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Review Article

Review Article

Noninvasive tests for liver fibrosis in 2024: are there different scales for different diseases?

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Abstract

Liver fibrosis is the common pathway from various chronic liver diseases and its progression leads to cirrhosis which carries a significant risk for the development of portal hypertension-related complications and hepatocellular carcinoma. It is crucial to identify and halt the worsening of liver fibrosis given its important prognostic implication. Liver biopsy is the gold standard for assessing the degree of liver fibrosis but is limited due to its invasiveness and impracticality for serial monitoring. Many noninvasive tests have been developed over the years trying to assess liver fibrosis in a practical and accurate way. The tests are mainly laboratory- or imaging-based, or in combination. Laboratory-based tests can be derived from simply routine blood tests to patented laboratory parameters. Imaging modalities include ultrasound and magnetic resonance elastography, in which vibration-controlled transient elastography is the most widely validated and adopted whereas magnetic resonance elastography has been proven the most accurate liver fibrosis assessment tool. Nonetheless, noninvasive tests do not always apply to all liver diseases, nor does a common cut-off value of a test mean the same degree of liver fibrosis in different scenarios. In this review, we discuss the diagnostic and prognostic performance, as well as the confounders and limitations, of different noninvasive tests on liver fibrosis assessment in various liver diseases.

Keywords: FIB-4; liver fibrosis; liver stiffness measurement; noninvasive test; vibration-controlled transient elastography

Introduction

Liver fibrosis is the common pathway from different chronic liver diseases to compensated advanced chronic liver disease (cACLD), decompensated cirrhosis and end-stage liver disease. The term cACLD is relatively new and was introduced at Baveno VI consensus guidelines in 2015 to denominate patients with chronic liver disease at risk of developing clinically significant portal hypertension based on liver stiffness measurement (LSM), one of the most well-recognised noninvasive assessments for liver fibrosis. Liver fibrosis is the formation of scar tissue in response to parenchymal injury secondary to chronic liver disease, e.g. chronic hepatitis B (CHB) and chronic hepatitis C (CHC), metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated fatty liver disease (MAFLD) (previously called non-alcoholic fatty liver disease [NAFLD]) or alcohol-related liver disease (ARLD). The continuous and progressive replacement of hepatocytes by extracellular matrix and fibrous tissue leads to cirrhosis, which is a strong risk factor for hepatocellular carcinoma (HCC). Liver fibrosis also serves as an important treatment indication in various chronic liver diseases. International management guidelines mentioned that the presence of significant fibrosis is a key indication for antiviral treatment of CHB, regardless of serum alanine aminotransferase (ALT) level [1–3]. There is now solid evidence supporting that liver fibrosis is potentially reversible. Therefore, it is important to diagnose and assess the severity of liver fibrosis in order to provide appropriate management for the prevention of further liver damage.

Liver biopsy has been the gold standard in assessing liver fibrosis in the last few decades and remains a non-disposable tool in many clinical trials. Nonetheless, it is impractical to perform liver biopsy on a large number of patients or to do it serially. Hence, various noninvasive assessments have been developed and adopted in some international management guidelines. While liver biopsy examination still has an important role in the diagnostic process, noninvasive assessments including vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), and serum biomarkers have high accuracy to diagnose advanced fibrosis and cirrhosis. This article focuses on the up-to-date noninvasive approaches for the diagnosis and assessment of liver fibrosis in 2024, with a special focus on the unique features of various chronic liver diseases.

Noninvasive testing for liver fibrosis

Noninvasive assessments of liver fibrosis are currently an integral part of the standard of care for patients with suspected or

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confirmed liver diseases. Less than two decades ago, many of these noninvasive assessments just became available; they have been vigorously tested and validated in different liver diseases and diverse patient cohorts since then. This field has been one of the most rapidly advancing fields in hepatology in the last two decades. As the novel therapeutics for chronic viral hepatitis focus on viral suppression and clearance, liver fibrosis assessment is now rarely included as one of the key study endpoints [4]. More often, the improvement in the values of these noninvasive assessments of liver fibrosis is associated with better prognosis by reducing the risk of cirrhosis and HCC [5].

In contrast, improvement in liver fibrosis with no worsening of metabolic dysfunction-associated steatohepatitis (MASH; previously known as non-alcoholic steatohepatitis [NASH]), on top of the resolution of MASH alone, is another accepted histologic endpoint for conditional approval of MASH therapeutics [6]. Looking forward, with the florid novel MASH therapeutics under clinical development of different phases at present, there is an urgent need to employ noninvasive tests to identify patients needing treatment and monitor treatment response. Data on the performance of noninvasive tests in the current phase 3 clinical trials will be pivotal in shaping clinical care in the years to come.

As of date, various laboratory- and/or imaging-based noninvasive tests (NITs) have been validated with different diagnostic performance and clinical utility. Table 1 summarises the available NITs for liver fibrosis.

Simple fibrosis scores

APRI

Aspartate aminotransferase (AST) to platelet ratio index (APRI) is calculated by [AST (upper limit of normal (ULN)) × 100]/platelet (10^9/L). It was initially developed in CHC patients with an area under the receiver operating characteristic curve (AUROC) of 0.92 to predict cirrhosis [7]. It performed better with higher AUROC and applied lower cut-off values to predict significant fibrosis or cirrhosis in patients aged ≥ 30 years than in those aged < 30 years [8]. In a cohort of patients with MASLD, APRI achieved an AUROC of 0.75 for identifying advanced fibrosis with negative predictive value (NPV) and positive predictive value (PPV) of 76.2% and 61.4%, respectively [9]. APRI demonstrated the least prognostic accuracy compared with Fibrosis-4 (FIB-4), Hepascore, FibroMeter and LSM. Conditions that affect its components, such as haematological disorders (affecting platelet count), heavy alcohol intake and medications (affecting serum AST level), can influence the APRI score independent of liver fibrosis.

FIB-4 index

The fibrosis-4 (FIB-4) index is calculated by [age (years) × AST (U/L)]/[platelet (10^9/L) × ALT (U/L)$^{1/2}$]. It was first developed in human immunodeficiency virus (HIV)/hepatitis C virus (HCV)–coinfected patients with AUROC of 0.765 to identify advanced fibrosis. It could rule out advanced fibrosis with a high NPV of 90% and sensitivity of 70% by a cut-off value of 1.45. In the validation group, 71% of individuals could avoid undergoing a liver biopsy [10]. For younger MASLD patients aged ≤35 years and those aged ≥65 years, the diagnostic performance of FIB-4 for advanced fibrosis was suboptimal, characterised by low AUROCs and a significant false positive rate due to its low specificity [11]. One cross-sectional study compared the diagnostic accuracy of NITs in patients with MASLD and showed that FIB-4 achieved a relatively high NPV of 81.7% to exclude advanced fibrosis in patients with MASLD but a suboptimal PPV of 58.6%. FIB-4 showed comparable prognostic accuracy for clinical outcomes with LSM and Hepascore by the Harrell C-index [9]. Similar to APRI, potential confounding factors include haematological disorders, excessive alcohol consumption and specific medications, as they can affect the components of FIB-4.

Forns index

Forns index was developed in patients with CHC and is calculated by $7.811 - 3.131 \times \ln$ [platelet (10^9/L)] + $0.781 \times \ln$ [gamma-glutamyl transferase (GGT) (IU/L)] + $3.467 \times \ln$ [age (years)] − 0.014 [cholesterol (mg/dL)]. It could accurately exclude significant fibrosis with a high NPV of 96% and AUROC higher than 80% in both estimation and validation groups [12]. In a prospective cohort study involving patients with early compensated alcohol-related liver disease, the Forns index achieved a time-dependent AUROC of 0.84 to predict liver-related events over time in patients with alcohol-related liver disease [13]. Haematological disorders, alcohol consumption, metabolic factors and certain medications may affect the reliability of the index by altering liver enzymes and platelet counts. Additionally, as age is a component of the index and can influence liver enzyme levels, it might change the precision of its predictions.

Fibroindex

Fibroindex was initially developed in patients with CHC to predict the stage of liver fibrosis and is calculated by $1.738 - 0.064 \times$ [platelet ($\times 10^4$/mm^3)] + $0.005 \times$ [AST (IU/L)] + $0.463 \times$ [gamma globulin (g/dL)]. The AUROC of Fibroindex to predict severe fibrosis was 0.82. It achieved a high PPV of 94% and specificity of 97% to identify significant fibrosis using the cut-off value of 2.25. It could eliminate the need for a liver biopsy in 35% of patients. There was a significant correlation between the change of Fibroindex and shafting stages of fibrosis [14]. Except for confounding factors that affect the platelet and AST, autoimmune disease and certain medications may affect the accuracy of the assessment by altering gamma globulin levels. While age is not part of the index, it may impact performance by affecting the baseline level of liver enzymes and blood cells.

NAFLD fibrosis score

NAFLD fibrosis score (NFS) was developed in patients with NAFLD (now called MASLD) and is calculated by $-1.675 + 0.037 \times$ age (years) + $0.094 \times$ body mass index (BMI) (kg/m^2) + $1.13 \times$ impaired fasting glycemia/diabetes (yes = 1, no = 2) + $0.99 \times$ AST/ALT ratio − $0.013 \times$ platelets (10^9/L) − $0.66 \times$ albumin (g/dL). The AUROC of the score to identify advanced fibrosis was higher than 0.8 [15]. It could exclude advanced fibrosis accurately with a high NPV of ≥88% and identify advanced fibrosis with a high PPV of ≥82% by using cut-off values of −1.455 and 0.68, respectively. This score could eliminate the need for a liver biopsy in 75% of patients while maintaining 90% prediction accuracy [15]. The prediction performance for advanced fibrosis declines in patients with MASLD aged ≤ 35 years and those aged ≥ 65 years [11]. This variation in predictive accuracy across different age groups highlights the need for age-specific considerations or adjustments when utilising this test to assess advanced fibrosis in patients with MASLD. In a retrospective analysis of patients with biopsy-proven MASLD, NFS achieved AUROCs of 0.72–0.92 to predict liver-related events and 0.70–0.83 to predict mortality [16]. Platelet count and serum albumin level, which can be altered by many other aetiologies and ethnicity, are potential confounding factors for the prediction performance of the NFS. MAFLD fibrosis score (MFS), composed of age, BMI, INR, AST, GGT, platelet count and presence of type 2 diabetes, has been recently developed and validated in an Asian

Table 1. Noninvasive assessments for liver fibrosis

Noninvasive assessment	Components	Diagnostic accuracy	Reproducibility	Clinical utility	Limitation
Common clinical and laboratory parameters					
AST/ALT ratio	AST, ALT	For F3 fibrosis: AUROC = 0.66–0.74 Sn = 40% Sp = 80%	Not tested but aminotransferases may change rapidly over time	High as common parameters involved	Modest accuracy
APRI	AST, platelet count	For F3 fibrosis: AUROC = 0.74 Sn = 65% Sp = 72%	Not tested but aminotransferases may change rapidly over time	High as common parameters involved	Modest accuracy
FIB-4	Age, AST, ALT, platelet count	For F3 fibrosis: AUROC = 0.80 Sn = 65% Sp = 97% (with dual cutoffs)	Not tested but aminotransferases may change rapidly over time	High as common parameters involved	
NFS	Age, BMI, IFG or T2D, albumin, AST, ALT, platelet count	For F3 fibrosis: AUROC = 0.75–0.82 Sn = 73-82% Sp = 96-98% (with dual cutoffs)	Not tested but aminotransferases may change rapidly over time	High as common parameters involved	Interpretation of BMI may differ across different ethnic groups
BARD score	AST, ALT, BMI, T2D	For F3 fibrosis: AUROC = 0.69-0.81 Sn = 62% Sp = 66%	Not tested but aminotransferases may change rapidly over time	High as common parameters involved	Interpretation of BMI may differ across different ethnic groups
Specialised liver fibrosis markers					
Hyaluronic acid	Important structural role of extracellular matrix	For F4 fibrosis/cirrhosis: AUROC = 0.988 for F4 Sn = 98% Sp = 100%)	Not tested	Important role in the common pathway of fibrosis of different aetiologies; included in a few blood panels	Cannot be used alone
PIIINP	Direct measurement of the synthesis and degradation of existing type III collagen fibrils	N/A	Not tested	Important role in the common pathway of fibrosis of different aetiologies; included in a few blood panels	Cannot be used alone
Pro-C3	Reflects true formation of type III collagen	N/A	Not tested	Correlated well with NAFLD activity score	Not well studied in other chronic liver diseases
Laminin	Non-collagenous glycoprotein in basement membranes	For any fibrosis: AUROC = 0.87 Sn = 82% Sp = 89%	Not tested	Important role in the common pathway of fibrosis of different aetiologies	Data from small studies only.

(continued)

Table 1. (continued)

Noninvasive assessment	Components	Diagnostic accuracy	Reproducibility	Clinical utility	Limitation
Specialised liver fibrosis panels					
Enhanced Liver Fibrosis	PIIINP, hyaluronic acid, TIMP-1	For F1 fibrosis: AUROC = 0.92 Sn = 88% Sp = 81% For F2 fibrosis: AUROC = 0.98 Sn = 94% Sp = 93% For F3 fibrosis: AUROC = 0.99 Sn = 100% Sp = 98%	Good	Good prognostic factor for clinical outcomes in patients with chronic liver diseases; similar results by using fresh blood or cryo-preserved blood	Not sensitive for early stages of fibrosis; age, low CD4+ T-cell count and other factors can affect ELF results
FibroTest	GGT, total bilirubin, α-2 macroglobulin, apolipoprotein A1, and haptoglobin	For any fibrosis: AUROC = 0.88 (nonbinary)	Good	Useful in different chronic liver disease; accurate in overweight or obese patients	Suboptimal for early-stage fibrosis
FibroMeter™ - Viral hepatitis (Virus) - NAFLD - ALD	body weight, prothrombin index, ALT, AST, ferritin and fasting glucose	For F2 fibrosis: AUROC = 0.76 Sn = 22% Sp = 97% For F3 fibrosis: AUROC = 0.77 Sn = 27% Sp = 95% For F4 fibrosis/cirrhosis: AUROC = 0.83	Good	Accurate for severe fibrosis in different liver diseases	High cost
Imaging-based assessments					
	Description	Limitations of all methods: infiltrative liver disease, liver congestion, acute hepatitis, liver inflammation, cholestasis			
FibroScan (VCTE)	Mechanically induced-impulse. Quantitative measurement of shear wave speed Two probes: M and XL probe (for patients with BMI > 30 kg/m^2)	***M probe*** For F2 fibrosis: AUROC = 0.84 Sn = 79% Sp = 76% For F3 fibrosis: AUROC = 0.90 Sn = 91% Sp = 75% For F4 fibrosis/cirrhosis: AUROC = 0.95 Sn = 92% Sp = 88% ***XL Probe*** For F2 fibrosis: AUROC = 0.80–0.85 Sn = 76% Sp = 65% For F3 fibrosis: AUROC = 0.84–0.90 Sn = 75% Sp = 74% For F4 fibrosis/cirrhosis: AUROC = 0.91–0.95 Sn = 88% Sp = 82%	ICC > 0.9	Short processing time (<10 minutes) Ambulatory clinic setting Immediacy of results Failures: 0 to 10% of measurements	Fasting 2 hours Requires a dedicated device

(continued)

Table 1. (continued)

Noninvasive assessment	Components	Diagnostic accuracy	Reproducibility	Clinical utility	Limitation
ARFI (pSWE)	Ultrasound induced-focused radiation force impulse at death. Quantitative measurement of shear wave speed	For F2 fibrosis: AUROC = 0.7–0.83 Sn = 56–90% Sp = 36–90% For F3 fibrosis: AUROC = 0.74–0.97 Sn = 59–90% Sp = 63–90% For F4 fibrosis/cirrhosis: AUROC = 0.78–0.89 Sn = 44–90% Sp = 67–90%	ICC 0.86–0.95	Implemented on a regular US machine Allows for simultaneous sonographic imaging of the liver	Fasting 2 hours Quality criteria not well defined
2D-3D SWE	Ultrasound induced-radiation force focus swept over depth faster than shear wave speed to create a Mach cone. Quantitative measurement of shears wave speed	For F2 fibrosis: AUROC = 0.85–0.92 Sn = 85% Sp = 94% For F3 fibrosis: AUROC = 0.88–0.95 Sn = 90% Sp = 92% For F4 fibrosis/cirrhosis: AUROC = 0.97 Sn = 100% Sp = 86%	ICC 0.92–0.95	Implemented on a regular US machine Allows for simultaneous sonographic imaging of the liver	Fasting 2 hours Experienced operators Quality criteria not well defined
MRE	Uses a modified phase-contrast method to image the propagation of the shear wave in the liver parenchyma	For F2 fibrosis: AUROC = 0.86–0.89 Sn = 73% Sp = 89% For F3 fibrosis: AUROC = 0.89–0.96 Sn = 86% Sp = 91% For F4 fibrosis/cirrhosis: AUROC = 0.88–0.97 Sn = 87% Sp = 93%	ICC 0.83 - 0.96	Implemented on a regular MRI machine Examination of the whole liver	Requires a MRI facility Time-consuming Costly

ALD = alcoholic liver disease, ALT = alanine aminotransferase, APRI = AST-to-platelet ratio index, AST = aspartate aminotransferase, ARFI = acoustic radiation force impulse, AST = aspartate aminotransferase, AUROC = area under the receiver-operating characteristics curve, BMI = body mass index, CAP = controlled attenuation parameter, CHB = chronic hepatitis B, CHC = chronic hepatitis C, FIB-4 = fibrosis-4 index, GGT = gamma-glutamyltransferase, ICC = intraclass correlation coefficient, IFG = impaired fasting glucose, NAFLD = nonalcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, NFS = NAFLD fibrosis score, NonBin = non-binary, N/A = not applicable, PIIINP = Procollagen III amino terminal peptide, pSWE = point shear wave elastography, Sn = sensitivity, Sp = specificity, SWE = shear wave elastography, T2D = type 2 diabetes = TIMP-1 = tissue inhibitor of metalloproteinase 1, US = ultrasound.

cohort with a high correct prediction rate of 90.4% using a dual cut-off approach [17].

BARD score

The BARD score, specifically developed for patients with MASLD, is calculated by summing points from three distinct criteria. It allocates one point for patients with a BMI exceeding 28, two points for those having an AST/ALT ratio greater than 0.80, and an additional point for individuals diagnosed with diabetes. It achieved AUROCs ranging from 0.81 to 0.83, indicating a high level of accuracy. Furthermore, the BARD score consistently maintained a high NPV, not falling below 95%, underscoring its reliability in ruling out advanced fibrosis [18]. The study revealed that, compared with other NITs like NFS, FIB-4 and APRI, it had a reduced ability to predict overall mortality and severe liver disease in patients with biopsy-confirmed MASLD. This was indicated by AUROC of 0.62 over an average follow-up period of 19.9 years [16]. Furthermore, the effectiveness of the BARD score appears to vary across different ethnic groups. The performance of the BARD score is reduced in Asian patients compared with Caucasians, which may be because of the variation in BMI.

SAFE score

Steatosis-associated fibrosis estimator (SAFE) score, composed of age, BMI, presence of diabetes, AST, ALT, globulin and platelet count, has the advantage of achieving a high NPV in primary care settings and hence facilitates triage of patients who are at low risk of having clinically significant fibrosis (F2 or above) [19].

2.2 Specific fibrosis biomarkers

ELF score

Enhanced liver fibrosis (ELF) score, created from a cohort mainly composed of CHC patients, is based on an algorithm that includes three serum biomarkers: tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), hyaluronic acid, and aminoterminal propeptide of type III procollagen (PIIINP). It achieved a high sensitivity of 90% to predict fibrosis and a high NPV of 92% to exclude significant fibrosis with an AUROC of 0.804 [20]. The dynamic changes in ELF score are associated with the dynamic changes in disease progress during antiviral treatment. It can also stratify the HCC risk of CHB patients falling into the grey zone of the LSM-HCC score. This value indicates a strong correlation between the score and actual liver health outcomes, suggesting its reliability in a broad, unselected population [21]. In a study assessing the ELF score within a general population cohort, the AUROCs of ELF predicting liver outcomes at five years was 0.81 in the general population and not less than 0.85 in those with risk factors [22]. A prospective cohort study revealed that the risk of liver-related events was 5%, 22% and 53% in subgroups of patients with ELF <9.8, 9.8–10.5 and >10.5, respectively. So, the ELF score could stratify liver-related events by using the cut-off values of 9.8 and 10.5 [13]. Other fibrotic diseases, bones fracture, cancer or inflammation may affect the prediction accuracy of the score by influencing PIIINP and TIMP-1.

PRO-C3 and ADAPT score

The N-terminal pro-peptide of type III collagen (PRO-C3) is a novel biomarker identified through enzyme-linked immunosorbent assay for the N-terminal propeptide of type III collagen. This biomarker has shown a notable capability to distinguish mild from moderate degrees of fibrosis, with its variation correlating closely with the progression of fibrosis. A meta-analysis comprising eight studies offers a comprehensive review of the diagnostic accuracy of PRO-C3 in detecting advanced fibrosis. The efficacy of PRO-C3 in identifying advanced fibrosis is supported by its specificity and sensitivity of 73% and 72%, respectively, and a summary estimate AUROC of 0.79 [23]. Notably, PRO-C3 levels are elevated in patients with severe obesity and advanced liver fibrosis, indicating a positive association with both insulin resistance markers and liver enzymes. Following bariatric surgery, a reduction in PRO-C3 has been observed, which aligns with the improvement in metabolic and liver parameters [24].

Age, presence of diabetes, PRO-C3 and platelet count (ADAPT) score, formulated based on PRO-C3 levels, age, platelet counts and diabetes, has been developed within a cohort of MASLD patients. This score achieved an AUROC of no less than 0.86 in detecting advanced fibrosis, showing superior performance compared with established scores such as APRI, FIB-4 and NFS [25]. In another study of patients with MASLD, ADAPT achieved AUROC of 0.865 for advanced fibrosis, with sensitivity and NPV of 82.2% and 96.1%, respectively. ADAPT outperformed PRO-C3 alone, APRI, FIB-4, BARD and NFS in detecting advanced fibrosis [26]. PRO-C3 and ADAPT effectively ruled out the presence of advanced fibrosis in patients with MASLD, which reduced the need for invasive liver biopsies. Based on these findings, PRO-C3 can serve as a routine blood biochemical test for detecting liver fibrosis and ADAPT has the potential to enhance the precision of fibrosis diagnosis.

MMPs and MP3

Matrix metalloproteinases (MMPs) are the main enzymes implicated in extracellular matrix degradation. MMPs do not only remodel the extracellular matrix but also regulate immune responses. MMPs are associated with many acute and chronic liver diseases. In the study cohort consisting of 194 patients with CHC who underwent liver biopsy prior to antiviral therapy and 194 matched healthy individuals, MP3 was developed based on MMP-1 and calculated by $0.5903 \times \log$ [PIIINP (ng/mL)] $- 0.1749 \times \log$ [MMP-1 (ng/mL)]. This score showed an AUROC of 0.82 for detecting significant fibrosis, achieving a sensitivity of 60% and a specificity of 92%. By using the cut-off value of 0.50, MP3 showed the best predictive value for significant fibrosis with a high specificity of 98.9% and PPV of 94.4% in another cohort of CHC patients [27]. MP3 can reliably indicate the degree of liver fibrosis in patients with CHC. Applying varying cut-off values allows the diagnosis of significant fibrosis with a high degree of certainty.

Fibrotest

Fibrotest was developed in CHC patients based on α_2 macroglobulin (α_2MG), GGT, apolipoprotein A1, haptoglobin, total bilirubin, age, and gender. The AUROCs were no less than 0.83 for clinically significant fibrosis. It obtained a high NPV value of 100% to exclude significant fibrosis and a high PPV value of larger than 90% by using the cut-off values of 0.10 and 0.60, respectively [28]. A study evaluated the 10-year prognostic value of Fibrotest and demonstrated good performance of Fibrotest in predicting 10-year liver-related survivals, achieving high AUROCs of 0.941 in MASLD patients and 0.875 in CHC patients [29]. Another study compared the performance of Fibrotest and other scores including Forns index, APRI, and Fibroindex in patients with CHC and those with other chronic liver diseases. It showed that the Fibrotest had excellent diagnostic accuracy for liver fibrosis, outperforming other scores and was equally effective in different aetiologies [30]. Possible confounding variables include haemolysis, which may affect haptoglobin and bilirubin; biliary pathology and Gilbert syndrome, which may affect bilirubin; and alcohol consumption, which may affect GGT level.

Hepascore

Hepascore was created in a cohort of CHC patients and composed of bilirubin, GGT, hyaluronic acid, α_2MG, age and gender. The AUROCs of the score for significant fibrosis, advanced fibrosis, and cirrhosis ranged from 0.82 to 0.85, 0.90 to 0.96 and 0.89 to 0.94, respectively. By applying certain cut-off values, it achieved specificity and sensitivity values ranging from 74% to 92% and 63% to 95% for significant fibrosis and advanced fibrosis, respectively [31]. A study compared the performance of six non-invasive scores to detect liver fibrosis in CHC patients and Hepascore achieved AUROCs of 0.79 and 0.85 to identify significant fibrosis and extensive fibrosis, respectively. By using the cut-off value of 0.50, Hepascore showed a high NPV of 89.6% to rule out extensive fibrosis. The diagnostic performance of Hepascore was similar to other tests [32]. Utilizing Hepascore may avoid liver biopsies in cases where cirrhosis is suspected. It can also assist in making decisions about screening for varices and HCC, and in planning for the appropriate follow-up strategy.

FibroMeters

FibroMeters are groups of biomarkers to assess liver fibrosis, including platelet count, prothrombin time, AST, α_2MG, hyaluronate, urea and age. Various versions of FibroMeters are being used for different chronic liver diseases including viral hepatitis, MASLD and ARLD. A systematic review evaluated the performance of various versions of FibroMeters in MASLD patients and found that combined FibroMeter-VCTE performed the best in identifying advanced fibrosis with sensitivity and specificity of 83.5% and 91.1%, respectively [33]. In a multicentre cohort of patients with MASLD, FibroMeter-VCTE achieved an AUROC of 0.84 to detect advanced fibrosis. It was superior to other fibrosis tests including NFS, FIB-4, Fibrotest and Hepascore, and significant number of liver biopsies were avoided due to the test [34]. FibroMeter showed effectiveness in categorising patients with MASLD into different groups by using the cut-off values of 0.499, 0.754 and 0.969 at baseline, with each group characterised by varying prognostic outcomes. The diagnostic accuracy was similar to LSM [9].

NIS4/NIS2+™

NIS4®, comprising four MASH-associated biomarkers (miR-34a-5p, alpha-2 macroglobulin, YKL-40 and glycated haemoglobin), and NIS2+ ™ (the optimized version of the blood-based NIS4®) were developed along with MASH therapeutic trials. They have satisfactory performance in identifying patients with at-risk MASH (i.e. F2-3 fibrosis and NAS ≥4) and hence a substantial number of unnecessary liver biopsies and screening costs can be reduced [35].

Ultrasound elastography

Shear wave-based ultrasound elastography techniques are commonly used imaging modalities in assessing liver fibrosis. These include VCTE, two-dimensional shear wave elastography (2D-SWE) and point-shear wave elastography (p-SWE).

VCTE

Vibration-controlled transient elastography (VCTE) produces low frequency (50 Hz) vibrations with shear wave transmission through the liver followed by ultrasound wave through a probe on the skin overlying the liver to attain LSM, which is calculated from the velocity of the shear wave propagating through the liver parenchyma. The higher the velocity, the higher LSM reading and the stiffer the liver parenchyma is. VCTE, being the most widely used ultrasound elastography modality, underwent numerous studies in the past decades and was validated, compared with liver biopsy as the gold standard, across different liver diseases, such as CHB [36–38], CHC [39–41], co-infection with HIV [42], MASLD [43], ARLD [44], autoimmune hepatitis (AIH) [45], primary biliary cirrhosis (PBC), primary sclerosing cholangitis [46], Wilson's disease and haemochromatosis [47]. VCTE has been proven a reproducible tool in diagnosing advanced fibrosis (F3) and cirrhosis (F4) with good overall accuracy [48–49]. In a meta-analysis including 50 studies on VCTE as liver fibrosis assessment, with liver biopsy as a reference and regardless of underlying liver diseases, the mean AUROC for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were 0.84, 0.89 and 0.94 respectively [48]. As well, VCTE has a high negative predictive value (NPV) of above 90%, with LSM <8 kPa generally accepted in ruling our advanced fibrosis regardless of underlying aetiology [50–51].

Different optimal cut-off values of LSM by VCTE apply to different liver diseases. Taking MASLD, with validation studies focusing on NAFLD as the old nomenclature, as an example, the LSM cut-off range of 8 to 12 kPa has an 84%–100% sensitivity and 83%–97% specificity for F3–F4 fibrosis [52]. In the validation study of VCTE on CHC, a cut-off value of 9.5 kPa had a sensitivity and specificity of 73% and 91% respectively for F3 fibrosis, and a cut-off value of 12.5 kPa had a sensitivity and specificity of 87% and 91% respectively for F4 fibrosis [39].

Apart from the use of VCTE in diagnosing or excluding advanced fibrosis or cirrhosis, LSM was validated in diagnosing cACLD which describes the spectrum of advanced fibrosis and compensated cirrhosis [53–54], without requiring liver biopsy for histological diagnosis of liver cirrhosis. For those with LSM <10kPa have cACLD ruled out, whereas those with LSM 10–15 kPa has a 74.9% sensitivity in ruling in cACLD and those with LSM >15 kPa are highly suggestive of cACLD [54–55]. The Baveno VII consensus also endorsed the use of LSM by VCTE, in combination with platelet count, in diagnosing clinically significant portal hypertension (CSPH) in patients with virus-related, alcohol-related or non-obese (BMI < 30 kg/m^2) NASH-related cACLD [54]. For instance, LSM >25 kPa or LSM 20–25 kPa with platelet <150 × 10^9/L, or LSM 15–20 kPa with platelet <110 × 10^9/L presume CSPH, signifying a higher risk of hepatic decompensation [54, 56]. VCTE, using a spleen-dedicated module (100 Hz), can obtain the spleen stiffness measurement to predict CSPH [57]. In other word, VCTE has not only been well validated with its diagnostic performance but carries prognostic values.

A new, wireless, palm-sized transient elastography system is now available, which enables a more convenient alternative to VCTE with comparative performance and a very high correlation of LSM results. This wireless tool brings forward a point-of-care NIT and facilitates upscaling of screening for liver fibrosis [58]. Comparisons between the three types of VCTE, namely Fibroscan®, iLivTouch©—Fibrotouch® and Liverscan®, are listed in Table 2.

Despite that, VCTE has suboptimal performance in distinguishing milder degrees of liver fibrosis, possibly due to variability in histological scoring of liver biopsy with milder fibrosis leading to an imperfect comparison between the two [59]. Nonetheless, VCTE is well proven with its ability to diagnose and rule out advanced fibrosis and cirrhosis as well as prognostication of liver disease, supporting it as a useful tool in assessing liver fibrosis. Although cut-off values for different severities of liver fibrosis have been established in adult individuals, the dedicated cut-off values in the paediatric population are not as well

Table 2. Similarities and differences of the three different types of vibration-controlled transient elastography (VCTE)

Feature	Fibroscan®	iLivTouch©—Fibrotouch®	Liverscan®
Company	Echosens, Frances	Wuxi Hisky Medical Technologies Co., Ltd. (Hisky Med), China	Eieling Technology Limited, Hong Kong, China
Machine size	Moderate to large	Moderate to large	Small
Wireless	No	No	Yes
Accuracy	Good	Good	Good
Real-time guidance	No	Yes	No

defined; most studies show that the results in the adult and paediatric groups are comparable [60].

Two-dimensional shear wave elastography

Shear wave elastography utilizes the acoustic radiation force impulse (ARFI) from the ultrasound probe to generate shear wave propagation through the liver parenchyma where the propagation velocity is measured. The velocity, expressed in metres over second (m/s), can be converted to kPa by Young's modulus [61]. Similarly, the higher the speed, the higher the LSM is. 2D-SWE has an advantage by making quantitative images of shear wave speed in a large region of interest (ROI) by placing the ARFI focus at multiple sequential locations, where they are free of large blood vessels or focal lesions which can confound the results, to detect the shear wave arrival time at multiple lateral locations, measuring the LSM in real-time. Compared with VCTE, it has a larger ROI that can be chosen in size and location by the operator [50].

Despite being a more recent modality of ultrasound elastography compared with VCTE, 2D-SWE has been well validated to show its comparable diagnostic performance to VCTE across different liver diseases. For instance, an individual patient data-based meta-analysis of 1,134 patients with liver biopsy showed that the AUROCs of 2D-SWE in patients with CHB, CHC and MASLD were 90.6%, 86.3% and 85.5% for diagnosing significant fibrosis, respectively, and 95.5%, 92.9% and 91.7% for diagnosing cirrhosis, respectively [62]. Similar performance was also shown in biopsy-proven autoimmune liver diseases by 2D-SWE [63]. The overall accuracy of 2D-SWE is comparable to that of VCTE [64] and appears even higher than that of VCTE when assessing the early stage of liver fibrosis [65–66]. Furthermore, 2D-SWE also carries prognostic value in cirrhosis with studies confirming its utilisation and reliability in predicting CSPH and survival in patients with cirrhosis [67–69].

Point-shear wave elastography

Similar to 2D-SWE, p-SWE utilizes the ARFI by the ultrasound probe in generating shear wave propagation for the calculation of the velocity which gives the LSM reading. On the contrary, it does not provide an elastographic map. Nonetheless, it has a high applicability and provides real-time LSM assessment. P-SWE provides a smaller ROI compared to VCTE with the measurement location chosen by the operator [50].

Likewise, p-SWE has been adequately validated with equivalent performance compared with VCTE in terms of diagnosing advanced fibrosis and cirrhosis across different liver diseases [70–73].

Confounding factors affecting diagnostic performance

Despite the favourable performance of shear wave ultrasound elastography in liver fibrosis assessment, multiple factors may affect the accuracy of the tests. The factors are largely disease- or patient-related.

Hepatic necroinflammation is one of the major disease-related factors leading to a falsely high LSM. The risk of falsely diagnosing cirrhosis by LSM increases significantly when the serum ALT is five times above the ULN [36]. On the other hand, LSM drops drastically after the necroinflammation resolves and that does not reflect genuine fibrosis regression [74]. Hepatic congestion and extrahepatic cholestasis also confound the assessment, causing a falsely high LSM reading. The presence of ascites affects the performance of VCTE, causing an invalid or inaccurate LSM. However, this is overcome by using 2D-SWE or p-SWE as these modalities appear unaffected by ascites [75].

Conventionally VCTE measures LSM by the M-probe. In situations where patients are obese, it is difficult for shear waves to penetrate through the thick subcutaneous and prehepatic fat, causing inaccurate LSM. Studies reported a BMI of 28–30 kg/m^2 as a factor associated with failed or unreliable LSM [76–77]. To overcome this, the XL-probe (which stands for Extra Large probe) was developed for obese patients, and the same cut-off values for LSM can be used when M-probe and XL-probe are used according to the appropriate BMI [78]. Besides, LSM is increased with a mean change by 1–2 kPa after meals and the value normalised within 180 minutes [79]. Thus, the patient should be fasted for 3–4 hours before receiving shear wave ultrasound elastography. Lastly, excessive alcohol intake may implicate LSM accuracy; current guidance suggests to repeat LSM by VCTE at least one week of alcohol abstinence or reduced drinking in case of elevated LSM and biochemical evidence of hepatic inflammation [50].

MRE

Magnetic resonance elastography (MRE) is performed on existing magnetic resonance imaging (MRI) machines using a phase contrast method with the required software to determine the degree of liver stiffness by assessing the mechanical wave propagation. With this technique, the whole liver is examined. MRE has emerged as the most accurate NIT for assessment of liver fibrosis, with high accuracy and reproducibility as well as high intra- and inter-observer agreement [80]. Its accuracy has been shown in various studies, including a prospective study involving 117 biopsy-proven NAFLD patients that showed a high AUROC of 0.92 for MRE in discriminating F3–F4 fibrosis from F0–F2 fibrosis and a threshold of >3.63 kPa having a sensitivity of 0.86 and specificity of 0.91 [81]. By the same token, a recent meta-analysis confirmed the findings by showing a high AUROC of 0.91 (sensitivity 78%, specificity 89%) for significant fibrosis (F2) and 0.92 (sensitivity 81%, specificity 90%) for advanced fibrosis (F3–F4) [82]. The excellent diagnostic performance appears consistent across sex, different levels of obesity and aetiologies of chronic liver disease [83].

Studies, mostly on MASLD patients, have also compared MRE with VCTE and showed its consistent superiority in diagnosing and differentiating liver fibrosis [84–85]. To conclude with a systematic review with individual patient data analysis involving

230 patients with biopsy-proven MASLD, the AUROCs of MRE and VCTE were 0.87 and 0.82, 0.92 and 0.87, 0.93 and 0.84, and 0.94 and 0.84 in the detection of ≥F1, ≥F2, ≥F3 and ≥F4 fibrosis, respectively [86]. This highlights a better diagnostic accuracy for MRE than for VCTE in the detection of each stage of fibrosis. Furthermore, MRE has a higher applicability than VCTE with >95% technical success rate as it is not affected by ascites and obesity [87], and can be performed in patients with altered hepatic anatomy. However, iron overload in the liver causes loss of magnetic resonance signal from the liver parenchyma, resulting in poor quality or uninterpretable MRE results [87].

Until recently, a novel method termed macromolecular proton fraction quantification based on spin-lock (MPF-SL) was developed to measure the relative macromolecule content in the liver, corresponding to liver fibrosis characterised by the deposition of collagen-rich fibrotic tissues in the extracellular region. Such detection of the collagen deposition in the liver has been showed by *in vivo* studies of patients with liver fibrosis [88]. Based on a retrospective study of 55 patients (22 with no fibrosis and 33 with F1–2 fibrosis), MPR-SL showed a positive correlation with liver fibrosis ($\rho = 0.59$) with no significant correlations with liver iron concentration ($\rho = 0.02$) or fat fraction ($\rho = 0.05$), and the AUROC of 0.85 in discrimination between F0 and F1–F2 fibrosis [89]. Further studies are required to validate and determine its role in liver fibrosis assessment, especially taking into consideration its high cost and limited availability in clinical practice.

Combinations of different modalities

A handful of well-validated scores by combining clinical, laboratory and elastography parameters are available to further improve the performance of NITs [90]. Agile 3+ takes into account LSM by VCTE, platelet count, ALT, AST, diagnosis of diabetes, age and sex, and has high diagnostic performance for F3; meanwhile, Agile 4 takes account of LSM, by VCTE, platelet count, ALT, AST, sex and presence of type 2 diabetes, and has high diagnostic performance for cirrhosis [90]. A combined score with MRE and FIB-4 (MEFIB score) provides a very high positive predictive value of 97.1% in identifying candidates with significant fibrosis [90].

Impact of specific aetiologies of liver disease

Different NITs have been validated in various aetiologies of liver disease with VCTE being the most widely validated modality. Nonetheless, there are confounding factors affecting the diagnostic performance of VCTE. Likewise, there are also factors affecting the accuracy of blood test-based NITs, not to mention that some are shown to have suboptimal performance in assessing liver fibrosis in certain kinds of liver diseases, such as an AUROC of <0.80 for FIB-4 in predicting histological stage in PBC [91].

To name a few, necroinflammation of hepatocytes takes place in active chronic viral hepatitis B or C, as well as MASH and autoimmune hepatitis, and can be reflected by a raised serum ALT and/or AST as surrogates. Serum albumin, as a negative acute-phase reactant, may drop during the inflammatory process. NITs involving these laboratory parameters, such as AST and ALT in FIB-4, and the addition of serum albumin in NFS, are prone to inaccurate results and hence a suboptimal liver fibrosis assessment. Accuracy of VCTE is not only affected by hepatic necroinflammation, but its validity in liver fibrosis reassessment after resolution of the hepatic inflammation is also questionable as best illustrated in CHC before and after sustained virologic response (SVR) that an improvement in LSM does not accurately reflect fibrosis regression [92]. MRE, despite proven its superiority, has its own weakness as the diagnostic performance is affected by iron overload as in cases of haemochromatosis. The similarities and differences in the impact of various liver diseases on diagnostic accuracy of NITs are listed in Table 3.

Chronic hepatitis B

Essentially all international management guidelines for CHB underscore the severity of liver fibrosis as one of the key treatment indications; antiviral therapy is indicated in the presence of significant fibrosis regardless of serum ALT level [1–3]. Yet, as ALT is one of the major confounding factors of LSM in CHB, the interpretation of LSM results should always be coupled with the ALT levels at the time of VCTE examination. An ALT-based algorithm has been developed and higher LSM cut-off values for different stages of liver fibrosis should be used in patients with elevated ALT levels up to 5 times of the ULN [36]. In more extreme

Table 3. Similarities and differences in the impact of various liver diseases in diagnostic accuracy of non-invasive tests

Characteristic	Chronic hepatitis B	Chronic hepatitis C	MASLD (or MAFLD)	PBC	AIH	Haemochromatosis
Similarities	• Elevated ALT and/or AST in acute infection or active disease	• Elevated ALT and/or AST in most cases of active chronic infection	• Elevated ALT/AST in NASH	• ALT/AST level can be mildly elevated	• Elevated ALT and/or AST in active/flare of disease	• Elevated ALT and/or AST
Differences	• Possibility of severe reactivation of disease leading to elevated ALT/AST	• Questionable accuracy in fibrosis reassessment post-SVR	• High prevalence of obesity affecting diagnostic performance of NITs	• Laboratory-based NITs not well validated	• Disease course monitoring by LSM and ALT/IgG after at least six months of immunosuppressive therapy	• Iron overloading as the pathophysiology of the disease
Involved/affected NITs	• APRI, FIB-4, SWE	• APRI, FIB-4, ELF™, SWE	• FIB-4, NFS, SWE	• VCTE	• VCTE	• MRE

AIH = autoimmune hepatitis, ALT = alanine transaminase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, ELF™ = Enhanced liver fibrosis test, FIB-4 = fibrosis-4 index, MAFLD = metabolic dysfunction-associated fatty liver disease, MASLD = metabolic dysfunction-associated steatotic liver disease, MRE = magnetic resonance elastography, NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, NFS = NAFLD fibrosis score, NITs = non-invasive tests, PBC = primary biliary cholangitis, SVR = sustained virologic response, SWE = shear wave elastography, VCTE = vibration-controlled transient elastography.

scenarios, falsely high LSM results reaching the level of cirrhosis or CSPH may occur during severe acute exacerbation of hepatitis B virus (HBV) [93]. This is because not only liver fibrosis but also other factors contribute to the stiffness of the liver. LSM has been consistently found to be falsely elevated in acute hepatitis manifested as ALT flares [94]. In this setting, LSM tends to decrease considerably after the resolution of acute hepatitis. Therefore, applying VCTE in this setting could be misleading and not recommended until at least three months after normalisation or at least stabilisation of ALT levels below five times ULN [36]. The impact of ALT flares on NITs based on common clinical and laboratory parameters is less defined. Nonetheless, ALT and/or AST are common components in nearly all of these NITs (Table 1); it is logical to believe that the results would also be falsely elevated when tested in patients with severe acute exacerbation of HBV [95].

NIT is also an important part of some HCC risk scores. For example, the LSM-HCC score, which is optimised from the CU-HCC score with LSM replacing clinical cirrhosis as the key component of the risk score, further increases the NPV to nearly 100% for HCC prediction in 3 to 5 years in CHB patients [96]. PAGE-B is another widely validated HCC risk score based on common clinical and laboratory parameters; the modified version (mPAGE-B) and PAGE-B itself are both accurate and highly sensitive to rule out CHB patients who are receiving antiviral therapy at risk of HCC [97].

Chronic hepatitis C

HCV infection is one of the leading causes of chronic liver disease which progresses from chronic inflammation to fibrosis and cirrhosis. These conditions can further develop complications such as HCC. A study comparing pre- and post-treatment liver biopsies in 38 HCV patients with cirrhosis found that 61% of these patients exhibited regression of cirrhosis and decreased fibrosis [98]. The performance of non-invasive methods to detect fibrosis regression after receiving treatment and achieving sustained virologic response (SVR) was crucial. Significant regression of VCTE values, FIB-4 and APRI were observed for CHC patients who received direct antiviral agents (DAAs) treatment [99]. However, it is unclear whether this regression is attributed to diminished inflammation or actual regression of liver fibrosis. One systematic review showed that SVR correlated with a significant reduction in liver stiffness. This effect was especially pronounced in patients who had high levels of inflammation initially or those who were treated with DAAs [100].

A meta-analysis involving 24 studies assessed the changes in LSM in CHC patients who achieved SVR and those who did not. This study revealed a median reduction in LSM of 28.2% among CHC patients who achieved SVR, in contrast to no significant change in LSM in patients who failed to achieve SVR. Among the 261 patients who achieved SVR and were initially classified as having advanced fibrosis or cirrhosis, 47.1% of them demonstrated a reduction in LSM to below 9.5 kPa after treatment. The short follow-up after SVR and potential confounders such as MASLD, diabetes and use of alcohol may influence liver stiffness [100]. However, a study involving 37 CHC cirrhotic patients with paired liver biopsy and LSM before and after SVR found that the AUROC of LSM to diagnose cirrhosis was 0.77 with specificity of 95% and a suboptimal sensitivity of 61% to rule out cirrhosis [74]. APRI and FIB-4 were analysed in another study involving 395 CHC patients treated with DAAs. Findings revealed a rapid and consistent decline in APRI and FIB-4 levels from the second week to the 12th week in patients who achieved SVR, which was likely attributed more to the decline in liver enzymes than to an actual regression of liver fibrosis [101]. These findings raise doubts about the reliability of non-invasive tests in detecting fibrosis regression and cACLD in CHC patients who achieved SVR. Cut-off values of NITs used before treatment may not be reliable after achieving SVR. It is necessary to validate the thresholds in extensive studies with longer follow-ups.

Even though fibrosis regression occurs, it does not eliminate the risk of HCC development in the years following treatment. In individuals with cACLD who have successfully achieved SVR with DAA treatment, the most common liver-related complication is the occurrence of HCC. In a retrospective single-centre study, 4.1% of patients who achieved SVR developed HCC during a median follow-up of 26 months. LSM ≥11 kPa was independently associated with the risk of HCC development 24 months after achieving SVR [102]. A meta-analysis of 29 cohort studies demonstrated that FIB-4, APRI and LSM had good performance in predicting HCC in CHC patients with SVR. In individuals achieving SVR post-DAA therapy, the pooled adjusted hazard ratio for LSM was 5.55, with a pooled AUROC of 0.84. Furthermore, FIB-4 and LSM were linked to overall mortality, having pooled adjusted hazard ratios of 2.07 and 4.04, respectively [103]. Measuring LSM after achieving SVR could aid a better understanding of the ongoing risk hepatic events in patients with CHC who have undergone antiviral treatment.

MASLD

MASLD is a prevalent liver disease affecting 32.4% of the global population and continues to increase over time [104]. A proportion of patients with MASLD develop advanced liver fibrosis that implicates both hepatic and extrahepatic complications and mortality [105]. Many NITs have been developed for fibrosis assessment in MASLD, notably fibrosis-4 (FIB-4) score and NFS. The low cut-off values of these two scores (1.3 for FIB-4 and −1.455 for NFS) have a high sensitivity to rule out advanced fibrosis whereas the high cut-off values (3.25 for FIB-4 and 0.676 for NFS) have a high specificity to rule in advanced fibrosis [50, 106]. However, around one-third of patients fall into the grey zone of the two tests [107]. As well, obesity implicates the performance of both FIB-4 and NFS. In a prospective study with 315 patients (71 non-obese and 244 obese, defined by BMI ≥25 kg/m^2), the AUROCs declined significantly from 0.97 to 0.84 for FIB-4 ($P = 0.002$) and 0.97 to 0.80 for NFS ($P < 0.001$) in the presence of obesity [108].

There are other NITs developed along with MASH therapeutic trials, such as NIS2+™, NIS4, MACK-3, MEFIB, FAST and MAST scores, in identifying patients with at-risk MASH which is defined as MASH with F2–F3 fibrosis and NAFLD activity score of ≥4. The overall accuracy is 0.72–0.88 and their use is constrained by limited availability (such as special blood components and MRE) and high cost [109].

VCTE is commonly used in patients with MASLD for assessing the degree of liver fibrosis and its performance in identifying advanced fibrosis has been well validated in numerous studies. In the meta-analysis involving 20 studies using VCTE, the AUROCs were 0.87 with M-probe, 0.86 with XL-probe for advanced fibrosis, 0.92 for M-probe and 0.94 for XL-probe for cirrhosis [107]. Although there are no universally accepted cut-off values for ruling in or out advanced fibrosis in patients with MASLD, LSM <8 kPa is most validated to rule out advanced fibrosis with a high NPV of >90% [50]. Also, in another study from a decade ago with 246 patients with NAFLD receiving VCTE using the M-probe and liver biopsy, a cut-off of 8.7 kPa had a sensitivity of 84% and specificity of 83% in diagnosing ≥F3 fibrosis (i.e. advanced fibrosis) and a cut-off of 10.3 kPa had sensitivity of 92% and specificity of

88% in diagnosing F4 fibrosis (i.e. cirrhosis) [43]. Obesity again has implications on the diagnostic performance of VCTE as it leads to failed or unreliable LSM. The XL-probe is used for obese patients who have longer skin-to-capsule distance and it reduces the chance of failed or unreliable LSM. Comparing M-probe with XL-probe in a study with patients from Asia and Europe, both probes were found to have nearly identical median LSM at each fibrosis stage with similar performance irrespective of the BMI, and thus same LSM cut-off values could be used for both probes [78]. However, high BMI appears to increase LSM [105, 110]. Additionally, from an analysis of 968 patients with biopsy-proven MASLD, LSM was found to be less accurate in obesity (AUROC 0.79 vs 0.90, $P < 0.001$) regardless of the type of VCTE probe used [111]. This is of particular importance to note as obesity is prevalent in patients with MASLD. MRE, despite being the most accurate NIT in detecting liver fibrosis as of date, is not routinely recommended in daily clinical practice given its high cost and limited availability.

Other aetiologies

LSM is useful and accurate across different chronic liver diseases on top of chronic viral hepatitis and MASLD, including PBC, PSC, AIH, Wilson's disease and haemochromatosis. In general, VCTE outperformed other NITs such as APRI, FIB-4, AST/ALT ratio, hyaluronic acid and the Mayo risk score for PBC. While VCTE is applicable to essentially all chronic liver diseases, interpretation with caution is warranted in the presence of extrahepatic cholestasis, hepatic congestion, hepatic amyloidosis and recent food intake as they are well- acknowledged to be associated with a falsely high LSM value [95].

In patients with AIH, LSM correlates better with histologic grade than stage at the beginning of immunosuppressive therapy; in contrast, the LSM correlates better with histologic stage than grade with longer treatment duration (at 6–18 months) [45]. LSM cut-off for ARLD is higher than that for chronic viral hepatitis owing to the different patterns of fibrosis distribution in ARLD [64]. The cut-off values for different stages of liver fibrosis are likewise higher in cholestatic liver diseases like PBC and PSC than in other liver diseases because cholestasis also contributes significantly to liver stiffness [112]. MRI-based techniques have decreased reliability in iron overload states (e.g. haemochromatosis) and passive congestion [47].

Conclusions

NITs for liver fibrosis, particularly imaging-based tests like VCTE, have been a routine investigation in clinical practice for patients with suspected or confirmed liver diseases (Figure 1). In 2024, more systemic implementation would be obliged to provide guidance for the management. While the clinical utility is mostly similar across various liver diseases, the application and interpretation may be unique in certain clinical contexts of different diseases. Serum markers are simple and easily accessible in low-resource settings; imaging tests provide better accuracy in stage liver fibrosis and predict clinical events and prognosis. More research will define the optimal cut-off values of various NITs to include patients in MASLD treatment programmes in the near future as the reimbursement criteria of novel MASH therapeutics. It is important to delineate the interpretation of changes in the results of various NITs in response to treatment.

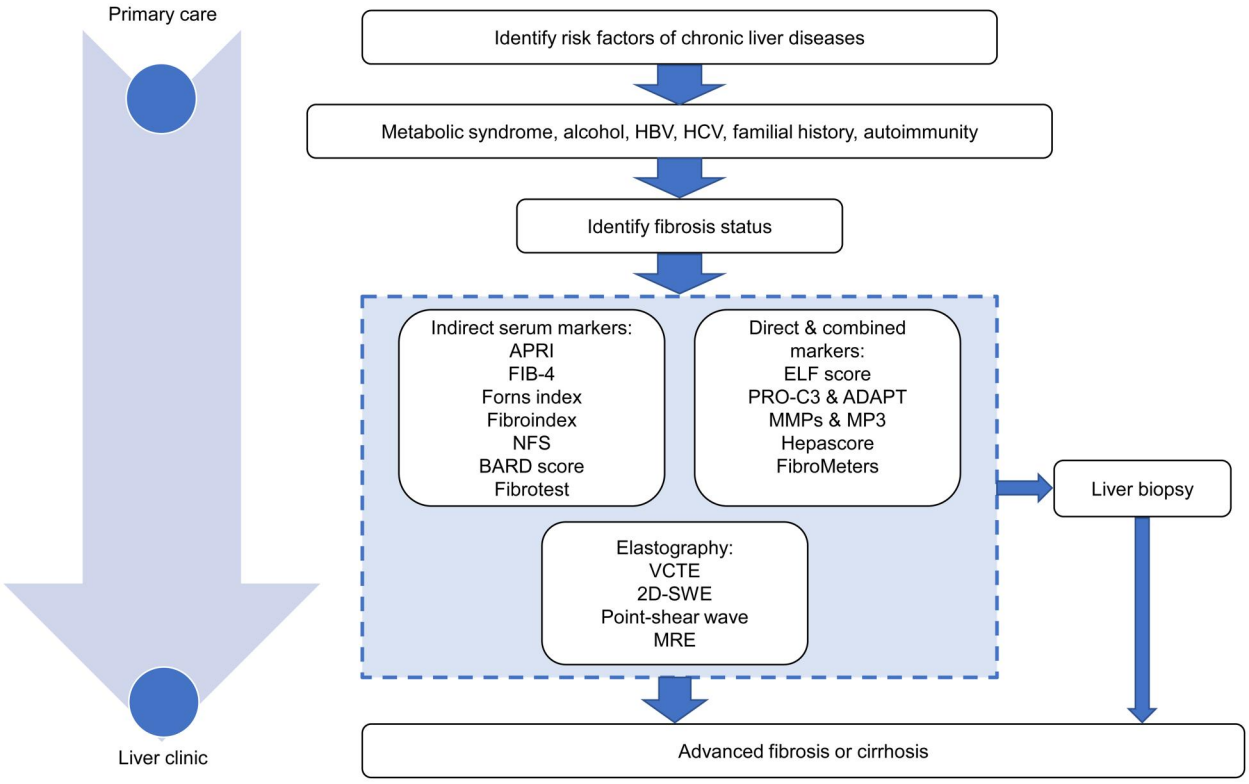

Figure 1. How to apply the tests in clinical practice. HBV = hepatitis B virus, HCV = hepatitis C virus, APRI = aspartate aminotransferase to platelet ratio index, FIB-4 = fibrosis-4, NFS = non-alcoholic fatty liver disease fibrosis score, ELF = enhanced liver fibrosis, ADAPT = Age, presence of diabetes, PRO-C3, and platelet count, MMPs = matrix metalloproteinases, VCTE = vibration-controlled transient elastography, 2D-SWE = 2D-shear wave elastography, MRE = magnetic resonance elastography.

Authors' Contributions

All authors were responsible for the study concept and design, acquisition and analysis of data, had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. G.W. is the submission's guarantor of the article. All authors were responsible for the interpretation of data, the drafting, and the critical revision of the manuscript for important intellectual content. All authors approved the final version of the article.

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Conflicts of Interest

Grace Wong has served as an advisory committee member for AstraZeneca, GlaxoSmithKline, Gilead Sciences and Janssen, and as a speaker for Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen and Roche. She has also received a research grant from Gilead Sciences. Jimmy Lai has served as an advisory committee member and a speaker for Gilead Sciences and Boehringer Ingelheim. Lilian Liang declares no competing interests.

Data Availability

The data that support the findings of this study are available on request from the corresponding author, GLW, subject to approval from the Ethics Committee. The data are not publicly available due to ethical restrictions.

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