 6.9–19.4      | 0.89 (0.84–0.93) | 76 (70–82)        | 88 (85–91)        |
| <b>MRE (kPa)</b>   |                          |                        |               |                  |                   |                   |
| F≥1                | 6 (391)                  | 60 (54–90)             | 2.50–3.14     | 0.87 (0.80–0.94) | 71 (60–81)        | 85 (78–91)        |
| F≥2                | 6 (209)                  | 31 (25–54)             | 2.86–4.14     | 0.91 (0.80–0.97) | 78 (67–85)        | 89 (83–94)        |
| F≥3                | 10 (214)                 | 19 (12–32)             | 2.99–4.80     | 0.92 (0.88–0.95) | <b>83 (77–88)</b> | <b>89 (86–92)</b> |
| F=4                | 5 (41)                   | 8 (6–9)                | 3.35–6.70     | 0.90 (0.81–0.95) | <b>81 (66–90)</b> | <b>90 (85–94)</b> |
| NASH               | 4 (224)                  | 69 (51–78)             | 2.53–3.26     | 0.83 (0.69–0.91) | 65 (46–80)        | 83 (69–91)        |
| <b>pSWE (m/s)</b>  |                          |                        |               |                  |                   |                   |
| F≥1                | 4 (276)                  | 73 (58–95)             | 1.11–1.81     | 0.77 (0.55–0.92) | 64 (48–77)        | 76 (65–84)        |
| F≥2                | 9 (805)                  | 46 (17–73)             | 1.18–1.81     | 0.86 (0.78–0.90) | 69 (59–77)        | 85 (80–88)        |
| F≥3                | 11 (1,209)               | 30 (17–52)             | 1.34–4.24     | 0.89 (0.83–0.95) | <b>80 (70–88)</b> | <b>86 (82–92)</b> |
| F=4                | 8 (759)                  | 17 (6–32)              | 1.36–2.54     | 0.90 (0.82–0.95) | 76 (59–87)        | 88 (82–92)        |
| <b>2DSWE (kPa)</b> |                          |                        |               |                  |                   |                   |
| F≥2                | 4 (488)                  | 55 (26–71)             | 8.3–11.6      | 0.75 (0.58–0.87) | 71 (56–83)        | 67 (43–84)        |
| F≥3                | 4 (488)                  | 36 (16–45)             | 9.3–13.1      | 0.72 (0.60–0.84) | 72 (65–78)        | 72 (52–86)        |
| F=4                | 3 (372)                  | 15 (7–16)              | 14.4–15.7     | 0.88 (0.81–0.91) | 78 (50–93)        | 84 (74–90)        |

Bold text indicates that the test met the minimum acceptable criteria of at least 80% sensitivity and specificity. sAUC, summary area under the curve; sSe, summary sensitivity; sSp, summary specificity.

3 2DSWE (n = 372) studies (Table 2; Figs. S18–S21 for forest plots). The respective sAUC, sensitivity and specificity for diagnosing stage F4 were VCTE: 0.89, 76%, 88%; MRE: 0.90, 81%, 90%; pSWE: 0.90, 76%, 88%; and 2DSWE: 0.88, 78%, 84%. Only MRE met the minimum acceptable criteria for diagnostic accuracy. The summary point estimate of the mean with a 95% confidence region and 95% prediction region for each index test modality is shown in Fig. 5.

#### Diagnosis of steatohepatitis (NASH vs. simple steatosis)

There were 5 VCTE studies<sup>30,39,46,49,62</sup> and 1 pSWE study<sup>90</sup> that reported the diagnostic accuracy of liver stiffness in distinguishing NASH from simple steatosis. Data pooling for meta-analysis in the VCTE papers was not possible due to variability in reporting performance characteristics. The diagnostic accuracy in detecting NASH was investigated in 4 MRE (n = 224) studies. The sAUC, sensitivity and specificity were 0.83, 65% and 83%, respectively (Table 2, Fig. 6), and these did not meet the minimum acceptable criteria for diagnostic accuracy.

#### Narrative synthesis of MRI techniques

A narrative synthesis of the MRI results is included in the [supplementary information](#).

#### Exploratory study of sources of heterogeneity in VCTE studies

Neither probe type nor study origin defined by the continent where the study was conducted were significant covariates of diagnostic performance for any of the fibrosis stages. Additionally, we found no significant difference in the diagnostic performance when comparing studies only allowing 3 months between VCTE and biopsy to all studies. Complete results of covariate testing, as well as sensitivity and subgroup analyses can be found in [Tables S8–S11](#).

## Discussion

There is an increasing clinical and research need to reduce reliance on liver biopsy to assess NAFLD disease severity given its

increasing prevalence worldwide. In this study, we conducted a systematic review of 82 studies (14,609 patients) and meta-analysis of 70 studies (12,547 patients) to summarise the evidence for the diagnostic accuracy of 5 elastography and imaging modalities in the non-invasive diagnosis of liver fibrosis and NASH in adult patients with NAFLD.

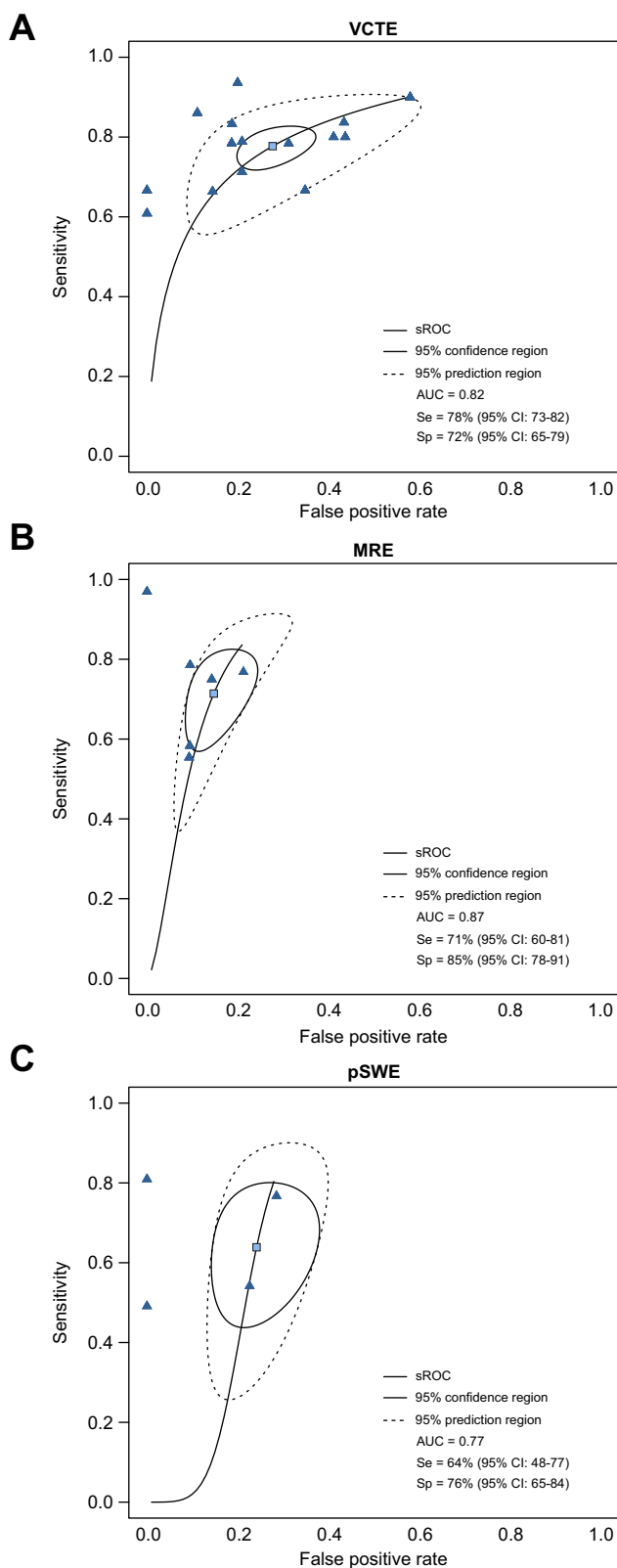
We defined the minimum acceptable performance criteria of greater than 80% for both sensitivity and specificity as the benchmark for diagnostic accuracy tests in NAFLD. In those patients with successful measurements of liver stiffness, these criteria were met by MRE and pSWE for the diagnosis of advanced fibrosis and by MRE for the diagnosis of cirrhosis, with the caveat that the lower limit of the 95% CIs of summary sensitivities was <80%. Further validation of these tests is therefore needed before they can be confidently recommended as alternatives to liver biopsy.

Whilst the diagnostic performance for both MRE and pSWE were similar with AUC >0.90, the 95% confidence and prediction regions for MRE appear to be smaller than for pSWE, suggesting that there was less heterogeneity in the MRE studies.

MRE was the only modality with sufficient studies for meta-analysis for the diagnosis of NASH. Even though the diagnostic accuracy was good, this did not reach the pre-defined minimum acceptable criteria defined in our study.

Meta-analysis on MRI data was impossible due to the low number of primary studies, and, as a result, the performance of cT1 by LMS, deMILI and DWI could not be evaluated using the minimum acceptable criteria. We do note, however, that cT1 had typically high sensitivity and low specificity, deMILI had moderate sensitivity and specificity and DWI had poor to moderate sensitivity and specificity.

VCTE was the modality with most available data. Even though it did not meet the minimum acceptable criteria for any of the target conditions, these results should be interpreted with some caution as some studies did not use the XL probe or may not have used it according to the manufacturer's recommendations. We did however find that the probe used was not a significant factor of heterogeneity in the VCTE studies. Recent improvements of



**Fig. 2. sROC curves and test performance to detect any degree of fibrosis (F0 vs. F1-4).** A bivariate logit-normal random effects model was used to estimate the mean sensitivity and mean specificity for liver stiffness measured using (A) VCTE, (B) MRE, and (C) pSWE. MRE, magnetic resonance elastography; pSWE, point shear wave elastography; sROC, summary receiver operating characteristic; VCTE, vibration-controlled transient elastography.

VCTE have been reported,<sup>98,99</sup> but these were not included in this study.

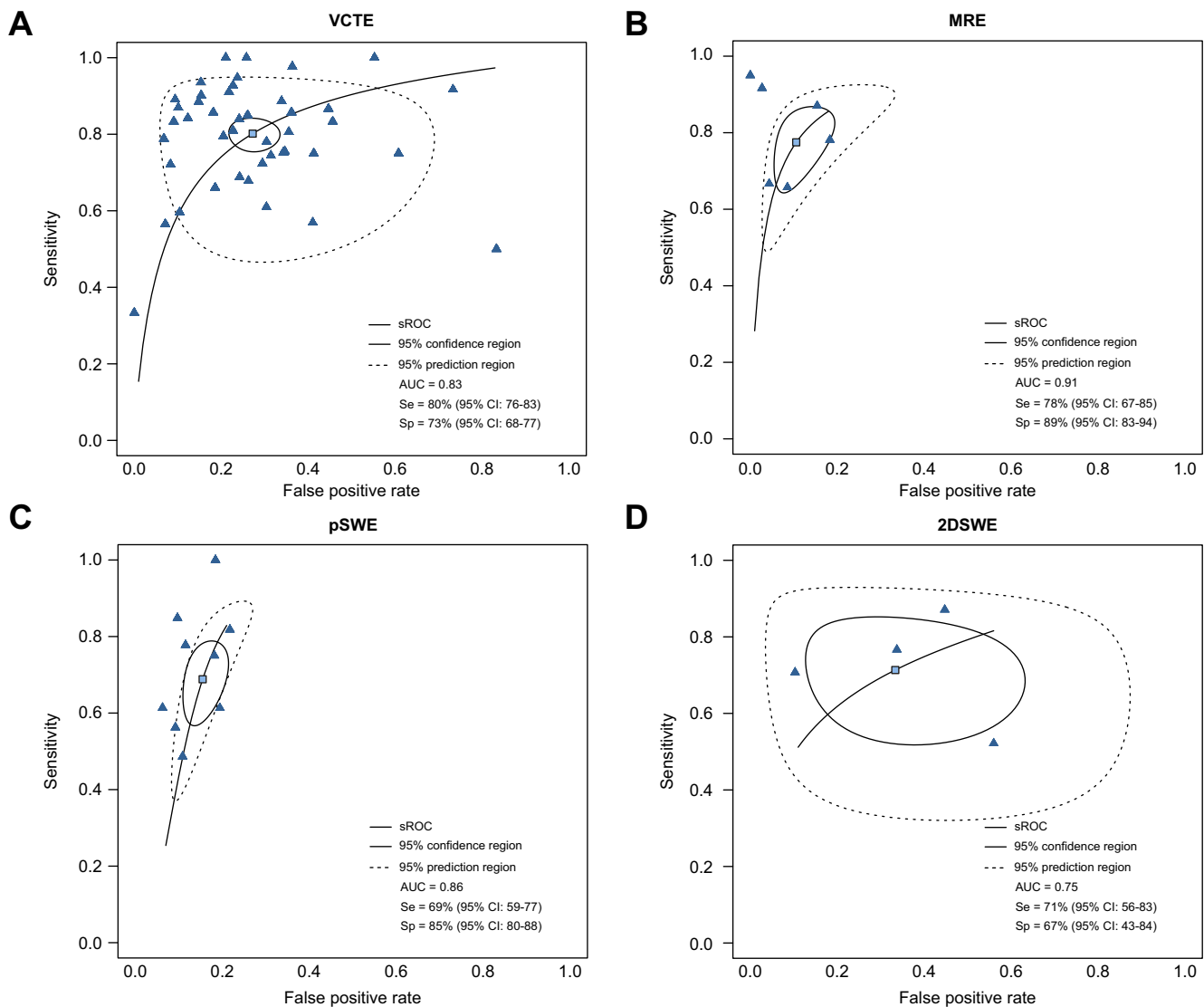
Several systematic reviews and meta-analyses (Table S12) have evaluated the diagnostic performance of different elastography and imaging modalities, but none so far have reported on the 5 main index tests as presented here. In particular, we found no previous meta-analyses for 2DSWE. The most recent pooled analysis of diagnostic accuracy by Liang *et al.* (12 studies, 910 patients),<sup>100</sup> examined the performance of MRE for staging liver fibrosis in NAFLD, and reported a better performance across all fibrosis stages with wider cut-off ranges, than the current and previous meta-analyses.<sup>101,102</sup> However, Liang *et al.*<sup>100</sup> included data from 4 mixed liver disease aetiology studies that we did not include as the studies did not use the NASH CRN histology scoring system, or discrete data for patients with NAFLD were not available. A unique feature of the present study is the analysis of the diagnostic performance of MRE in distinguishing NASH from simple steatosis as a recent meta-analysis only carried out a narrative synthesis of the data.<sup>103</sup>

Xiao *et al.* 2017 (64 studies, 13,046 patients with NAFLD)<sup>102</sup> comprehensively examined the diagnostic performance of VCTE and MRE alongside 4 serum tests for staging hepatic fibrosis against liver biopsy.<sup>102</sup> Whilst a large proportion of the included patients had NAFLD, their study data was more heterogeneous as 203 patients with viral hepatitis, 45 patients with other liver diseases, and 554 children were also included. Moreover, the time interval between index tests and liver biopsy was undefined, and studies using 3 other histological classification systems were also included.

The diagnostic accuracy of pSWE exclusively in patients with NAFLD was examined in a meta-analysis by Jiang *et al.* 2018 (9 studies, 982 patients),<sup>104</sup> which reported higher summary sensitivities in detecting advanced fibrosis and cirrhosis than our study, despite having similar sAUCs.<sup>104</sup> We, however, excluded 3 studies that were included by Jiang *et al.* due to the time interval between pSWE and biopsy being over 6 months, inclusion of a subset of paediatric population and duplication of data from the same study, respectively. The authors also reported a rather optimistically low rate of failed measurements (<1%) compared to us, most likely due to differences in the definition of a technical failure.

Most of the primary studies reported the experience of the index test operators or readers, however, data on intra- or inter-observer agreements were lacking. Similarly, the inter- and intra-observer variability in liver biopsy interpretation is well-known, particularly in classifying the intermediate stages of fibrosis. Despite this fact, the histology was read by a single pathologist in many studies. If liver histology is to be used as the reference standard, it would be preferable that at least 2 histopathologists review the liver biopsy specimen, preferably with consensus.

Our review has identified several areas where data in the literature are lacking. All but 2 of the studies we included in this systematic review and meta-analysis were scored as being at high risk of bias in at least 1 domain. This was mainly due to the fact that very few studies conducted validation of pre-defined cut-offs or intention-to-diagnose analyses. Without prospective validation of pre-defined cut-offs it is difficult to know how clinicians could apply these tests, while the lack of intention-to-diagnose analyses makes it difficult to fully evaluate the true impact of these tests in clinical practice. The true applicability is also difficult to evaluate as many studies did not report success



**Fig. 3. sROC curves and test performance to detect significant fibrosis (F0-1 vs. F2-4).** A bivariate logit-normal random effects model was used to estimate the mean sensitivity, and mean specificity for liver stiffness measured using (A) VCTE, (B) MRE, (C) pSWE and (D) 2DSWE. 2DSWE, 2-dimensional shear wave elastography; MRE, magnetic resonance elastography; pSWE, point shear wave elastography; sROC, summary receiver operating characteristic; VCTE, vibration-controlled transient elastography.

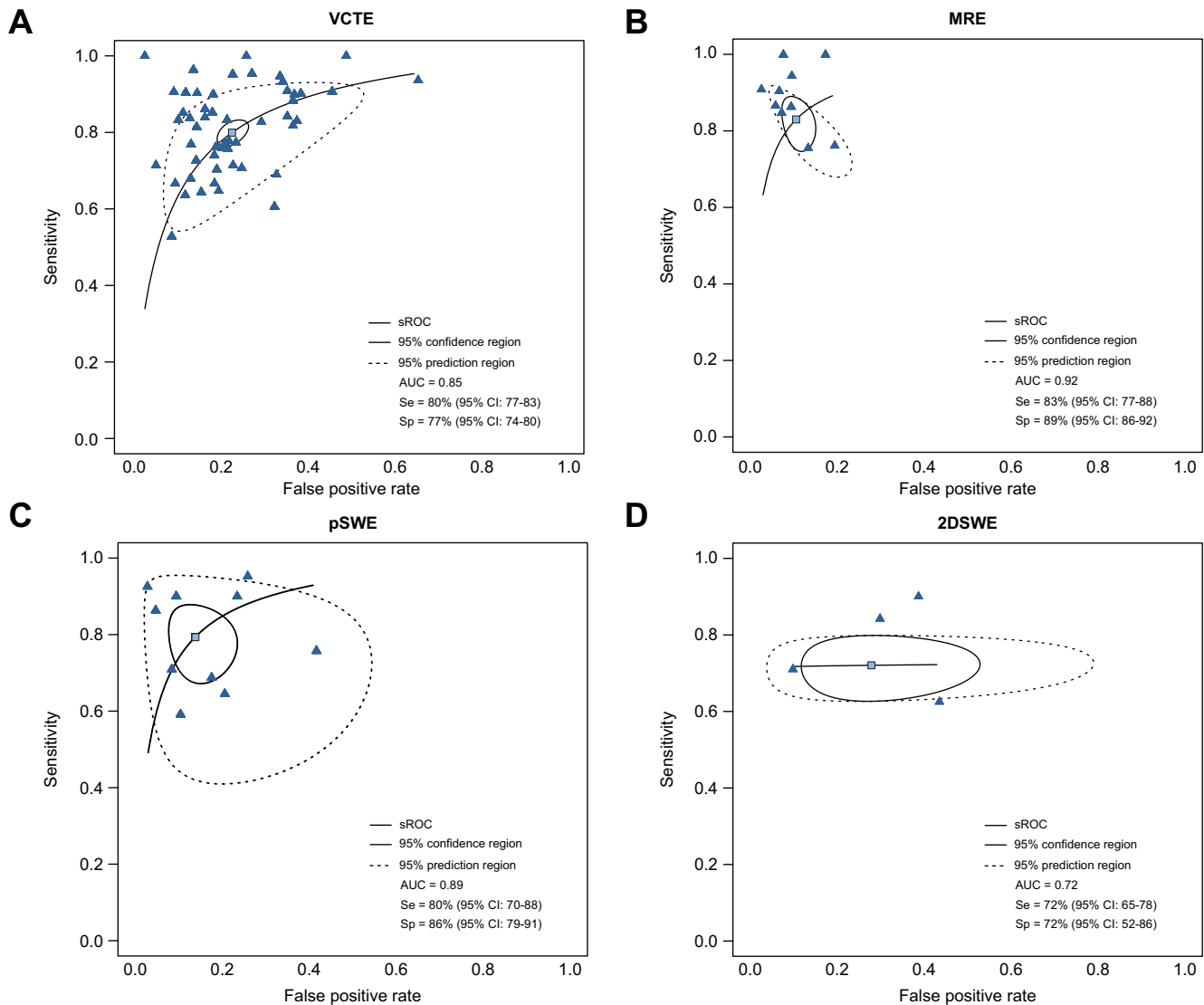
rates of index tests. These gaps in the literature are reflected in current society guidelines which suggest that elastography tests could be used as screening tests for advanced fibrosis, but with no specific cut-off recommendations for this context.<sup>105</sup>

Furthermore, the available data address the use of these index tests exclusively in the context of the diagnosis of the target conditions in secondary care. Data for their performance in other contexts (e.g. screening for a target condition in primary care, or using an index test to indicate prognosis or predict treatment response) are therefore needed. In addition, for the 2 other ultrasound elastography techniques (pSWE and 2DSWE) there is also a lack of data on validated reliability criteria.

Another area where data are lacking is the diagnostic performance of these tests for NASH. While traditionally the modalities we examined in this review were developed for fibrosis assessment, it is becoming increasingly important to be able to

identify patients with significant fibrosis and NASH, as these patients are thought to be more likely to benefit from pharmacological treatments. Several recent studies have sought to address this using combination index tests,<sup>106-108</sup> but as we only included single index tests here, we did not evaluate these.

Beyond diagnostic accuracy, the clinical utility of any non-invasive biomarker needs to also consider the cost-effectiveness for the healthcare provider, the opportunity costs for the patient (e.g. costs of scheduling an appointment and costs of travel to the appointment), and availability of alternative options. The equipment used for VCTE acquisitions can only be used for the purpose of liver stiffness measurement, but it is a point-of-care test. On the other hand, pSWE and 2DSWE may be performed by technicians trained in shear wave elastography and are incorporated into conventional ultrasound machines that can be used for alternative purposes beyond liver stiffness

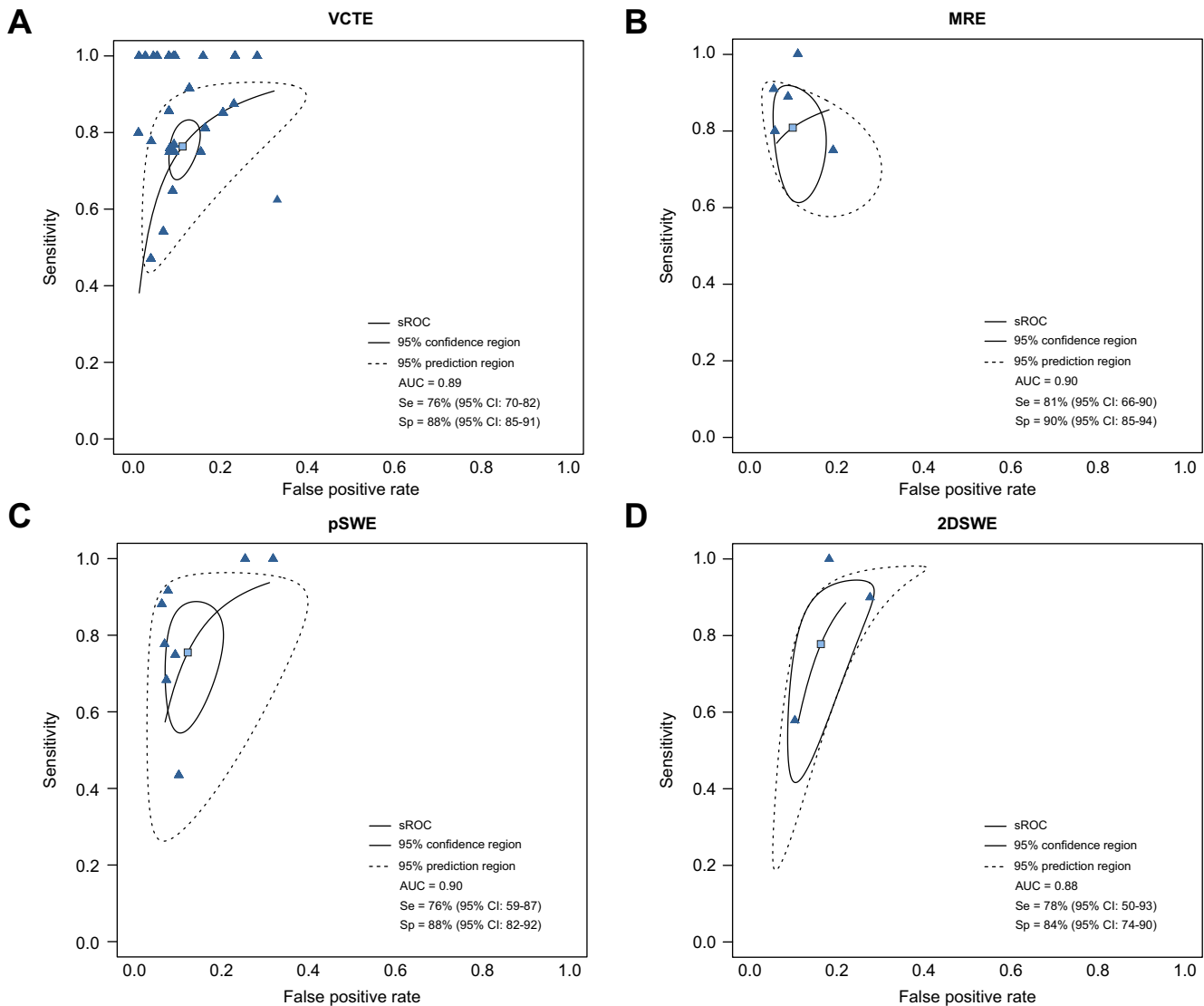


**Fig. 4. sROC curves and test performance to detect advanced fibrosis (F0-2 vs. F3-4).** A bivariate logit-normal random effects model was used to estimate the mean sensitivity, and mean specificity for liver stiffness measured using (A) VCTE, (B) MRE, (C) pSWE and (D) 2DSWE. 2DSWE, 2-dimensional shear wave elastography; MRE, magnetic resonance elastography; pSWE, point shear wave elastography; sROC, summary receiver operating characteristic; VCTE, vibration-controlled transient elastography.

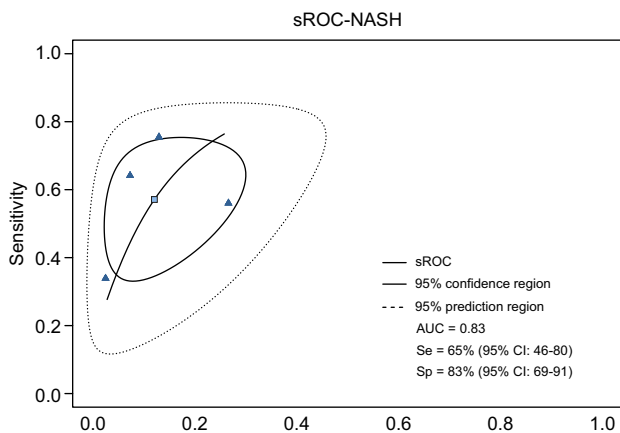
measurement. MRE requires additional hardware and therefore has costs associated with installation, but reporting can be done by the local radiologists without any additional costs thereafter. On the other hand, LMS and deMILI can be performed in scanners with certain specifications and have fewer installation costs, but require a post-acquisition reporting service with a per-scan cost. Some data on the cost-effectiveness of LMS in combination with FibroScan® are available,<sup>30,109</sup> but a health economics analysis was beyond the aims of this systematic review and may need to be considered in the future.

We acknowledge several limitations of our study. We were able to evaluate diagnostic accuracy at different thresholds in only 6 studies reporting VCTE findings, as most studies reported only a single cut-off value. Having only a few studies in our multiple-threshold analysis also prevented us from proposing

cut-off values for pre-defined levels of sensitivity and specificity. However, we note that in the studies included in the multiple-threshold meta-analysis, PPV was low when considering prevalences typically seen in routine practice (prevalence <30%). Furthermore, statistical comparison between the imaging biomarkers was not possible because of the inadequate number of studies that examined these biomarkers contemporaneously in the same study population. Whilst some studies reported subgroup analysis for patients with increased BMI, the impact of other potential confounding factors such as abdominal wall thickness, inflammation and steatosis were not explored in our study. A time interval of up to 6 months between index test and liver biopsy allowed us to include a large number of studies in our meta-analysis. However, regression of steatosis and fibrosis can occur within 6 months, particularly if patients have had



**Fig. 5. sROC curves and test performance to detect cirrhosis (F0-3 vs. F4).** A bivariate logit-normal random effects model was used to estimate the mean sensitivity, and mean specificity for liver stiffness measured using (A) VCTE, (B) MRE, (C) pSWE and (D) 2DSWE. 2DSWE, 2-dimensional shear wave elastography; MRE, magnetic resonance elastography; pSWE, point shear wave elastography; sROC, summary receiver operating characteristic; VCTE, vibration-controlled transient elastography.



**Fig. 6. sROC curves (bivariate logit-normal model) for the diagnostic accuracy of MRE to detect NASH (simple steatosis vs. NASH).** MRE, magnetic resonance elastography; NASH, non-alcoholic steatohepatitis; sROC, summary receiver operating characteristic.

significant weight loss in the intervening period. Nevertheless, our sensitivity analysis showed that there was no difference in diagnostic accuracy when considering only studies that included paired biopsy and index biomarker within a 3-month interval. The patient population recruited to the included studies was not completely uniform and included patients with biopsy-proven NAFLD (from cohorts who underwent biopsy to evaluate known or suspected NAFLD), patients from exclusively bariatric cohorts and NAFLD sub-populations from cohorts of patients with mixed liver disease aetiologies. These factors need to be taken into consideration when interpreting the median prevalence and diagnostic accuracy data reported in our study.

In conclusion, in patients with NAFLD where liver stiffness can be measured successfully, VCTE, MRE, pSWE and 2DSWE have a good diagnostic accuracy for the assessment of fibrosis, but only MRE and pSWE meet the minimum acceptable criteria of at least 80% sensitivity and specificity for the diagnosis of advanced fibrosis. These promising results however, are likely to



be overestimates of the true diagnostic accuracy as intention-to-diagnose analyses and validation of pre-specified cut-offs are lacking from the literature. Future studies, like the LITMUS Imaging Study being conducted in Europe and the USA currently, should also evaluate the newer 2DSWE and MRI techniques, and provide data on head-to-head comparisons of the various techniques.

### Abbreviations

2DSWE, two-dimensional shear wave elastography; cT1, iron-corrected T1 relaxation time; deMILI, detection of metabolic liver injury; DWI, diffusion-weighted imaging; LMS, Liver-MultiScan™; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; PPV, positive predictive value; pSWE, point shear wave elastography; sAUC, summary area under the curve; sROC, summary receiver operating characteristic curve; VCTE, vibration-controlled transient elastography.

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### Conflict of interest

EAS, FEM, MHZ, YV, JAL, CKL, LAJY, NP, CHL, GPA and PMB have nothing to declare. ANAJ, SN and MP are shareholders of Perspective Ltd. MRG reports grant funding from Gilead Sciences and Intercept; consultancy from Allergan, Gilead Science, Intercept, Medimmune, Shionogi, ProSciento, Kaleido, Siemens, Abbvie, Novo Nordisk, Genfit and Zydus. MJB and TAT are shareholders and employees of Pfizer. QMA is coordinator of the IMI2 LITMUS consortium and he reports research grant funding from Abbvie, Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd., Vertex; consultancy on behalf of Newcastle University for Abbott Laboratories, Acuitas Medical, Allergan/Tobira, Blade, BNN Cardio, Cirus, CymaBay, EcoR1, E3Bio, Eli Lilly & Company Ltd., Galmed, Genfit SA, Gilead, Grunthal, HistoIndex, Indalo, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Kenes, Madrigal, MedImmune, Metacrine, NewGene, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, Pfizer Ltd., Poxel, ProSciento, Raptor Pharma, Servier, Viking Therapeutics; and speaker fees from Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Fishawack, Genfit SA, Gilead, Integrity Communications, MedScape. SAH has research grants from Aker, Axcella, Cirus, CiVi Biopharma, Cymabay, Galectin, Galmed, Genfit, Gilead Sciences, Hepion Pharmaceuticals, Hightide Therapeutics, Intercept, Madrigal, Metacrine, NGM Bio, Northsea Therapeutics, Novartis, Novo Nordisk, Poxel, Sagimet, Viking. He has received consulting fees from Aker, Altimune, Alentis, Arrowhead, Axcella, Canfite, Cirus, CiVi, Cymabay, Echosens, Enyo, Fibronostics, Foresite Labs, Fortress Biotech, Galectin, Genfit, Gilead Sciences, Hepion, Hightide, HistoIndex, Intercept, Kowa, Madrigal, Metacrine, NGM, Northsea, Novartis,

Novo Nordisk, Poxel, Prometic, Ridgeline, Sagimet, Terns, and Viking. Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

MP, FEM, EAS, ANAJ, CKL, MHZ, PMB and TAT contributed in designing the study. EAS prepared the draft manuscript. The search strategy has been developed by MP. EAS, FEM, ANAJ, CKL, LAJY, NP, CHL and MP screened the references resulted from the literature search and extracted the required data. Statistical analyses and interpretation have been performed by FEM, MHZ and PMB. GPA, MRG, JB, TT, QMA, SN, SH, PMB and MP secured funding for the study. All authors reviewed and critically revised the manuscript.

### Data availability statement

This study has not generated any primary data. The data for this study were extracted from previously published manuscripts. Therefore, the data are already freely available in the manuscripts of the published studies which were included in this systematic review.

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.04.044>.

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