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Diagnosis and non-invasive assessment of MASLD in type 2 diabetes and obesity

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Summary

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease and an important cause of cirrhosis and hepatocellular carcinoma. It is strongly associated with type 2 diabetes and obesity. Because of the huge number of patients at risk of MASLD, it is imperative to use non-invasive tests appropriately.

Aims: To provide a narrative review on the performance and limitations of non-invasive tests, with a special emphasis on the impact of diabetes and obesity.

Methods: We searched PubMed and Cochrane databases for articles published from 1990 to August 2023.

Results: Abdominal ultrasonography remains the primary method to diagnose hepatic steatosis, while magnetic resonance imaging proton density fat fraction is currently the gold standard to quantify steatosis. Simple fibrosis scores such as the Fibrosis-4 index are well suited as initial assessment in primary care and non-hepatology settings to rule out advanced fibrosis and future risk of liver-related complications. However, because of its low positive predictive value, an abnormal test should be followed by specific blood (e.g. Enhanced Liver Fibrosis score) or imaging biomarkers (e.g. vibration-controlled transient elastography and magnetic resonance elastography) of fibrosis. Some non-invasive tests of fibrosis appear to be less accurate in patients with diabetes. Obesity also affects the performance of abdominal ultrasonography and transient elastography, whereas magnetic resonance imaging may not be feasible in some patients with severe obesity.

Conclusions: This article highlights issues surrounding the clinical application of non-invasive tests for MASLD in patients with type 2 diabetes and obesity.

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1 | INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), recently renamed from non-alcoholic fatty liver disease (NAFLD) and metabolic-associated fatty liver disease, is currently the most common chronic liver disease affecting around 30% of the global adult population.[1] In Western countries, metabolic dysfunction-associated steatohepatitis (MASH)—the active form of MASLD characterised by lobular inflammation, hepatocyte ballooning and accelerated fibrosis progression—has already become one of the leading causes of cirrhosis and hepatocellular carcinoma.

MASLD is strongly associated with metabolic risk factors, most notably diabetes and obesity.[2,3] In a systematic review and meta-analysis of 156 studies, the global prevalence of MASLD, MASH and advanced fibrosis among patients with type 2 diabetes (T2D) was 65.0%, 31.6% and 15.0%, respectively.[4] Similarly, in another systematic review and meta-analysis of 151 studies, the prevalence of MASLD and MASH among overweight or obese individuals was 70.0% and 33.5%, respectively, and 6.7% of overweight patients with MASLD had advanced fibrosis.[3] The estimated global prevalence of diabetes among 20- to 70-year-olds was 10.5% (537 million people) in 2021, rising to 12.2% (783 million) in 2045.[5] Globally, the number of adult women with obesity increased from 69 million in 1975 to 390 million in 2016; the number of adult men with obesity increased from 31 million to 281 million during the same period.[6]

The huge number of patients with diabetes and obesity has important implications in our field. First, current guidelines support MASLD assessment in patients with metabolic risk factors,[7–10] and we need to devise ways to make this happen. Second, unlike other chronic liver diseases, most patients with MASLD are seen in primary care settings (Figure 1).[11] Therefore, the availability and cost of testing should be considered, and colleagues outside the hepatology field should be involved in the development of clinical care pathways.[9] Third, current non-invasive tests of MASLD are not perfect, and extreme body mass index (BMI) and diabetes happen to be recognised confounders of some of these tests (Table 1).[12,13]

The limitations of liver biopsy in the assessment of MASLD have been extensively discussed.[14] It is an invasive procedure with a small but genuine risk of complications, notably bleeding. More importantly, there is considerable sampling, intra-observer and inter-observer variability, rendering the assessment unreliable. The focus should thus be non-invasive assessment in the vast majority of patients.

In this article, we discuss the use of non-invasive tests in the assessment of MASLD, with an emphasis on test performance in patients with diabetes and obesity. We also cover new data and recommendations on the use of non-invasive tests to assess portal hypertension and predict clinical outcomes.

2 | DIAGNOSIS OF MASLD

2.1 | Should MASLD be routinely looked for in patients with diabetes and obesity?

As discussed above, the strong association between MASLD and metabolic risk factors is beyond doubt. In fact, the diagnosis of MASLD requires the presence of hepatic steatosis plus at least one component of the metabolic syndrome.[15] According to the classical Wilson and Jungner criteria, there are arguments for MASLD screening in patients with diabetes and obesity. Above all, MASLD is common, especially among at-risk individuals. Based on prior

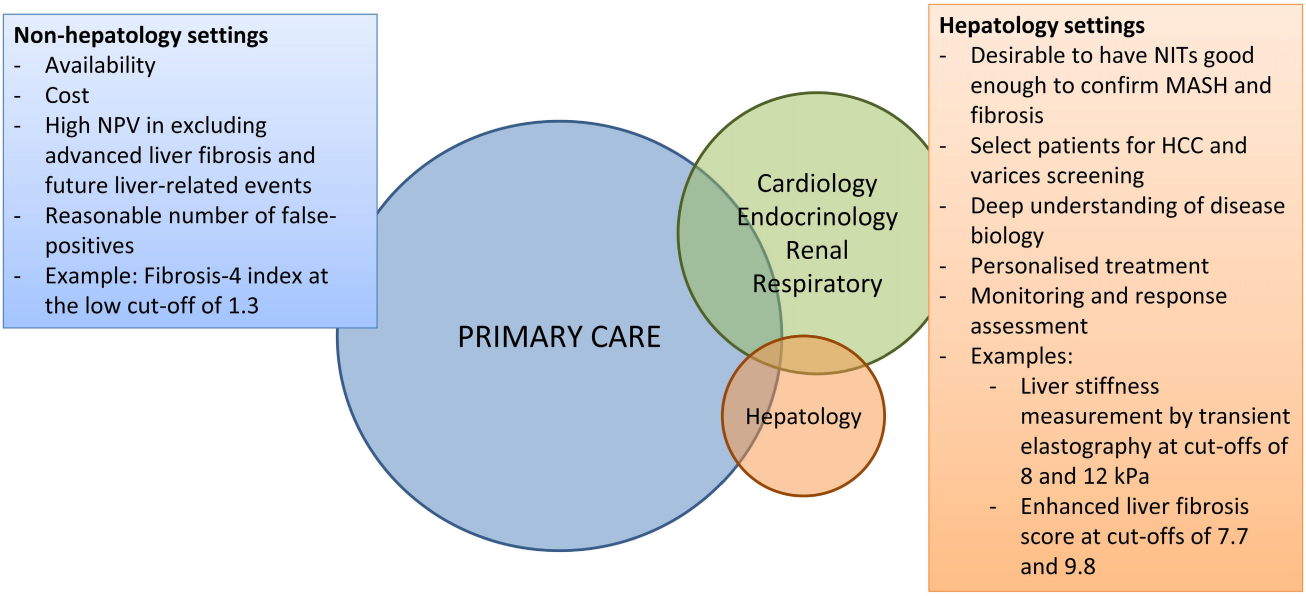

FIGURE 1 Context of use determines the key considerations in the choice non-invasive tests in different settings. It is important to remember that the vast majority of patients with MASLD are seen at primary care and non-hepatology settings. HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test; NPV, negative predictive value.

TABLE 1 Potential impact of diabetes and obesity on non-invasive tests.

Test	Impact
General considerations	• The pre-test probability of MASH and advanced liver fibrosis is higher in patients with diabetes and obesity. This would reduce the negative predictive value of non-invasive tests in general
Serum models of hepatic steatosis and fibrosis	• Models including metabolic factors (e.g. glycated haemoglobin and lipids) are affected by treatments • Some fibrosis scores (e.g. Fibrosis-4 index) appear to be less accurate in patients with diabetes
Abdominal ultrasonography	• Examination is more difficult in obese patients
Vibration-controlled transient elastography	• The failure rate is higher in obese patients • Extreme body mass index is associated with falsely high liver stiffness measurement
Magnetic resonance imaging	• Patients with severe obesity may not be able to fit in some machines

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

screening studies in patients with T2D, the number needed to screen is only 1.5–2 to identify one case of MASLD and 5–6 to identify one case of significant liver fibrosis.[16] The diagnostic tools for MASLD and liver fibrosis are reasonably accurate, acceptable and available, and there are settings to perform such assessments (Table 2).

Screening or case finding would be meaningless if there are no effective treatments. The pre-cirrhotic stage represents a window where intervention may alter the disease trajectory and thereby prevent liver-related complications in the long run. Weight reduction through lifestyle intervention or bariatric surgery can improve liver histology and clinical outcomes.[17–20] Nevertheless, one may argue that healthy lifestyle should be emphasised regardless of the diagnosis of MASLD anyway. The introduction of effective treatments for MASH, however, will make a stronger case for the diagnosis of MASLD.

Several studies suggest that screening for MASLD or fibrosis in patients with metabolic syndrome or T2D is cost-effective.[21–23] It is important to note that cost-effective studies are based on numerous assumptions, some of which may be based on less robust data (e.g. the impact of treatment on clinical outcomes). Again, the analyses need to be repeated when pharmacological treatments and the corresponding natural history data become available.

2.2 | Serum-based modalities for hepatic steatosis assessment

Most serum tests for hepatic steatosis include both liver enzymes and metabolic risk factors.[14] When applied in a population where all patients are either diabetic or obese, the discriminatory function of these tests may thus decrease.

SteatoTest, a proprietary panel using FibroTest-ActiTest, BMI, cholesterol, triglyceride and glucose, exhibits an area under the receiver-operating characteristic curve (AUROC) of 0.80, (cut-off of 0.3; 91% sensitivity and cut-off of 0.7; 89% specificity) for diagnosis of hepatic steatosis (HS) (liver fat content ≥5%).[24] BMI > 35 kg/m^2 did not affect its performance, with a meta-analysis of 494 such patients reporting an AUROC of 0.8 to detect steatosis >33%.[25] In the context of diabetes, conflicting data have been observed regarding performance of SteatoTest.[26,27] As a commercial test, cost and accessibility have limited its utility.

Incorporating BMI, waist circumference, triglyceride and GGT, Fatty Liver Index (FLI) demonstrates an accuracy of 0.84 for detection of HS (FLI <30; 87% sensitivity and FLI ≥60; 86% specificity).[28] FLI performs satisfactorily in both lean and obese subjects, albeit with different optimal cut-offs.[29] However, in diabetic patients, FLI may underperform (AUROC 0.647).[30]

Further modifying FLI specifically for the American population, the United States FLI (USFLI) included age, race-ethnicity, waist circumference, GGT, fasting insulin and glucose, reporting an AUROC of 0.80 to detect HS in all subjects.[31]

Hepatic Steatotic Index (HSI), using gender, T2D, ALT/AST ratio and BMI, has an AUROC of 0.812 (HSI <30; 93.1% sensitivity, >36; 92.4% specificity).[32] HSI may also underperform in the setting of obesity and T2D.[29,30] Originally developed using a Korean cohort, external validation in different populations is warranted.

Developed using machine learning techniques, NAFLD ridge score demonstrates an AUROC of 0.87 (cut-offs of 0.24 and 0.44, 92% sensitivity, 90% specificity).[33]

Other biomarkers including K-NAFLD score (AUROC 0.929)[34] and NAFLD screening score (NSS) (AUROC 0.825–0.861)[35] require further validation.

Overall, direct comparison of these indices remains challenging, being validated against different reference standards. These serum biomarkers can provide a qualitative but not a quantitative measure of HS, limiting their clinical utility. Nevertheless, they may remain useful for large epidemiologic studies.

2.3 | Imaging modalities for assessment of hepatic steatosis

Conventional B-mode ultrasound (US) is the most used imaging modality to diagnose HS, reporting an AUROC of 0.93 (84.8%

TABLE 2 Non-invasive tests of hepatic steatosis.

Tests	Performance	Performance in type 2 diabetes or obesity	Potential caveats
SteatoTest GGT, total bilirubin, α2m, Apo A1, Haptoglobin, ALT, BMI, total cholesterol, Tg, glucose; adjusted for age/gender	AUROC 0.80; sensitivity 0.9, specificity 0.54, using dual cut-offs[24]	Unaffected by obesity[25] Conflicting data on the impact of T2D[26,27]	Commercial test; limitation of cost/accessibility
Fatty Liver Index (FLI) GGT, Tg, BMI, waist circumference	AUROC 0.84; sensitivity 0.87, specificity 0.86, using dual cut-offs[28]	Unaffected by obesity May underperform with T2D[29,30]	Developed using ultrasound as reference standard Used in population epidemiologic studies
United States Fatty Liver Index (USFLI) Age, ethnicity, waist circumference, GGT, fasting insulin and glucose	AUROC 0.80; sensitivity 0.62–0.86, specificity 0.48–0.88, using dual cut-offs[31]	Limited data about impact of obesity/T2D	Modified specifically for multiethnic American population
Hepatic steatosis index (HSI) Gender, T2D status, BMI, ALT/AST ratio	AUROC 0.812; sensitivity 0.93, specificity 0.92, using dual cut-offs[32]	Affected by obesity/T2D[29,30]	Developed in Korean cohort using ultrasound as reference standard External validation may be warranted
NAFLD ridge score ALT, HDL-C, Tg, Hba1c, WBC, hypertension status	AUROC 0.88; sensitivity 0.92, specificity 0.90, using dual cut-offs[33]	Limited data on impact of obesity/T2D	Developed using machine learning approach using MRS as reference standard. Further validation warranted
B-mode Ultrasound (US)	AUROC 0.93; sensitivity 0.85, specificity 0.94[36]	Unaffected by T2D Reduced performance with morbid obesity (Sensitivity 0.49, Specificity 0.75)[37]	Operator dependent Reduced performance in context of mild hepatic steatosis Newer improved quantitative US techniques being developed and established
Controlled attenuation parameter (CAP)	AUROC 0.70–0.87, sensitivity 0.70–0.80, specificity 0.63–0.83[42,43]	Affected by obesity/T2D	Improved performance with XL probe in patients with obesity Further studies needed to validate continuous CAP
Computer tomography (CT)	Sensitivity 0.46–0.72, specificity 0.88–0.95[56]	Unaffected by obesity/T2D	Poor performance in detecting mild hepatic steatosis, radiation exposure, lack of validated thresholds
Magnetic resonance spectroscopy (MRS)	Sensitivity 0.73–0.89, specificity 0.92–0.96[56]	Potential physical limitation of MRI scanner to fit patients with morbid obesity	Limited availability, complexity in operation and interpretation
MRI proton density fat fraction (PDFF)	AUROC 0.90–0.98, sensitivity 0.75–0.93, specificity 0.87–0.94[58]	Potential physical limitation of MRI scanner to fit patients with morbid obesity	Overall sensitivity and specificity decrease with increased liver fat content

Abbreviations: ALT, Alanine aminotransferase; ApoA1, Apolipoprotein A1; AUROC, Area under receiver-operating curve; BMI, Body Mass Index; GGT, gamma-glutamyl transferase; HbA1c, Haemoglobin A1C; HDL-C, High-density lipoprotein cholesterol; T2D, type 2 diabetes mellitus; Tg, Triglyceride; WBC, White blood cell.

sensitivity, 93.6% specificity) to detect moderate-to-severe HS in a meta-analysis of 49 studies.[36] However, accuracy of the US may be limited in lower grades of HS (<20%). Performance may also be reduced in patients with obesity, with a much lower 49.1% sensitivity and 75% specificity observed.[37] Intra/inter-reader variability and limited quantitative assessment have been partially addressed with various scoring systems like Hamaguchi score[38] or hepatorenal index (HRI).[39]

Newer US techniques promise improved performance and quantification of HS, utilising acoustic properties such as attenuation parameter, backscatter coefficient and speed of sound estimates. Modalities such as controlled attenuation parameter (CAP), attenuation imaging (ATI), ultrasound-guided attenuation parameter (UGAP), fatty liver attenuation index (ATT) and tissue attenuation imaging (TAI) have been introduced across various commercial platforms, albeit in different phases of establishment for clinical use.[40]

CAP provided by the vibration-controlled transient elastography (VCTE) platform is most widely used currently. In a meta-analysis of 2735 patients, optimal cut-offs were identified, as 248 dB/m (above S0),

268 dB/m (above S1) and 280 dB/m (above S2), with AUROC of 0.823, 0.865 and 0.882, respectively. In this meta-analysis, as CAP values were also higher with the presence of T2D and increasing BMI, adjustments to CAP cut-offs were proposed in this context.[41] Nonetheless, the meta-analysis included patients with different liver diseases. In cohorts of patients known or suspected to have MASLD, the optimal cut-offs for steatotic liver were deemed higher at around 300 dB/m.[42,43] T2D and obesity are also independent factors associated with CAP failure.[44] In part, the advent of the XL probe has helped to mitigate VCTE failure and improve performance in patients with obesity.[45] CAP measurement by XL probe to detect HS remains satisfactory (AUROC of 0.819).[46] However, when applied to the same patient, XL probe tends to yield higher CAP values than M probe.[47,48] Caussy et al. thus proposed the CAP cut-offs of 294 and 307 dB/m for the detection of MRI-PDFF ≥5% by the M and XL probes, respectively.[48]

While limitations of CAP assessment remain, including the considerable overlap of CAP values across steatosis grades and heterogeneous optimal cut-offs reported across different studies, the recent introduction of continuous CAP may reduce measurement variability, but the impact on accuracy remains to be proven.[49,50] Further studies also need to evaluate its performance in obese individuals.

Computer tomography (CT) can also be used to assess HS, with fat having a lower attenuation value than soft tissue. However, it is not routinely used due to poor performance in detecting mild HS, radiation exposure, lack of validated thresholds and cost.[51]

Magnetic resonance (MR) methods, including MR spectroscopy (MRS) and MRI proton density fat fraction (PDFF), are accepted as the most accurate modalities for HS detection and quantification with similar performance between the two techniques.[52] Although the performance of MRI-PDFF is generally not affected by diabetes or obesity,[48,53] it may be challenging to accommodate a patient with morbid obesity in the MRI machine (also exceeding the weight limit of the table). The large field of view may affect image quality. There is also increased risk of thermal burns from contact with the bore, and there may be other confounding factors.[54]

MRS directly measures chemical compositions of liver fat, with ability to detect HS as little as 2%.[55] In a meta-analysis of 46 studies, mean sensitivity of 73%–89% and mean specificity of 92%–96% were observed with MRS, performing better than US and CT.[56] However, limited availability, complexity in operation and interpretation have constrained its use in clinical practice.[57] MRI-PDFF overcomes some of these limitations by being widely available on commercial MRI systems. A meta-analysis of 635 patients reported MRI-PDFF to have an excellent diagnostic accuracy to detect HS and quantify the different grades with high sensitivity and specificity; AUROC of PDFF to detect HS ≥5%, ≥33% and ≥ 66% were 0.98, 0.91 and 0.90, respectively.[58]

Overall, imaging modalities are routinely used in clinical assessment of MASLD patients, choice of modality depending on the clinical context, cost, accessibility and diagnostic performance. T2D and obesity do impact some of these modalities and need to be taken into consideration when using them.

3 | DIAGNOSIS OF AT-RISK MASH

Fibrotic or at-risk MASH has been defined as the presence of active MASH (NAFLD activity score of ≥4 with at least grade 1 each for hepatic steatosis, lobular inflammation and hepatocyte ballooning) and significant fibrosis (≥F2), and has been of interest due to the associated risk of progressive disease and being the target for clinical trials (Table 3).[59] Currently, Phase 3 drug development for MASH may employ two clinical trial designs running simultaneously. The first clinical trial design targets patients with active MASH and F2–F3 fibrosis with the primary endpoints being resolution of MASH with no worsening of fibrosis, or fibrosis improvement with no worsening of MASH, or both resolution of MASH and fibrosis improvement, and it aims for an accelerated approval. The second clinical trial design targets patients with MASH cirrhosis with the primary endpoint being a reduction in adverse clinical outcomes, which is required for a full approval.[60]

3.1 | Prediction models

There are several notable prediction models for MASH and at-risk MASH using readily available parameters. The NASHmap is a machine learning model that utilises 14 readily available clinical parameters for the diagnosis of MASH. It has an AUROC of 0.82 with a sensitivity of 81% and precision of 81%. The sensitivity and precision appeared better in patients with diabetes at 86% and 88%, respectively, compared with patients without diabetes at 77% and 74%, respectively.[61] The acNASH index, which utilises serum creatinine and aspartate aminotransferase (AST) levels, was developed for the diagnosis of MASH with NAFLD activity score of ≥5. It demonstrated an AUROC of 0.81 with a sensitivity and specificity of 96% and 86%, respectively. The diagnostic performance was similar in patients with and without diabetes.[62] Another prediction model, which utilises serum AST, HDL cholesterol and glycated haemoglobin for the diagnosis of fibrotic MASH in patients with morbid obesity, had AUROCs of 0.80–0.95 in its external validation cohorts with sensitivity and specificity ranging from 0.87 to 1 and 0.73 to 0.94, respectively, using ≤0.10 and ≥0.33 cut-offs; 45.7%–49.8% of patients were in the grey zone. Notably, one of the external validation cohorts included only patients with BMI ≥25 kg/m^2 (mostly with morbid obesity and eligible for bariatric surgery), one cohort included patients with at least three metabolic risk abnormalities, and the other included patients with BMI ≥25 kg/m^2 and/or diabetes.[63] However, the proportion of patients with diabetes was relatively low at 38%, 4% and 8%, respectively. Another machine learning model developed using data from the LITMUS meta-cohort utilises 25 readily available clinical parameters for the diagnosis of at-risk MASH with AUROC of 0.83. Interestingly, the addition of ten specific blood-based and imaging biomarkers did not appear to improve the performance of the model. The results of further studies on this promising tool are awaited.[64,65]

TABLE 3 Non-invasive tests of at-risk MASH.

Tests	Performance	Performance in type 2 diabetes or obesity	Potential caveats
Fibrotic NASH Index (uses AST, HDL cholesterol and HbA_{1c})[63]	AUROC 0.80–0.95, sensitivity 0.87–1, specificity 0.73–0.94	Developed using data from morbidly obese individuals undergoing bariatric surgery and had intra-operative liver biopsy Most individuals in the validation cohorts had BMI ≥25 kg/m^2	Validation cohorts varied in their inclusion criteria[a] and reference standard for fibrotic NASH[b] The proportion of individuals with type 2 diabetes was relatively low at 16%, in the derivation cohort, and 38%, 4% and 8% in the three validation cohorts, respectively
Clinical GBM Model (composite) (using 15 clinical variables)[64]	AUROC 0.83 Additional novel biomarkers in the Extended GBM model did not improve the AUROC	Mean BMI was 34 kg/m^2 in both the derivation and validation cohorts, and the proportion of patients with type 2 diabetes was 43.9% in the derivation cohort and 36.4% in the validation cohort	Further validation in external cohort required
MACK-3 (uses HOMA, AST and CK-18)[68]	AUROC 0.79, sensitivity 91%, specificity 85%	Not affected by type 2 diabetes or obesity	Need for fasting serum insulin and CK-18 levels, which are not routinely performed
NIS4 (uses miR-34a-5p, alpha-2 macroglobulin, YKL-40 and HbA1c)[69]	AUROC 0.80, sensitivity 82%, specificity 87%	Not affected by obesity Higher sensitivity, lower specificity in type 2 diabetes	Need for miR-34a-5p, alpha-2 macroglobulin and YKL-40, which are not routinely performed
NIS2+ (uses miR-34a-5p and YKL-40, with correction of sex effect on miR-34a-5p)[70]	AUROC 0.81, sensitivity 85%, specificity 85%	Not affected by type 2 diabetes or obesity	Need for miR-34a-5p and YKL-40, which are not routinely performed
SomaSignal (based on 37 analytes)[71]	AUROC 0.85, sensitivity 87%, specificity 63%	Not affected by type 2 diabetes Mean BMI was 34 kg/m^2	Need for large number of analytes
FAST[78]	AUROC 0.79, sensitivity 89%, specificity 89%	Sensitivity affected by BMI and specificity affected by type 2 diabetes	Need for VTCE device, which may not be widely available
MAST[79]	AUROC 0.93, sensitivity 89%, specificity 90%	May be affected in extreme cases of morbid obesity	Need for MRI, which may not be easily accessible, and hardware for MRE, which is limited in availability
MEFIB[81]	AUROC 0.84	May be affected in extreme cases of morbid obesity	Need for MRI, which may not be easily accessible, and hardware for MRE, which is limited in availability

Abbreviations: AST, aspartate aminotransferase; AUROC, area under receiver-operating characteristic curve; BMI, body mass index; CK-18, cytokeratin-18; FAST, Fibroscan-AST; FIB-4, fibrosis-4 index; GBM, gradient boosting machine; HOMA, homeostatic model assessment; MASH, metabolic dysfunction-associated steatohepatitis; MAST, MRI-AST; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; VCTE, vibration-controlled transient elastography.

[a]The first cohort included individuals eligible for bariatric surgery and individuals with BMI ≥25 kg/m^2 undergoing liver biopsy for suspected NASH, the second cohort included blood donors with at least three metabolic risk abnormalities, and the third cohort included individuals with BMI ≥25 kg/m^2 and/or type 2 diabetes from the UK Biobank.

[b]The reference standard for the first cohort was liver biopsy, the second cohort was based on FAST score >0.35, the third cohort was based on MRI-PDFF >5.5%, cT1 > 800 ms and FIB-4 index ≥1.3.

3.2 | Specific biomarkers

MACK-3, which utilises homeostatic model assessment of insulin resistance, AST and cytokeratin-18 levels, was developed for the diagnosis of fibrotic MASH. It demonstrated an AUROC of 0.85 in the validation set of the original study[66] and 0.80 in an external validation cohort.[67] A subsequent international multicentre study found the AUROC to be 0.79, with a sensitivity and specificity of 91% and 85%, respectively. The AUROC was not affected by diabetes or BMI and was comparable to the FibroScan-AST (FAST) score (see below), except for an 8% higher rate of patients included in the grey zone.[68] MACK-3 has the advantage of being a completely blood-based biomarker but is limited by the need for fasting serum insulin and cytokeratin-18 levels, which are not routinely performed. NIS4, which utilises miR-34a-5p, alpha-2 macroglobulin, YKL-40 and glycated haemoglobin, was developed for the diagnosis of fibrotic MASH. It demonstrated an AUROC of 0.80 in the pooled external validation cohort, with a sensitivity and specificity of 82% and 87%, respectively. The diagnostic

performance was not affected by BMI.[69] Subsequently, NIS4 was optimised, leading to the development of NIS2+, which utilises miR-34a-5p and YKL-40, with correction of sex effect on miR-34a-5p. NIS2+ had an AUROC of 0.81 for the diagnosis of fibrotic NASH, and was not affected by BMI or diabetes.[70] Using modified-aptamer proteomics, 37 analytes were identified and formed the basis for four protein models for the identification of clinically relevant severity of steatosis (0 vs. 1–3), lobular inflammation (0–1 vs. 2–3), hepatocyte ballooning (0 vs. 1–2) and fibrosis (0–1 vs. 2–4). In addition, fibrotic NASH was predicted by multiplying the outputs of each of the individual components (SomaSignal), which demonstrated an AUROC of 0.85 in the validation set.[71] In a comparative diagnostic accuracy study, SomaSignal had the highest AUROC at 0.81 followed by ADAPT (developed for the diagnosis of advanced fibrosis, see below) and MACK-3 at 0.77 and 0.76, respectively. The performance of SomaSignal and MACK-3 was similar in patients with diabetes, but it was marginally lower for ADAPT.[72,73]

3.3 | Imaging tests

Imaging studies have made significant strides in identifying steatosis and fibrosis; however, detecting MASH has historically posed challenges due to the reliance on histological tests to assess inflammation and ballooning. Nonetheless, predictive models that integrate imaging parameters such as steatosis (e.g. CAP or MRI-PDFF), fibrosis metrics (e.g. VCTE or magnetic resonance elastography [MRE]) and blood tests (e.g. AST or FIB-4) have been developed to predict the presence of at-risk MASH.[74] In addition, features of two-dimensional shear wave elastography may reflect lobular inflammation and other properties of MASH.[64,75,76]

The FAST score identifies at-risk MASH by combining liver stiffness measurement (LSM), CAP, and AST.[59] Two cut-offs have been proposed: ≤0.35 for sensitivity ≥0.90 (to rule out) and≥0.67 for specificity ≥0.90 (to rule in). The derived AUROC value was 0.80, with a positive predictive value (PPV) of 0.83 and a negative predictive value (NPV) of 0.85. External validation cohorts were employed to confirm its performance. Notably, 30%–39% of cases fell within the grey zone, indicating the need for further evaluation, possibly through liver biopsy. While one validation study demonstrated consistent FAST score performance across different BMI and T2D statuses,[77] a recent meta-analysis revealed variation in sensitivity for the rule-out cut-off based on BMI and in specificity for the rule-in cut-off depending on the presence of T2D.[78]

The MAST (MRI and AST) score employs MRI-PDFF, MRE and AST for at-risk MASH prediction.[79] Cut-offs are 0.165 (90% sensitivity, 98% NPV) and 0.242 (90% specificity, 50% PPV). MAST, with an AUROC of 0.93, outperformed NFS, FIB-4 and FAST. It minimised grey zone indeterminacy. Recent research shows MAST's accuracy in predicting liver-related clinical events (c-Statistic 0.92).[80] Primarily for trials, MAST reduces biopsies in MASH trials.

Jung et al. evaluated MEFIB – an MRE and FIB-4 combo – in detecting NASH fibrosis.[81] Cut-offs are ≥3.3 kPa (MRE) and ≥1.6 (FIB-4). MEFIB achieved 97.1% PPV, AUROC 0.90 for fibrosis. Validation maintained MEFIB efficacy (91.0% PPV, AUROC 0.84). MEFIB, like MAST, predicted clinical liver events effectively.[82]

Comparison studies found MAST's smaller grey zone and better correct classification, while MEFIB exhibited slightly higher AUC and PPV.[83,84] Larger, unbiased studies from big consortia are needed for clear distinctions. Both tests hold promise for assessing at-risk MASH, offering significant prognostic insight. Although data regarding the performance of MAST or MEFIB in individuals with T2DM versus those without, as well as differences across various BMI categories, are lacking, prior research indicates that the performance of MRI-PDFF and MRE remains unaffected by diabetes or BMI (except in extreme cases of morbid obesity).[48,53,85]

Lastly, iron-corrected T1 mapping (cT1) emerges as a promising tool for MASH assessment, with studies showing a correlation with the components of NAS and fibrosis.[86,87] Other studies connected cT1 with at-risk MASH and clinical events.[88] Multiparametric MRI has potential in MASLD, pending validation data.

4 | ASSESSMENT OF FIBROSIS

Cohort studies demonstrated that the severity of liver fibrosis—not MASH—is the main driver of liver events, extrahepatic events and mortality in patients with MASH (Table 4).[89–92] This evidence was confirmed in a meta-analysis reporting that the risk of liver events is 2.6, 5.2 and 12.7 times higher in patients with F2, F3 and F4 fibrosis, respectively, compared to those with F0 fibrosis.[93] Consequently, international regulatory agencies encourage focusing drug development in phase IIb and III clinical trials on non-cirrhotic MASH with liver fibrosis (MASH + F2–F3 fibrosis), or on patients with compensated MASH-related cirrhosis.[94] Moreover, these international agencies identified the improvement in at least one stage of liver fibrosis without MASH impairment as one of the main outcomes for the conditional approval of new drugs while waiting for hard clinical outcomes.[94]

4.1 | Serum fibrosis tests

Serum fibrosis tests such as FIB-4 (age, aspartate aminotransferase [AST], alanine aminotransferase [ALT], platelet), NAFLD fibrosis score (NFS; age, BMI, impaired fasting glucose/diabetes, AST, ALT, platelet and albumin) and AST-to-platelet ratio index are easy-to-use and validated tools for non-invasive assessment of liver fibrosis in MASLD. FIB-4 and NFS are based on the use of rule-out and rule-in cut-offs, and have acceptable AUROCs (0.76 and 0.73, respectively) and sensitivities (74% and 76%) for advanced fibrosis, despite an indeterminate area of 34% and 39%, respectively.[95] An individual patient data meta-analysis (IPDMA) reported that the accuracy of FIB-4 for advanced fibrosis in obese patients (AUROC 0.74) was similar to that of overweight (AUROC 0.77) but lower than that of normal weight patients (AUROC 0.81), while the diagnostic

TABLE 4 Non-invasive tests of hepatic fibrosis.

Tests	Performance	Performance in type 2 diabetes or obesity	Potential caveats
FIB-4 (age, aspartate aminotransferase [AST], alanine aminotransferase [ALT], platelet)	AUROC: 0.76, sensitivity 74% for advanced fibrosis and indeterminate area of 34%[95]	FIB-4 showed the highest specificity (93%) and PPV at a low-risk cut-off, while NFS had the highest sensitivity (88%) in predicting advanced fibrosis in MASLD and T2D patients. In an IPDMA, FIB-4 had similar accuracy for advanced fibrosis in obese (AUROC 0.74) and overweight (AUROC 0.77) patients but lower than in normal weight patients (AUROC 0.81)[95]	In T2D, reducing FIB-4's cut-off from 1.3 to 1.0 improved its sensitivity without clear information on false-positive results and liver referral burden[96]
NAFLD fibrosis score (NFS) (age, BMI, impaired fasting glucose/diabetes, AST, ALT, platelet and albumin)	AUROC: 0.73, sensitivity 76% for advanced fibrosis and indeterminate area of 39%[95]	In an IPDMA, NFS performed poorly and significantly worse than FIB-4 in obese patients (AUROC 0.69)[95]	Society guidelines do not include NFS and instead recommend using FIB-4 for screening high-risk populations, including individuals with T2D
HepaMet Fibrosis Score	AUROC curve value of 0.85 whereas NFS or FIB-4 in that study showed AUROC values of 0.80 ($p=0.0001$). Has 97.2% specificity, 74% sensitivity, a 92% NPV, a 76.3% PPV[99]	Has higher accuracy in non-obese or non-diabetic patients	Limited by the need for availability of insulin serum levels
Enhanced Liver fibrosis or ELF (combines type III procollagen peptide, hyaluronic acid and tissue inhibitor of metalloproteinase-1)	The AUROC for advanced fibrosis in MASLD was 0.83, with a specificity and sensitivity of 0.86 and 0.65, respectively, at a threshold of 9.8[100]	AUROC 0.71 for T2D, 0.63 for no T2D	
FibroTest (on gamma-glutamyltransferase (GGT), total bilirubin, alpha-2-macroglobulin, apolipoprotein A1 and haptoglobin)	AUROC of 0.77 for detecting advanced fibrosis[101]	AUROC 0.71 for T2D, 0.78 for no T2D	Had lower accuracy in patients with T2D because of a decrease in specificity
Fibrometer (age, gender, α2-macroglobulin, INR, platelet count, AST and GGT)	AUROC of 0.79 for advanced fibrosis[102]	AUROC 0.74 for T2D, 0.85 for no T2D	Had lower accuracy in patients with T2D because of a decrease in specificity
PRO-C3	AUROC 0·74 for T2D, 0.67 for no T2D[138]	The impact of obesity should be explored in future studies	Not available for clinical use
ADAPT score (age, T2D, PRO-C3 and platelet)	AUROCs of 0.86 and 0.87 in MASLD training and validation cohorts, respectively[103]	The impact of obesity and T2D should be explored in future studies	Not available for clinical use
SomaSignal	AUROC 0·89 for T2D, 0.90 for no T2D[71,72]	The impact of obesity should be explored in future studies	Might be difficult to do in clinical setting
VCTE	AUROC values of 0.77, 0.80 and 0.89 for fibrosis stages ≥F2, ≥F3 and F4, respectively[43]	VCTE with both M and XL probes displayed similar LSM values and accuracy for fibrosis stages in patients with BMI <30 and ≥ 30 kg/m^2.[111] A comparison between T2DM vs. none is needed	Other ultrasound-based systems are available but are less studied than VCTE
AGILE 3+	AUROC of 0.90 [0.88–0.91][112,114]	Recent prospective study in patients with T2D failed to demonstrate superior diagnostic accuracy of the Agile scores over VCTE alone	Growing studies are now showing its prognostic values[113]

TABLE 4 (Continued)

Tests	Performance	Performance in type 2 diabetes or obesity	Potential caveats
AGILE 4	AUROC of 0.91 (95% CI 0.89–0.92) in the testing cohort and 0.89 (95% CI 0.87–0.92) in the internal validation[112,114]	Recent prospective study in patients with T2D failed to demonstrate superior diagnostic accuracy of the Agile scores over VCTE alone	Growing studies are now showing Its prognostic values[113]
MRE	MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[117] while ≥5 kPa has excellent specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[82]	A meta-analysis has determined MRE cut-off values while demonstrating that BMI and T2DM have minimal influence on these thresholds[82]	Not available for wide use though the number of MREs is increasing around the world

performance of NFS was not acceptable and significantly lower in obese patients (AUROC 0.69).[95]

A recent large IPDMA also showed that FIB-4 and NFS performed similarly for predicting advanced fibrosis irrespectively of T2D, but when considering cut-offs from the literature, in diabetic patients both FIB-4 and NSF had lower specificity and a higher uncertainty area, and NFS also lowers sensitivity.[96] The AUROC of FIB-4, NFS and APRI for advanced fibrosis in patients with MASLD and T2D was 0.75, 0.72 and 0.68, respectively. FIB-4 had the highest proportion of patients at low risk of advanced fibrosis (46%), the lowest indeterminate area (40% vs. 55.8% for NFS), the highest specificity (93%) and the highest PPV (75%), while NFS had the highest sensitivity (88%).[96] Subgroup analyses observed that both FIB-4 and NFS had a trend for a better accuracy in patients older than 35 years and with normal ALT, and performed significantly better in non-obese patients.[96] In a recent prospective study in patients with T2D, the sensitivity of FIB-4 for advanced fibrosis increased from 81.6% to 95.9% when the low cut-off was reduced from 1.3 to 1.0, though the impact on false-positive results and the burden on hepatology service need further studies.[97] Another randomised controlled trial testing a clinical care pathway showed that around 20% of patients with T2D and increased FIB-4 had LSM ≥10 kPa.[98] Another serum fibrosis test named Hepamet fibrosis score, limited by the need for availability of insulin serum levels, has been recently proposed and externally validated as an accurate score for the non-invasive evaluation of advanced fibrosis; notably, it showed a higher accuracy in non-obese or in non-diabetic patients.[99] All in all, the available literature suggests that in obese and/or diabetic patients, FIB-4 has an acceptable accuracy for excluding advanced fibrosis even if the large proportion of patients falling in the indeterminate area of the test leads to a high need for second-line tests and/or specialistic referral.

4.2 | Specific fibrosis biomarkers

Serum markers reflecting liver fibrogenesis include the enhanced liver fibrosis (ELF) test that combines type III procollagen peptide, hyaluronic acid and tissue inhibitor of metalloproteinase-1; FibroTest based on gamma-glutamyltransferase (GGT), total bilirubin, alpha-2-macroglobulin, apolipoprotein A1 and haptoglobin; FibroMeter including age, gender, α2-macroglobulin, INR, platelet count, AST and GGT; and ADAPT score combining age, T2D, PRO-C3 (a marker of type III collagen formation) and platelet. Multi-marker scores like SomaSignal containing eight protein analytes are also under investigation.

In a meta-analysis of 11 studies, the ELF test had an AUROC of 0.83 for advanced fibrosis in MASLD with a specificity and sensitivity of the 9.8 threshold of 0.86 and 0.65, respectively.[100] A meta-analysis of five studies reported instead a lower AUROC (0.77) of FibroTest for detecting advanced fibrosis.[101] FibroMeter showed an AUROC of 0.79 for advanced fibrosis in a large MASLD cohort,[102] and the ADAPT score had AUROCs of 0.86 and 0.87 in MASLD training and validation cohorts, respectively.[103] The impact of obesity and diabetes on these tests should be explored in future studies.

When looking at patients with MASLD with T2D and/or obesity, FibroTest (AUROC 0.71 for T2D, 0.78 for no T2D) and FibroMeter (AUROC 0.74 for T2D, 0.85 for no T2D) had lower accuracy in patients with T2D because of a decrease in specificity.[13] The ADAPT score (AUROC 0.75 for T2D, 0.73 for no T2D) and SomaSignal (AUROC 0.89 for T2D, 0.90 for no T2D) had a similar performance according to T2D, while PROC-3 (AUROC 0.74 for T2D, 0.67 for no T2D) and ELF score (AUROC 0.71 for T2D, 0.63 for no T2D) had a higher even if not significant AUROC in T2D patients.[72] BMI did not affect ADAPT accuracy for advanced fibrosis.[104]

All in all, available data suggest an acceptable/good accuracy—higher than FIB-4—of specific fibrosis biomarkers for the diagnosis of advanced fibrosis in MASLD patients with T2D and/or obesity, even if the impact of obesity is understudied. These scores are, however, costly and not widely available and worthy to be used as second/third-line tests and/or in the context of referral centres.

4.3 | Imaging tests

Non-invasive methods for assessing liver fibrosis in patients with MASLD have gained traction due to their potential to replace invasive

liver biopsies, particularly in terms of imaging.[105] One standout technique is VCTE, which employs induced shear waves to measure liver stiffness. LSM, gauged through VCTE, reflects hepatic fibrosis severity.[105] A study by Eddowes et al. highlighted LSM's accuracy in identifying varying fibrosis stages, with AUROC values of 0.77, 0.80 and 0.89 for fibrosis stages ≥F2, ≥F3 and F4, respectively.[43] Siddqui et al. optimised cut-off values through a prospective study for enhanced clinical relevance.[106] Additionally, VCTE and a number of US systems allow evaluation of liver stiffness and steatosis during the same examination.

LSM's predictive power determined by VCTE is established. Boursier et al.[107] linked higher baseline LSM levels to poorer overall survival and liver-related complications-free survival. This predictive capacity was reaffirmed by another study from Italy.[108] However, LSM's potential for tracking drug responses and correlating with histology requires further exploration.[109] The XL probe allows the assessment of liver stiffness and steatosis in patients with high BMI.[110] In a significant study of MASLD patients,[111] VCTE with both M and XL probes displayed similar LSM values and diagnostic accuracy for various fibrosis stages in patients with BMI <30 and ≥30 kg/m^2. While VCTE's performance in patients with T2DM is assumed to mirror that in non-T2DM patients, more data are needed to confirm this.

To address VCTE's limitations in advanced fibrosis diagnosis, novel scores—Agile 3+ and Agile 4—incorporate demographic data, blood tests and VCTE-derived LSM to improve F ≥ 3 and F4 fibrosis stage identification and predict outcomes.[112–114] However, a recent prospective study in patients with T2D failed to demonstrate superior diagnostic accuracy of the Agile scores over VCTE alone.[97]

Point-shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE) are other US-based elastographies that have been more extensively evaluated.[14] Unlike VCTE, both pSWE and 2D-SWE are performed under real-time US examination. pSWE has a relatively small region of interest, and this results in a high measurement success rate, but possibly lower accuracy for fibrosis assessment compared with 2D-SWE and VCTE.[115] In head-to-head comparison in patients with MASLD, 2D-SWE had similar overall accuracy as VCTE as a second-line test in patients with abnormal FIB-4.[116]

MRE, a two-dimensional technique, is a highly accurate tool for assessing MASLD fibrosis. MRE studies demonstrate strong sensitivity and specificity, particularly for ≥F3 and F4 stages.[117] MRE's prognostic potential for liver outcomes is established, including its ability to predict cirrhosis and decompensated cirrhosis.[82,118] Moreover, MRE's value for longitudinal fibrosis monitoring is confirmed by Gidener et al.,[119] identifying baseline LSM ranges for optimal follow-up timing. Despite its accuracy, MRE's availability is limited to advanced centres, unlike VCTE, a point-of-care test with lower costs. A comprehensive meta-analysis establishes MRE cut-off values for significant fibrosis (3.14 kPa), advanced fibrosis (3.53 kPa) and cirrhosis (4.45 kPa), with BMI and T2DM having minimal impact.[120]

Threshold values for pSWE and other US-based techniques are emerging as potential alternatives, but validation remains incomplete compared to VCTE and MRE.[74]

Despite the promise of these imaging-based non-invasive tests, further validation and research are crucial to establish their clinical roles. While VCTE and MRE offer diagnostic and prognostic insights, ongoing studies are needed to verify their effectiveness in monitoring treatment responses and disease regression. The evolving landscape of non-invasive liver fibrosis assessment holds potential to enhance patient care while minimising invasive procedures.[121]

5 | ASSESSMENT OF PORTAL HYPERTENSION

Clinically significant portal hypertension (CSPH), defined as hepatic venous pressure gradient (HVPG) ≥10 mmHg, represents the critical stage where hepatic decompensation starts to develop. The PREDESCI trial is a landmark study that established the use of non-selective beta-blockers (NSBBs) or carvedilol in patients with CSPH.[122] At a median follow-up of 37 months, the primary endpoint (cirrhotic complications or death) occurred in 16% of patients in the beta-blockers group and 27% in the placebo group (hazard ratio 0.51). Thus, unless contraindicated, NSBBs should be prescribed to patients with CSPH rather than waiting until they develop large oesophageal varices.

The caveat of this approach is that HVPG is invasive and is not a routine assessment outside research settings. Accordingly, the Baveno VII consensus recommends the use of LSM by VCTE to make treatment decisions.[123] Patients with LSM ≤15 kPa and platelet count ≥150 × 10^9/L are unlikely to have CSPH, whereas LSM ≥25 kPa is considered sufficient to rule in CSPH. However, obesity is known to increase LSM,[12] thus the rule-in criteria only apply to MASLD patients who are non-obese. To tackle this problem, Pons and colleagues proposed the ANTICIPATE-NASH model based on LSM, platelet count and adjustment by BMI.[124] Rather than dichotomising patients as having CSPH or not, the model provides the probability of CSPH. However, as the model was only based on 248 patients with MASH, further validation is needed.

A patient with probable CSPH by the Baveno VII or ANTICIPATE-NASH models can be started on NSBB or carvedilol. On the other hand, if beta-blockers are contraindicated, it would be meaningful to determine if there are varices needing treatment as the alternative would be endoscopic variceal ligation. In this situation, the Baveno VI criteria can be used, which state that a patient has a <5% chance of harbouring varices needing treatment when LSM is <20 kPa and platelet count is ≥150 × 10^9/L.[125] These criteria have been validated in patients with MASH-related cirrhosis and with both the M and XL probes.[126]

Another interesting development is spleen stiffness measurement (SSM). The spleen is directly connected to the portal venous system via the splenic vein. Patients with CSPH often have

TABLE 5 Prognostication of MASLD by non-invasive tests.

Tests	Performance	Performance in type 2 diabetes or obesity	Potential caveats
FIB-4[139]	Time-dependent AUC for primary outcome[a] was 0.69, 0.74 and 0.81 at 3, 5 and 10 years, respectively Cumulative sensitivity (FIB-4 ≥ 1.3 vs. <1.3) 82.6% Dynamic specificity (FIB-4 > 2.67 vs. ≤2.67) 87.7%	Median BMI was 29 kg/m^2, and the proportion of individuals with type 2 diabetes was 45.9%–47.5%	No subgroup analysis for patients with type 2 diabetes or obesity
NFS[139]	Time-dependent AUC for primary outcomea was 0.61, 0.70 and 0.76 at 3, 5 and 10 years, respectively Cumulative sensitivity (NFS ≥-1.455 vs <−1.455) 78.9%. Dynamic specificity (NFS >0.676 vs ≤0.676) 84.6%	Median BMI was 29 kg/m^2, and the proportion of individuals with type 2 diabetes was 45.9%–47.5%	No subgroup analysis for patients with type 2 diabetes or obesity
ELF[134]	Time-dependent AUC for liver-related outcomes[b] was 0.81 and 0.71 at 5 and 10 years, respectively At 5 years, sensitivity and specificity were 59.9% and 88.9%, respectively. At 10 years, sensitivity and specificity were 43.1% and 91.8%, respectively	Mean BMI was 26.9 kg/m^2, and the proportion of individuals with type 2 diabetes was 9.9%. Among individuals with BMI ≥30 kg/m^2, AUC at 5 years and 10 years was 0.85 and 0.78, respectively. Among individuals with type 2 diabetes, AUC at 5 years and 10 years was 0.87 and 0.69, respectively	60% of liver-related outcome still occurred among individuals with ELF <9.8 at baseline
LSM-VCTE[139]	Time-dependent AUC for primary outcome[a] was 0.74, 0.76 and 0.79 at 3, 5 and 10 years, respectively Cumulative sensitivity (LSM-VCTE ≥10 kPa vs <10 kPa) 70.6% Dynamic specificity (LSM-VCTE >20 kPa vs ≤20 kPa) 92.0%	Median BMI was 29 kg/m^2, and the proportion of individuals with type 2 diabetes was 45.9%–47.5%	No subgroup analysis for patients with type 2 diabetes or obesity. Need for VTCE device, which may not be widely available
MAST[140]	AUC for primary outcome[c] was 0.92. Adverse event hazard ratio for MAST score 0.165–0.242 and 0.242–1.0 was 7.75 and 22.11, respectively, compared with 0.000–0.165	Median BMI was 30.6 kg/m^2, and the proportion of individuals with type 2 diabetes was 34.4%	No subgroup analysis for patients with type 2 diabetes or obesity. Need for MRI, which may not be easily accessible, and hardware for MRE, which is limited in availability
MRE[135]	Individuals who developed ascites, hepatic encephalopathy or oesophageal varices or died from any cause had significantly higher liver stiffness	Median BMI was 32 kg/m^2, and the proportion of individuals with type 2 diabetes was 49.6%	No subgroup analysis for patients with type 2 diabetes or obesity. Need for MRI, which may not be easily accessible, and hardware for MRE, which is limited in availability
MEFIB[136]	Adjusted odds ratio for primary outcome[d] was 24.1 for a positive MEFIB (MRE ≥3.3 kPa and FIB-4 ≥ 1.6) compared with negative MEFIB	Mean BMI was 32 kg/m^2, and the proportion of individuals with type 2 diabetes was 18.9%	No subgroup analysis for patients with type 2 diabetes or obesity. Need for MRI, which may not be easily accessible, and hardware for MRE, which is limited in availability
MRE-based multivariable model (uses age, MRE, albumin, AST and platelet)[137]	AUC for hepatic decompensation (variceal haemorrhage, ascites or hepatic encephalopathy) was 0.87 and 0.88 at 3 and 5 years, respectively	Median BMI was 28.8 kg/m^2, and the proportion of individuals with type 2 diabetes was 35%	No subgroup analysis for patients with type 2 diabetes or obesity Need for MRI, which may not be easily accessible, and hardware for MRE, which is limited in availability

Abbreviations: AST, aspartate aminotransferase; AUC, area under curve; BMI, body mass index; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MAST, MRI-AST; MEFIB; MRE combined with FIB-4; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; VCTE, vibration-controlled transient elastography.

[a]Primary outcome was a composite endpoint that included all-cause mortality, liver transplantation, hepatocellular carcinoma, cirrhosis decompensation (variceal bleeding, ascites, hepatic encephalopathy) and increase in MELD score to 15 or higher.

[b]Based on national registers for hospitalisation, cancer and death.

[c]Primary outcome was a composite outcome of manor adverse liver outcome (ascites, hepatic encephalopathy, bleeding oesophageal varices), liver transplant, hepatocellular carcinoma or liver-related death.

[d]Primary outcome was ascites, hepatic encephalopathy, varices needing treatment, HCC and death.

splenomegaly, and the pathophysiology is more precisely reflected by SSM. Several systematic reviews and meta-analyses showed that SSM by VCTE, point-shear wave elastography and two-dimensional shear wave elastography had 70%–90% sensitivities and specificities in predicting CSPH, oesophageal varices and varices needing treatment.[127,128] A randomised controlled trial in 548 patients with cirrhosis also showed that LSM plus SSM by VCTE was non-inferior to endoscopy in detecting varices needing treatment and predicting future acute variceal haemorrhage.[129,130] Another interesting study in 106 Korean patients with oesophageal varices showed that SSM response by point-shear wave elastography could reflect HVPG response to carvedilol, thus determining the adequacy of beta-blockade.[131] However, it is important to note that most studies included few patients with MASLD. Besides, the existing VCTE studies used the original 50 Hz liver probe for SSM, but the latest model of VCTE has a dedicated 100 Hz probe for SSM. The impact on SSM performance and optimal cut-offs should be scrutinised in future studies.

6 | PROGNOSTICATION

One of the earliest reports on non-invasive tests for prognostication of patients with MASLD was by Boursier and colleagues, who found that LSM by VCTE was able to stratify patients into categories with significantly different prognoses (Table 5).[132] More recently, an IPDMA found that simple non-invasive tests (i.e. LSM, FIB4 and the NFS) were found to perform as well as histologically assessed fibrosis in predicting the composite endpoint of all-cause mortality, hepatocellular carcinoma, liver transplantation or cirrhosis complications (i.e. ascites, variceal bleeding, hepatic encephalopathy or progression to a MELD score ≥ 15).[133] In the study, patients were stratified using literature-based cut-offs (i.e. <10 kPa, 10–19.9 kPa and ≥20 kPa for LSM; <1.3, 1.3–2.67 and >2.67 for FIB4; and <−1.455, −1.455–0.676 and >0.676 for the NFS). Patients in the least severe category at baseline had a very low cumulative incidence of developing the composite endpoint, ranging from 1.3% to 2.2%, compared with patients in the most severe category, which ranged from 13.5% to 21.9%. Further analysis of the data to look at the incidence of developing the composite endpoint among patients in the least severe category of non-invasive tests within a certain interval (e.g. 1 and 3 years) could provide a useful evidence-based guide on the interval for repeating non-invasive tests in clinical practice. While the study consisted of a substantial proportion of patients with T2D (46.1%) and obesity (39.4% had a BMI of ≥30 kg/m^2), data on the performance of the non-invasive tests specifically in these populations would be desirable. Other non-invasive tests, such as the ELF

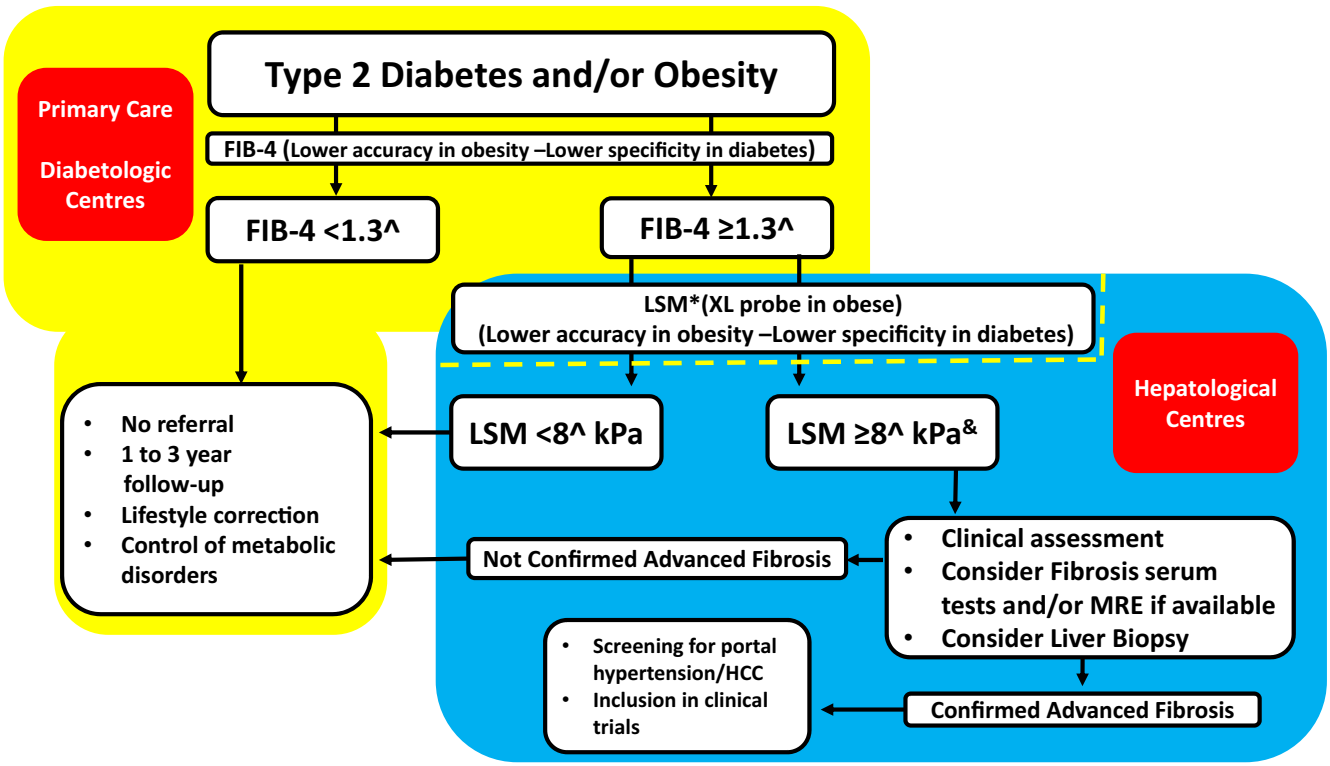

FIGURE 2 Clinical care pathway for patients with MASLD and diabetes/obesity. ^Specific cut-offs for diabetic and/or obese patients may require further validation. *According to local availability, specific fibrosis biomarkers could be an alternative; ELF accuracy seems not affected by diabetes, while the effect of obesity on ELF is uncertain. &LSM≥12 kPa indicates high risk of advanced fibrosis; the management of patients with LSM 8–12 kPa should be based on the local setting and practice. FIB-4, Fibrosis-4 index; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; MRE, magnetic resonance elastography.

panel, MRI-AST (MAST) score and MRE, either alone or in combination with FIB4 (called MEFIB index), have also been shown to be predictive of liver-related events and mortality.[80,119,134–136] A new model based on MRE, albumin, AST and platelets achieved high accuracy in predicting hepatic decompensation in MASLD.[137] However, MRI-based evaluations are more costly and not widely available; hence, their use may be restricted to only some large tertiary care settings.

7 | CONCLUSIONS

Patients with T2D and/or obesity are at risk of advanced liver fibrosis and major adverse liver outcomes and should be screened in primary care and diabetes clinics according to international guidelines.[7–10] The first-line test to be implemented is FIB-4 because of its good NPV for advanced fibrosis (Figure 2). Patients with an FIB-4 indicating an intermediate-high risk of advanced fibrosis should then undergo LSM by VCTE or specific serum fibrosis tests according to local availability. Patients at low risk of advanced fibrosis by FIB-4 or LSM should be reassessed at 1–3 years according to risk factors, and both lifestyle correction and control of metabolic disorders should be promoted. In case of LSM values ≥8 kPa, indicating an intermediate-high risk of advanced fibrosis—LSM ≥12 kPa instead suggestive of a high risk of advanced fibrosis—patients should be referred to hepatology centres. Patients with advanced fibrosis will be finally directed towards HCC and portal hypertension screening and if possible, included in dedicated clinical trials for new developing drugs.

AUTHOR CONTRIBUTIONS

Wah-Kheong Chan: Writing – original draft; writing – review and editing. **Salvatore Petta:** Writing – original draft; writing – review and editing. **Mazen Noureddin:** Writing – original draft; writing – review and editing. **George Boon Bee Goh:** Writing – original draft; writing – review and editing. **Vincent Wai-Sun Wong:** Conceptualization; funding acquisition; project administration; writing – original draft; writing – review and editing.

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REFERENCES

1. Yip TC, Vilar-Gomez E, Petta S, Yilmaz Y, Wong GL, Adams LA, et al. Geographical similarity and differences in the burden and genetic predisposition of NAFLD. Hepatology. 2023;77(4):1404–27.
2. Huang DQ, Noureddin N, Ajmera V, Amangurbanova M, Bettencourt R, Truong E, et al. Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: an individual participant-level data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8:829–36.
3. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(1):20–30.
4. En Li Cho E, Ang CZ, Quek J, Fu CE, Lim LKE, Heng ZEQ, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Gut. 2023;72(11):2138–48.
5. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
6. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42.
7. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
8. Wong VW, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, et al. Asia-Pacific working party on non-alcoholic fatty liver disease guidelines 2017-part 1: definition, risk factors and assessment. J Gastroenterol Hepatol. 2018;33(1):70–85.
9. Kanwal F, Shubrook JH, Adams LA, Pfotenhauer K, Wai-Sun Wong V, Wright E, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology. 2021;161(5):1657–69.
10. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD practice guidance on the clinical

assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797–835.
11. Wong VWS, Zelber-Sagi S, Cusi K, Carrieri P, Wright E, Crespo J, et al. Management of NAFLD in primary care settings. Liver Int. 2022;42(11):2377–89.
12. Wai JW, Fu C, Wong VW. Confounding factors of non-invasive tests for nonalcoholic fatty liver disease. J Gastroenterol. 2020;55(8):731–41.
13. Boursier J, Canivet CM, Costentin C, Lannes A, Delamarre A, Sturm N, et al. Impact of type 2 diabetes on the accuracy of noninvasive tests of liver fibrosis with resulting clinical implications. Clin Gastroenterol Hepatol. 2023;21(5):1243–1251 e1212.
14. Wong VW, Adams LA, de Lédinghen V, Wong GL, Sookoian S. Noninvasive biomarkers in NAFLD and NASH—current progress and future promise. Nat Rev Gastroenterol Hepatol. 2018;15(8):461–78.
15. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78(6):1966–86.
16. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65(8):1359–68.
17. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149(2):367–78. e365; quiz e314-365.
18. Wong VW, Wong GL, Chan RS, Shu SS, Cheung BH, Li LS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol. 2018;69(6):1349–56.
19. Verrastro O, Panunzi S, Castagneto-Gissey L, de Gaetano A, Lembo E, Capristo E, et al. Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. Lancet. 2023;401(10390):1786–97.
20. Aminian A, al-Kurd A, Wilson R, Bena J, Fayazzadeh H, Singh T, et al. Association of Bariatric Surgery with Major Adverse Liver and Cardiovascular Outcomes in patients with biopsy-proven nonalcoholic steatohepatitis. Jama. 2021;326(20):2031–42.
21. Phisalprapa P, Supakankunti S, Charatcharoenwitthaya P, Apisarnthanarak P, Charoensak A, Washirasaksiri C, et al. Cost-effectiveness analysis of ultrasonography screening for nonalcoholic fatty liver disease in metabolic syndrome patients. Medicine (Baltimore). 2017;96(17):e6585.
22. Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME, et al. Screening for nonalcoholic fatty liver disease in persons with type 2 diabetes in the United States is cost-effective: a comprehensive cost-utility analysis. Gastroenterology. 2020;159(5):1985–1987 e1984.
23. Choo BP, Goh GBB, Chia SY, Oh HC, Tan NC, Tan JYL, et al. Non-alcoholic fatty liver disease screening in type 2 diabetes mellitus: a cost-effectiveness and price threshold analysis. Ann Acad Med Singapore. 2022;51(11):686–94.
24. Poynard T, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, et al. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. Compar Hepatol. 2005;4:10.
25. Poynard T, Lassailly G, Diaz E, Clement K, Caïazzo R, Tordjman J, et al. Performance of biomarkers FibroTest, ActiTest, SteatoTest, and NashTest in patients with severe obesity: meta analysis of individual patient data. PloS One. 2012;7(3):e30325.
26. Poynard T, Peta V, Deckmyn O, Pais R, Ngo Y, Charlotte F, et al. Performance of liver biomarkers, in patients at risk of nonalcoholic steato-hepatitis, according to presence of type-2 diabetes. Eur J Gastroenterol Hepatol. 2020;32(8):998–1007.
27. Bril F, McPhaul MJ, Caulfield MP, Castille JM, Poynard T, Soldevila-Pico C, et al. Performance of the SteatoTest, ActiTest, NashTest and FibroTest in a multiethnic cohort of patients with type 2 diabetes mellitus. Clinical research. 2019;67(2):303–11.
28. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33.
29. Li C, Guo P, Zhang R, Zhang M, Li Y, Huang M, et al. Both WHR and FLI as better algorithms for both lean and overweight/obese NAFLD in a Chinese population. J Clin Gastroenterol. 2019;53(6):e253–60.
30. Guiu B, Crevisy-Girod E, Binquet C, Duvillard L, Masson D, Lepage C, et al. Prediction for steatosis in type-2 diabetes: clinico-biological markers versus 1H-MR spectroscopy. Eur Radiol. 2012;22(4):855–63.
31. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and nutrition examination survey. Aliment Pharmacol Ther. 2015;41(1):65–76.
32. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Digest Liver Dis. 2010;42(7):503–8.
33. Yip TC, Ma AJ, Wong VW, Tse YK, Chan HL, Yuen PC, et al. Laboratory parameter-based machine learning model for excluding non-alcoholic fatty liver disease (NAFLD) in the general population. Aliment Pharmacol Ther. 2017;46(4):447–56.
34. Jeong S, Kim K, Chang J, Choi S, Kim SM, Son JS, et al. Development of a simple nonalcoholic fatty liver disease scoring system indicative of metabolic risks and insulin resistance. Ann Translat Med. 2020;8(21):1414.
35. Zhou YJ, Zhou YF, Zheng JN, Liu WY, van Poucke S, Zou TT, et al. NAFL screening score: a basic score identifying ultrasound-diagnosed non-alcoholic fatty liver. Clin Chim Acta; Int J Clin Chem. 2017;475:44–50.
36. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54(3):1082–90.
37. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004;14(5):635–7.
38. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol. 2007;102(12):2708–15.
39. Webb M, Yeshua H, Zelber-Sagi S, Santo E, Brazowski E, Halpern Z, et al. Diagnostic value of a computerized hepatorenal index for sonographic quantification of liver steatosis. Am J Roentgenol. 2009;192(4):909–14.
40. Seneviratne N, Fang C, Sidhu PS. Ultrasound-based hepatic fat quantification: current status and future directions. Clin Radiol. 2023;78(3):187–200.
41. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66(5):1022–30.
42. Caussy C, Alquiraish MH, Nguyen P, Hernandez C, Cepin S, Fortney LE, et al. Optimal threshold of controlled attenuation parameter with MRI-PDFF as the gold standard for the detection of hepatic steatosis. Hepatology. 2018;67(4):1348–59.
43. Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156(6):1717–30.

44. de Lédinghen V, Vergniol J, Capdepont M, Chermak F, Hiriart JB, Cassinotto C, et al. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. J Hepatol. 2014;60(5):1026–31.
45. Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology. 2012;55(1):199–208.
46. Petroff D, Blank V, Newsome PN, Shalimar, Voican CS, Thiele M, et al. Assessment of hepatic steatosis by controlled attenuation parameter using the M and XL probes: an individual patient data meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(3):185–98.
47. Chan WK, Nik Mustapha NR, Mahadeva S, Wong VWS, Cheng JYK, Wong GLH. Can the same controlled attenuation parameter cut-offs be used for M and XL probes for diagnosing hepatic steatosis? J Gastroenterol Hepatol. 2018;33(10):1787–94.
48. Caussy C, Brissot J, Singh S, Bassirian S, Hernandez C, Bettencourt R, et al. Prospective, same-day, direct comparison of controlled attenuation parameter with the M vs the XL probe in patients with nonalcoholic fatty liver disease, using magnetic resonance imaging-proton density fat fraction as the standard. Clin Gastroenterol Hepatol. 2020;18(8):1842–1850 e1846.
49. Audière S, Labourdette A, Miette V, Fournier C, Ternifi R, Boussida S, et al. Improved ultrasound attenuation measurement method for the non-invasive evaluation of hepatic steatosis using FibroScan. Ultrasound Med Biol. 2021;47(11):3181–95.
50. Nogami A, Iwaki M, Kobayashi T, Honda Y, Ogawa Y, Imajo K, et al. Real-world assessment of SmartExam, a novel FibroScan computational method: a retrospective single-center cohort study. J Gastroenterol Hepatol. 2023;38(2):321–9.
51. Nogami A, Yoneda M, Iwaki M, Kobayashi T, Honda Y, Ogawa Y, et al. Non-invasive imaging biomarkers for liver steatosis in non-alcoholic fatty liver disease: present and future. Clin Mol Hepatol. 2023;29(Suppl):S123–35.
52. Dunn W, Castera L, Loomba R. Roles of radiological tests in clinical trials and the clinical management of nonalcoholic fatty liver disease. Clin Liver Dis. 2023;27(2):363–72.
53. Hsu C, Caussy C, Imajo K, Chen J, Singh S, Kaulback K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. Clin Gastroenterol Hepatol. 2019;17(4):630–637 e638.
54. Uppot RN, Sahani DV, Hahn PF, Gervais D, Mueller PR. Impact of obesity on medical imaging and image-guided intervention. Am J Roentgenol. 2007;188(2):433–40.
55. Guiu B, Petit JM, Loffroy R, Ben Salem D, Aho S, Masson D, et al. Quantification of liver fat content: comparison of triple-echo chemical shift gradient-echo imaging and in vivo proton MR spectroscopy. Radiology. 2009;250(1):95–102.
56. Bohte AE, van Werven JR, Bipat S, Stoker J. The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis. Eur Radiol. 2011;21(1):87–97.
57. Starekova J, Reeder SB. Liver fat quantification: where do we stand? Abdom Radiol. 2020;45(11):3386–99.
58. Gu J, Liu S, Du S, Zhang Q, Xiao J, Dong Q, et al. Diagnostic value of MRI-PDFF for hepatic steatosis in patients with non-alcoholic fatty liver disease: a meta-analysis. Eur Radiol. 2019;29(7):3564–73.
59. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020;5(4):362–73.
60. Matsubayashi T. Drug development for nonalcoholic steatohepatitis (NASH) with fibrosis: a regulatory perspective. https://sbiaevents.com/files2/NASH-Webinar-January-2021.pdf
61. Docherty M, Regnier SA, Capkun G, Balp MM, Ye Q, Janssens N, et al. Development of a novel machine learning model to predict presence of nonalcoholic steatohepatitis. J Am Med Inform Assoc. 2021;28(6):1235–41.
62. Wu XX, Zheng KI, Boursier J, Chan WK, Yilmaz Y, Romero-Gómez M, et al. acNASH index to diagnose nonalcoholic steatohepatitis: a prospective derivation and global validation study. EClinicalMedicine. 2021;41:101145.
63. Tavaglione F, Jamialahmadi O, de Vincentis A, Qadri S, Mowlaei ME, Mancina RM, et al. Development and validation of a score for fibrotic nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2023;21(6):1523–1532.e1.
64. Lee J, Westphal M, Vali Y, Boursier J, Petta S, Ostroff R, et al. Machine learning algorithm improves the detection of NASH (NAS-based) and at-risk NASH: a development and validation study. Hepatology. 2023;78(1):258–71.
65. Chang D, Truong E, Mena EA, Pacheco F, Wong M, Guindi M, et al. Machine learning models are superior to noninvasive tests in identifying clinically significant stages of NAFLD and NAFLD-related cirrhosis. Hepatology. 2023;77(2):546–57.
66. Boursier J, Anty R, Vonghia L, Moal V, Vanwolleghem T, Canivet CM, et al. Screening for therapeutic trials and treatment indication in clinical practice: MACK-3, a new blood test for the diagnosis of fibrotic NASH. Aliment Pharmacol Ther. 2018;47(10):1387–96.
67. Chuah KH, Wan Yusoff WNI, Sthaneshwar P, Nik Mustapha NR, Mahadeva S, Chan WK. MACK-3 (combination of hoMa, Ast and CK18): a promising novel biomarker for fibrotic non-alcoholic steatohepatitis. Liver Int. 2019;39(7):1315–24.
68. Canivet CM, Zheng MH, Qadri S, Vonghia L, Chuah KH, Costentin C, et al. Validation of the blood test MACK-3 for the noninvasive diagnosis of fibrotic nonalcoholic steatohepatitis: an international study with 1924 patients. Clin Gastroenterol Hepatol. 2023;21:3097–3106.e10.
69. Harrison SA, Ratziu V, Boursier J, Francque S, Bedossa P, Majd Z, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020;5(11):970–85.
70. Harrison SA, Ratziu V, Magnanensi J, Hajji Y, Deledicque S, Majd Z, et al. NIS2+, an optimisation of the blood-based biomarker NIS4(R) technology for the detection of at-risk NASH: a prospective derivation and validation study. J Hepatol. 2023;79:758–67.
71. Sanyal AJ, Williams SA, Lavine JE, Neuschwander-Tetri BA, Alexander L, Ostroff R, et al. Defining the serum proteomic signature of hepatic steatosis, inflammation, ballooning and fibrosis in non-alcoholic fatty liver disease. J Hepatol. 2023;78(4):693–703.
72. Vali Y, Lee J, Boursier J, Petta S, Wonders K, Tiniakos D, et al. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. Lancet Gastroenterol Hepatol. 2023;8(8):714–25.
73. Noureddin M, Truong E, Mayo R, Martínez-Arranz I, Mincholé I, Banales JM, et al. Serum identification of At-risk MASH: the metabolomics-advanced steatohepatitis fibrosis score (MASEF). Hepatology. 2023;79:135–48.
74. Sanyal AJ, Castera L, Wong VW. Noninvasive assessment of liver fibrosis in NAFLD. Clin Gastroenterol Hepatol. 2023;21(8):2026–39.
75. Sugimoto K, Moriyasu F, Oshiro H, Takeuchi H, Abe M, Yoshimasu Y, et al. The role of multiparametric US of the liver for the evaluation of nonalcoholic steatohepatitis. Radiology. 2020;296(3):532–40.

76. Sugimoto K, Lee DH, Lee JY, Yu SJ, Moriyasu F, Sakamaki K, et al. Multiparametric US for identifying patients with high-risk NASH: a derivation and validation study. Radiology. 2021;301(3):625–34.
77. Woreta TA, van Natta M, Lazo M, Krishnan A, Neuschwander-Tetri BA, Loomba R, et al. Validation of the accuracy of the FAST score for detecting patients with at-risk nonalcoholic steatohepatitis (NASH) in a North American cohort and comparison to other non-invasive algorithms. PloS One. 2022;17(4):e0266859.
78. Ravaioli F, Dajti E, Mantovani A, Newsome PN, Targher G, Colecchia A. Diagnostic accuracy of FibroScan-AST (FAST) score for the non-invasive identification of patients with fibrotic non-alcoholic steatohepatitis: a systematic review and meta-analysis. Gut. 2023;72(7):1399–409.
79. Noureddin M, Truong E, Gornbein JA, Saouaf R, Guindi M, Todo T, et al. MRI-based (MAST) score accurately identifies patients with NASH and significant fibrosis. J Hepatol. 2022;76(4):781–7.
80. Truong E, Gornbein JA, Yang JD, Noureddin N, Harrison SA, Alkhouri N, et al. MRI-AST score accurately predicts major adverse liver outcome, hepatocellular carcinoma, liver transplant, and liver-related death. Clin Gastroenterol Hepatol. 2023;21(10):2570–2577.e1.
81. Jung J, Loomba RR, Imajo K, Madamba E, Gandhi S, Bettencourt R, et al. MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis. Gut. 2021;70(10):1946–53.
82. Ajmera V, Kim BK, Yang K, Majzoub AM, Nayfeh T, Tamaki N, et al. Liver stiffness on magnetic resonance elastography and the MEFIB index and liver-related outcomes in nonalcoholic fatty liver disease: a systematic review and meta-analysis of individual participants. Gastroenterology. 2022;163(4):1079–1089 e1075.
83. Kim BK, Tamaki N, Imajo K, Yoneda M, Sutter N, Jung J, et al. Head-to-head comparison between MEFIB, MAST, and FAST for detecting stage 2 fibrosis or higher among patients with NAFLD. J Hepatol. 2022;77(6):1482–90.
84. Noureddin M, Harrison SA, Alkhouri N. MEFIB vs MAST and FAST: not a competition but useful tools. J Hepatol. 2024;80(1):E35–6.
85. Nogami A, Yoneda M, Iwaki M, Kobayashi T, Kessoku T, Honda Y, et al. Diagnostic comparison of vibration-controlled transient elastography and MRI techniques in overweight and obese patients with NAFLD. Sci Rep. 2022;12(1):21925.
86. Andersson A, Kelly M, Imajo K, Nakajima A, Fallowfield JA, Hirschfield G, et al. Clinical utility of magnetic resonance imaging biomarkers for identifying nonalcoholic steatohepatitis patients at high risk of progression: a multicenter pooled data and meta-analysis. Clin Gastroenterol Hepatol. 2022;20(11):2451–2461 e2453.
87. Dennis A, Kelly MD, Fernandes C, Mouchti S, Fallowfield JA, Hirschfield G, et al. Correlations between MRI biomarkers PDFF and cT1 with histopathological features of non-alcoholic steatohepatitis. Front Endocrinol (Lausanne). 2020;11:575843.
88. Jayaswal ANA, Levick C, Selvaraj EA, Dennis A, Booth JC, Collier J, et al. Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. Liver Int. 2020;40(12):3071–82.
89. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61(5):1547–54.
90. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but No other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015;149(2):389–397 e310.
91. Sanyal AJ, van Natta M, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med. 2021;385(17):1559–69.
92. Pennisi G, Enea M, Romero-Gomez M, Viganò M, Bugianesi E, Wong VWS, et al. Liver-related and extrahepatic events in patients with non-alcoholic fatty liver disease: a retrospective competing risks analysis. Aliment Pharmacol Ther. 2022;55(5):604–15.
93. Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology. 2020;158(6):1611–1625 e1612.
94. US Food and Drug Administration. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment. Guidance for Industry [Draft Guidance]. December 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/noncirrhotic-nonalcoholicsteatohepatitis-liver-fibrosis-developing-drugs-treatment. Accessed 1 July 2023
95. Mózes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M, Boursier J, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. Gut. 2022;71(5):1006–19.
96. Pennisi G, Enea M, Falco V, Aithal GP, Palaniyappan N, Yilmaz Y, et al. Noninvasive assessment of liver disease severity in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes. Hepatology. 2023;78(1):195–211.
97. Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol. 2023;78(3):471–8.
98. Zhang X, Yip TC, Wong GL, Leow WX, Liang LY, Lim LL, et al. Clinical care pathway to detect advanced liver disease in patients with type 2 diabetes through automated fibrosis score calculation and electronic reminder messages: a randomised controlled trial. Gut. 2023;72:2364–71.
99. Ampuero J, Pais R, Aller R, Gallego-Durán R, Crespo J, García-Monzón C, et al. Development and validation of Hepamet fibrosis scoring system-a simple, noninvasive test to identify patients with nonalcoholic fatty liver disease with advanced fibrosis. Clin Gastroenterol Hepatol. 2020;18(1):216–225 e215.
100. Vali Y, Lee J, Boursier J, Spijker R, Löffler J, Verheij J, et al. Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: a systematic review and meta-analysis. J Hepatol. 2020;73(2):252–62.
101. Vali Y, Lee J, Boursier J, Spijker R, Verheij J, Brosnan M, et al. FibroTest for evaluating fibrosis in non-alcoholic fatty liver disease patients: a systematic review and meta-analysis. J Clin Med. 2021;10(11):2415.
102. Boursier J, Guillaume M, Leroy V, Irlès M, Roux M, Lannes A, et al. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. J Hepatol. 2019;71(2):389–96.
103. Daniels SJ, Leeming DJ, Eslam M, Hashem AM, Nielsen MJ, Krag A, et al. ADAPT: an algorithm incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis. Hepatology. 2019;69(3):1075–86.
104. Qadri S, Ahlholm N, Lønsmann I, Pellegrini P, Poikola A, Luukkonen PK, et al. Obesity modifies the performance of fibrosis biomarkers in nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2022;107(5):e2008–20.
105. Younossi ZM, Noureddin M, Bernstein D, Kwo P, Russo M, Shiffman ML, et al. Role of noninvasive tests in clinical gastroenterology practices to identify patients with nonalcoholic steatohepatitis at high risk of adverse outcomes: expert panel recommendations. Am J Gastroenterol. 2021;116(2):254–62.

106. Siddiqui MS, Yamada G, Vuppalanchi R, Loomba R, Guy C, Brandman D, et al. Diagnostic accuracy of noninvasive fibrosis models to detect change in fibrosis stage. Clin Gastroenterol Hepatol. 2019;17(9):1877–1885 e1875.
107. Boursier J, Hagström H, Ekstedt M, Moreau C, Bonacci M, Cure S, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. J Hepatol. 2022;76(5):1013–20.
108. Petta S, Sebastiani G, Viganò M, Ampuero J, Wai-Sun Wong V, Boursier J, et al. Monitoring occurrence of liver-related events and survival by transient elastography in patients with nonalcoholic fatty liver disease and compensated advanced chronic liver disease. Clin Gastroenterol Hepatol. 2021;19(4):806–815.e5.
109. Rinella ME, Dufour JF, Anstee QM, Goodman Z, Younossi Z, Harrison SA, et al. Non-invasive evaluation of response to obeticholic acid in patients with NASH: results from the REGENERATE study. J Hepatol. 2022;76(3):536–48.
110. Wong VW, Vergniol J, Wong GL, Foucher J, Chan AW, Chermak F, et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. Am J Gastroenterol. 2012;107(12):1862–71.
111. Wong VW, Irles M, Wong GL, Shili S, Chan AW, Merrouche W, et al. Unified interpretation of liver stiffness measurement by M and XL probes in non-alcoholic fatty liver disease. Gut. 2019;68(11):2057–64.
112. Noureddin M, Mena E, Vuppalanchi R, Samala N, Wong M, Pacheco F, et al. Increased accuracy in identifying NAFLD with advanced fibrosis and cirrhosis: independent validation of the Agile 3+ and 4 scores. Hepatol Commun. 2023;7(5):e0055.
113. Pennisi G, Enea M, Pandolfo A, Ciccioli C, Infantino G, Parisi S, et al. AGILE 3+ score for the diagnosis of advanced fibrosis and for predicting liver-related events in NAFLD. Clin Gastroenterol Hepatol. 2022;54:S17–8.
114. Sanyal AJ, Foucquier J, Younossi ZM, Harrison SA, Newsome PN, Chan WK, et al. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based Agile scores. J Hepatol. 2023;78(2):247–59.
115. Cassinotto C, Boursier J, de Lédinghen V, Lebigot J, Lapuyade B, Cales P, et al. Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology. 2016;63(6):1817–27.
116. Cassinotto C, Boursier J, Paisant A, Guiu B, Irles-Depe M, Canivet C, et al. Transient versus two-dimensional shear-wave elastography in a multistep strategy to detect advanced fibrosis in NAFLD. Hepatology. 2021;73(6):2196–205.
117. Loomba R, Wolfson T, Ang B, Hooker J, Behling C, Peterson M, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology. 2014;60(6):1920–8.
118. Han MA, Saouaf R, Ayoub W, Todo T, Mena E, Noureddin M. Magnetic resonance imaging and transient elastography in the management of nonalcoholic fatty liver disease (NAFLD). Expert Rev Clin Pharmacol. 2017;10(4):379–90.
119. Gidener T, Ahmed OT, Larson JJ, Mara KC, Therneau TM, Venkatesh SK, et al. Liver stiffness by magnetic resonance elastography predicts future cirrhosis, decompensation, and death in NAFLD. Clin Gastroenterol Hepatol. 2021;19(9):1915–1924 e1916.
120. Liang JX, Ampuero J, Niu H, Imajo K, Noureddin M, Behari J, et al. An individual patient data meta-analysis to determine cut-offs for and confounders of NAFLD-fibrosis staging with magnetic resonance elastography. J Hepatol. 2023;79:592–604.
121. Harrison SA, Allen AM, Dubourg J, Noureddin M, Alkhouri N. Challenges and opportunities in NASH drug development. Nat Med. 2023;29(3):562–73.
122. Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. Beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2019;393(10181):1597–608.
123. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII—renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959–74.
124. Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, et al. Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol. 2021;116(4):723–32.
125. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63(3):743–52.
126. Petta S, Sebastiani G, Bugianesi E, Viganò M, Wong VWS, Berzigotti A, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. J Hepatol. 2018;69(4):878–85.
127. Manatsathit W, Samant H, Kapur S, Ingviya T, Esmadi M, Wijarnpreecha K, et al. Accuracy of liver stiffness, spleen stiffness, and LS-spleen diameter to platelet ratio score in detection of esophageal varices: systemic review and meta-analysis. J Gastroenterol Hepatol. 2018;33(10):1696–706.
128. Liu Y, Tan HY, Zhang XG, Zhen YH, Gao F, Lu XF. Prediction of high-risk esophageal varices in patients with chronic liver disease with point and 2D shear wave elastography: a systematic review and meta-analysis. Eur Radiol. 2022;32(7):4616–27.
129. Wong GLH, Kwok R, Hui AJ, Tse YK, Ho KT, Lo AOS, et al. A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: a randomized trial. Liver Int. 2018;38(4):636–44.
130. Wong GL, Liang LY, Kwok R, Hui AJ, Tse YK, Chan HL, et al. Low risk of variceal bleeding in patients with cirrhosis after variceal screening stratified by liver/spleen stiffness. Hepatology. 2019;70(3):971–81.
131. Kim HY, So YH, Kim W, Ahn DW, Jung YJ, Woo H, et al. Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices. J Hepatol. 2019;70(3):412–22.
132. Boursier J, Vergniol J, Guillet A, Hiriart JB, Lannes A, le Bail B, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol. 2016;65(3):570–8.
133. Mozes FE, Lee JA, Vali Y, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(8):704–713.
134. Saarinen K, Färkkilä M, Jula A, Erlund I, Vihervaara T, Lundqvist A, et al. Enhanced liver fibrosis(R) test predicts liver-related outcomes in the general population. JHEP Rep. 2023;5(7):100765.
135. Han MAT, Vipani A, Noureddin N, Ramirez K, Gornbein J, Saouaf R, et al. MR elastography-based liver fibrosis correlates with liver events in nonalcoholic fatty liver patients: a multicenter study. Liver Int. 2020;40(9):2242–51.
136. Ajmera V, Nguyen K, Tamaki N, Sharpton S, Bettencourt R, Loomba R. Prognostic utility of magnetic resonance elastography and MEFIB index in predicting liver-related outcomes and mortality in individuals at risk of and with nonalcoholic fatty liver disease. Therap Adv Gastroenterol. 2022;15:17562848221093869.
137. Kim BK, Bergstrom J, Loomba R, Tamaki N, Izumi N, Nakajima A, et al. Magnetic resonance elastography-based prediction model for hepatic decompensation in NAFLD; a multi-center cohort study. Hepatology. 2023;78:1858–66.

138. Boyle M, Tiniakos D, Schattenberg JM, Ratziu V, Bugianessi E, Petta S, et al. Performance of the PRO-C3 collagen neo-epitope biomarker in non-alcoholic fatty liver disease. JHEP Rep. 2019;1(3):188–98.
139. Mózes FE, Lee JA, Vali Y, Alzoubi O, Staufer K, Trauner M, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(8):704–13.
140. Truong E, Gornbein JA, Yang JD, Noureddin N, Harrison SA, Alkhouri N, et al. MRI-AST (MAST) score accurately predicts major adverse liver outcome, hepatocellular carcinoma, liver transplant, and liver-related death. Clin Gastroenterol Hepatol. 2023;21(10):2570–2577 e2571.

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