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REVIEW

Non-Invasive Tests for the Detection of MASLD: Biomarkers and Imaging for Staging Steatosis, MASH, and Fibrosis

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Abstract: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has become the predominant cause of liver diseases, with a rising incidence globally, has gained considerable attention. As a heterogeneous disease, it imposes a significant economic burden on society and can progress to severe outcomes like cirrhosis, hepatocellular carcinoma (HCC) and even death. However, awareness, attention, and early intervention for MASLD are lacking, as the disease often starts insidiously and remains asymptomatic in its initial stages. The traditional diagnostic approaches, including liver biopsy and routine laboratory tests, are limited by their invasiveness, acceptance, and specificity. Similarly, imaging methods struggle with high costs and insufficient sensitivity. Early diagnosis and management of MASLD are critical to preventing the onset and decelerating the progression of liver fibrosis, thereby improving liver health. These challenges have prompted considerable efforts to develop non-invasive tests for diagnosing and managing MASLD. Using serum alone or in combination with imaging technology has the potential to improve early diagnostic accuracy, allowing clinicians to better assess and classify the disease. This article offers a comprehensive overview of the current state of non-invasive assessments for MASLD, discussing their applicability and exploring their potential in diagnosing and staging steatosis, MASH, and fibrosis, thereby enhancing patient management and care.

Keywords: MASLD, MASH, fibrosis, non-invasive assessment, diagnosis

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver diseases worldwide.[1] MAFLD encompasses a wide spectrum of liver diseases ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, with potential progression towards cirrhosis, hepatocellular carcinoma (HCC) and liver failure.[2–4]

While obesity and diabetes mellitus type 2 (T2DM) were not yet highly prevalent, ethanol abuse and malnutrition were primary causes of fatty liver disease. In 1980, non-alcoholic steatohepatitis was coined after liver biopsies revealed that some patients with unexplained hepatitis exhibited pathological changes akin to those seen in alcoholic hepatitis.[5] The spectrum of the disease was further expanded to non-alcoholic fatty liver disease (NAFLD) in 1986, and the diagnosis required the exclusion of other various causes which were known to cause fatty liver disease like alcohol consumption.[6] Non-alcoholic hepatic steatosis was defined as a presence of a minimum of 5% hepatic steatosis and no evidence of hepatocellular injury of the hepatocyte balloon. Non-alcoholic steatohepatitis was at least 5% hepatic steatosis and inflammation with hepatocellular injury.[7–9]

The limitations of the original exclusive terminology, which did not include etiology and pathogenesis, became increasingly apparent and had seriously affected the current screening, diagnosis, prevention and management of NAFLD. In 2020, an international panel of experts proposed renaming NAFLD as MAFLD, but the nomenclature had

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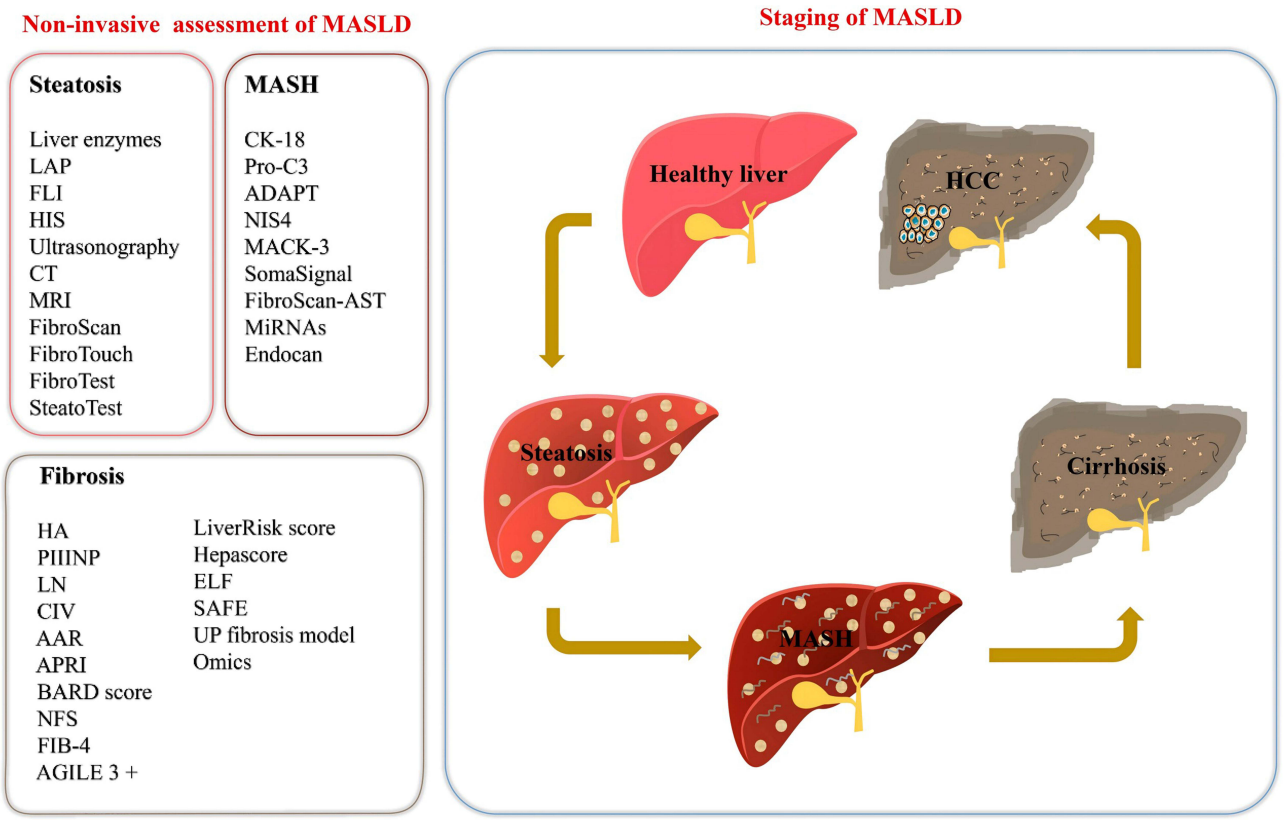
Graphical Abstract



not yet been standardized in clinical practice.[10] The renaming was supported by the Asia Pacific Association of the Society of Hepatology, the Chinese Medical Association Section of Hepatology and the North African and Middle Eastern Hepatology Society, with the guideline issuing or the diagnosis and treatment of MAFLD in 2020.[10–12] Recently, due to the necessity for a revised nomenclature to address the exclusivity and stigmatization associated with the term MAFLD, three major international hepatology societies—the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Latin American Association for the Study of the Liver, engaged in a consultative process and ultimately selected Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) as the replacement terminology for both NAFLD and MAFLD.[13,14]

The prevalence rate of MASLD among adults reached up to 38%, with the highest prevalence being in Latin America (44.37%), then Middle East and North Africa (36.53%), followed by South Asia (33.83%), South-East Asia (33.07%), North America (31.20%), East Asia (29.71%) as well as Asia Pacific (28.02%).[15,16] In a 2017–2022 study of nearly 5.8 million adults, the incidence of steatosis, severe steatosis, advanced fibrosis and cirrhosis were found to be 44.39%, 10.57%, 2.85% and 0.87%, respectively. Moreover, the prevalence of MASLD was higher in males than females, and more prevalent in Northern China compared to Southern China.[17]

Liver biopsy has been the gold standard for diagnosing MASLD, providing definitive insights into the extent and nature of liver damage.[18] Nevertheless, liver biopsy still has well-known limitations, including invasiveness, poor acceptability, potentially life-threatening complications, sampling variability and high cost.[19] Liver biopsy assessment is impractical, and this has prompted efforts to develop non-invasive tests to diagnose MASLD. Key non-invasive tools for diagnosing and staging MASLD, MASH, and liver fibrosis include serum biomarkers (eg, FLI, FIB-4, NFS, ELF, PRO-C3, CK-18) and imaging techniques such as FibroScan, MRI, and CT, which together enable accurate risk

stratification and reduce the need for liver biopsy. Recently, non-invasive tools, ranging from serum biomarkers to advanced imaging techniques, have enabled accurate risk stratification and disease staging, offering a practical and safer alternative to liver biopsy. Early non-invasive diagnosis facilitates timely intervention, effectively halting disease progression to advanced stages such as fibrosis, cirrhosis, or hepatocellular carcinoma, thereby improving long-term patient prognosis and reducing associated mortality and disease burden.[20–22] In this article, we summarize the development of non-invasive assessment and their diagnostic accuracy for diagnosing and staging steatosis, MASH, and liver fibrosis.

Non-Invasive Assessment of Liver Steatosis

Liver Enzymes

Laboratory tests, such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), and total bilirubin, are crucial for assessing and monitoring liver problems. Liver enzyme concentrations remain within normal ranges in over half of MAFLD patients, showing a poor correlation with disease severity. The ALT concentration being twice the upper limit of normal indicates that the sensitivity for predicting MASH was 50% and the specificity was 61%.[7] ALT, AST and GGT are important components of most scores and are often combined with different laboratory markers or demographic characteristics to diagnose liver steatosis, MASH, and fibrosis. Previous studies have suggested associations between serum liver enzyme levels and both the stage and severity of MASLD; however, specific diagnostic thresholds remain undefined.[23,24] In clinical practice, liver enzymes are routinely used as screening and monitoring markers. Nevertheless, their sensitivity and specificity are limited, necessitating a comprehensive assessment that integrates tools such as the fibrosis-4 index (FIB-4), imaging modalities, or liver stiffness measurement to accurately evaluate the stage of liver injury.[25]

LAP, FLI and HIS

Lipid accumulation product (LAP) is a metric that combines measurements of waist circumference and triglyceride. This composite index serves as a reliable indicator for the screening MASLD. Its reliability lies in its ability to capture the synergistic effects of central obesity and dyslipidemia, which are key contributors to hepatic lipid accumulation and subsequent liver pathology. A meta-analysis with 96,101 participants suggests that lipid accumulation supports the effectiveness of LAP, with the sensitivity of 94% (CI95: 72–99%) and the specificity of 85% (CI95: 62–96%).[26]

The fatty liver index (FLI), another diagnostic measure for hepatic steatosis, incorporates body mass index (BMI), waist circumference, triglyceride and GGT. Zhu, Y et al indicated this index is an effective predictor of MAFLD and a potential alternative to ultrasonography for diagnosing the degree of steatosis. This comprehensive index provides clinicians with a practical and non-invasive tool to facilitate early detection and intervention strategies.[27]

The hepatic steatosis index (HSI) is a regular measurement based on gender, BMI, AST: ALT ratio (AAR) and T2DM. HSI is a good indicator for the identification of the presence or absence of hepatic steatosis and can assess the severity of MAFLD.[28] Besides, FLI and HSI are also associated with metabolic syndrome, insulin resistance and T2DM.[27–29] These composite scores integrate routine clinical and laboratory data, offering practical, non-invasive tools for steatosis screening with good predictive performance. However, they are influenced by metabolic comorbidities and may lack standardization across populations, limiting their generalizability.

Ultrasonography, CT and MRI

Conventional ultrasonography remains the primary method of detecting steatosis, being widely utilized in clinical practice. While conventional ultrasonography is a widely used, effective first-line tool for detecting moderate-to-severe steatosis, its sensitivity for detecting advanced fibrosis is comparatively lower.[30] Ultrasonography performed at an early stage can be used to determine in which patients further testing should be performed, potentially reducing false-positive results and minimizing the need for extensive follow-up testing. The diagnostic accuracy of ultrasonography for ≥10% steatosis was between 0.91 and 0.93, with a sensitivity of 0.88–0.97 and a specificity of 0.69–0.92.[31]

Compared to ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) offer more detailed insights into liver condition and are effective in diagnosing cirrhosis or portal hypertension. However, their widespread use is limited due to higher costs, less widely availability, in and for CT, exposure to radiation.[32] A retrospective study shows that CT can assess steatosis in liver donor candidates with unacceptable steatosis, potentially avoiding unnecessary biopsies.[33] Proton magnetic resonance spectroscopy, a quantitative referential standard for the assessment of hepatic fat content, is shown strong correlation with hepatic steatosis as assessed in liver biopsies. Moreover, it is the preferred technique for monitoring changes in steatosis.[34,35] Ultrasound is widely accessible and effective for detecting moderate-to-severe steatosis, while CT and MRI provide detailed fat quantification and anatomical assessment, but ultrasound has low sensitivity for mild steatosis and fibrosis, CT involves radiation exposure, and MRI is costly and less accessible.

FibroScan and FibroTouch

FibroScan is a non-invasive tool which accurately assesses fat deposition and liver stiffness. It includes a module called controlled attenuation parameter that correctly identifies patients with steatosis. The area under the receiver operating characteristic curve (AUROC) for steatosis ≥S1, 87% (95% CI 82–92%), 77% (95% CI 71–82%) for steatosis ≥S2, and the AUROC for steatosis ≥S3 is 70% (95% CI 64–75%).[36,37] Ultrasound-based vibration-controlled transient elastography is now broadly used, with FibroScan in Europe serving as a first-line tool for evaluating and improving diagnostic accuracy of liver fibrosis. However, this method is limited to determining the degree of fibrosis or the presence of cirrhosis and cannot be used to diagnose or rule out MASH.[37–39] This limitation points to a potential gap in its application and suggests a need for complementary diagnostic tools or methods.

FibroTouch uses attenuation parameters and liver stiffness measurement to quantify hepatic steatosis and fibrosis.[40] It shows satisfactory consistency with FibroScan in assessing liver fibrosis but have a significantly higher success rate.[41] FibroTouch is widely used in many countries to diagnose hepatic steatosis and fibrosis. Previous studies demonstrate that FibroTouch is highly consistent with AST: platelet ratio index (APRI), fibrosis 4 score (FIB-4) and liver biopsy. It also demonstrates significant diagnostic value in identifying severe liver fibrosis and early cirrhosis.[42,43] FibroScan and FibroTouch enable simultaneous assessment of steatosis and fibrosis with high diagnostic accuracy and reproducibility, yet they are operator-dependent, may be unreliable in obese patients, and cannot diagnose MASH or differentiate inflammatory activity.

FibroTest and SteatoTest

FibroTest is a panel of serum biomarkers including α2-macroglobulin, total bilirubin, GGT, haptoglobin, and apolipoprotein-A1, adjusted for age, sex, and BMI. Originally designed for fibrosis assessment, FibroTest has demonstrated good diagnostic performance in predicting advanced fibrosis in patients with MASLD, with superior accuracy compared to simple serum scores such as BARD and FIB-4. Beyond its diagnostic utility, FibroTest also holds high prognostic value for predicting liver-related mortality in MASLD patients.[44,45]

SteatoTest is an extended panel that includes all FibroTest components plus cholesterol, triglycerides, fasting glucose, and BMI, adjusted for age and sex. It was developed specifically for the detection of hepatic steatosis and shows moderate accuracy in predicting steatosis, potentially reducing the need for liver biopsy in some patients.[46] However, SteatoTest is not widely used in clinical practice due to its inability to discriminate between different grades of steatosis and its relatively high cost.

In summary, these tools enable a practical approach to patient management: For ruling out steatosis, highly sensitive indices like HSI or ultrasonography are recommended due to their high negative predictive value. For confirming the diagnosis, tools with high specificity, such as the FLI or FibroScan CAP, are preferred to minimize false positives. If results from different methods are discordant, a second-line imaging modality like MRI-PDFT for quantitative fat assessment or a specialist referral for further evaluation is recommended. Table 1 summarizes common non-invasive tools for liver steatosis, including indices like LAP, FLI, HSI, and imaging methods such as ultrasonography and FibroScan.

Table 1 Common Biomarker Models for Liver Steatosis

Index	Algorithm	AUROC	Sensitivity	Specificity	Endpoint
Lipid accumulation product[26]	Lipid accumulation product = (waist circumference [cm] - 65) * triglyceride (mmol/L)) for men, = (waist circumference [cm] - 58) * triglyceride [mmol/L]) for women	0.82 (95% CI: 0.79–0.85)	0.94 (95% CI:0.72–0.99)	0.85 (95% CI:0.62–0.96)	Steatosis
Fatty liver index[47]	Fatty liver index = $(e^{0.953 * \log e (\text{triglyceride}) + 0.139 * BMI + 0.718 * \log e (GGT) + 0.053 * \text{waist circumference} - 15.745})/(1 + e^{0.953 * \log e(\text{triglycerides}) + 0.139 * BMI + 0.718 * \log e [GGT] + 0.053 * \text{waist circumference} - 15.745}) * 100$	0.83 (95% CI: 0.82–0.84)	0.81 (95% CI:0.79–0.82)	0.70 (95% CI:0.69–0.73)	Steatosis
HIS[48]	HIS = 8 * AAR + BMI (+ 2, if female; + 2, if diabetes mellitus)	0.82 (95% CI: 0.81–0.83)	0.93 (95% CI:0.92–0.94)	0.40 (95% CI:0.38–0.42)	Steatosis
Ultrasonography[32]	–	0.91–0.93	0.93 (95% CI:0.88–0.97)	0.83 (95% CI:0.69–0.92)	Steatosis
FibroScan-based Index[37]	–	0.87 (95% CI: 0.82–0.92)	0.80 (95% CI:0.75–0.84)	0.83 (95% CI:0.69–0.92)	5% steatosis
		0.77 (95% CI: 0.71–0.82)	0.70 (95% CI:0.63–0.75)	0.76 (95% CI:0.68–0.83)	34% steatosis
		0.70 (95% CI: 0.64–0.75)	0.72 (95% CI: 0.63–0.79)	0.63 (95% CI: 0.56–0.69)	67% steatosis

Abbreviations: AUROC, Area Under the Receiver Operating Characteristic curve; AAR, AST to ALT Ratio; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; CI, Confidence Interval; BMI, Body Mass Index; GGT, Gamma-Glutamyl Transferase; AAR, AST to ALT Ratio; HSI, Hepatic Steatosis Index.

Non-Invasive Assessment of MASH

CK-18

Cytokeratin 18 (CK-18), a marker derived from hepatocyte apoptosis and necrosis, exhibits an increase in levels correlating with these cellular processes. It demonstrates a sensitivity of 66–78% and a specificity of 82%–87%.[49,50] To improve diagnostic utility, some researchers have proposed combining serum levels of CK-18 with the apoptosis-mediated surface antigen. However, CK-18 alone has been constrained by the absence of commercially available, standardized assays and low sensitivity at the individual level, and these limitations have led to limited clinical application so far.[49] When combined with other tests, CK-18 may be a promising diagnostic marker for MASH.[51] That highlights the ongoing efforts to refine diagnostic tools to better manage and identify liver diseases, particularly in the complex conditions like MASH. CK-18 reflects hepatocyte apoptosis and shows moderate diagnostic accuracy for MASH, especially when combined with other markers, but its clinical use is limited by lack of standardization, variable sensitivity, and absence of commercially available assays.

PRO-C3 and ADAPT

The N-terminal type III collagen pro-peptide (PRO-C3) is linked to the disease activity, progression and clinical outcomes of MAFLD. PRO-C3 is independently associated with significant and advanced fibrosis. Recent findings suggest that PRO-C3 is higher in patients with MASH than those with simple steatosis, and the use of PRO-C3 may appropriately identify patients with advanced fibrosis in T2DM patients.[52]

ADAPT, a non-invasive composite algorithm, incorporates PRO-C3, T2DM status, platelet count, and age. It is capable of accurately identifying patients with MASH and advanced fibrosis, showing enhanced performance in detecting disease activity and fibrosis. ADAPT demonstrates superior performance that diagnostic accuracy for fibrosis is significantly better than APRI, AAR, PRO-C3and FIB-4.[53] Although PRO-C3 is directly linked to fibrogenesis and ADAPT integrates it with clinical variables to improve detection of advanced fibrosis and MASH, these tools require further validation in diverse populations and may not be widely available in routine practice.

NIS4, MACK-3 and SomaSignal

NIS4 is a diagnostic panel used to identify high-risk MASH. It incorporates microRNA-34a-5p, α2-macroglobulin, glycated haemoglobin and human chitinase-3-like protein 1.[54] Its diagnostic performance is unaffected by liver enzyme concentrations, BMI, age and gender, providing an effective way to diagnose or rule out high-risk MASH. Harrison et al have demonstrated that NIS4 in clinical settings or trials has the potential to significantly reduce unnecessary liver biopsies in patients with a low risk of disease progression.[55]

The MACK-3 score is a combination of three biomarkers associated with AST, CK18, and homeostasis model assessment. This composite score serves as a precise tool for improving patient selection in MASH therapeutic trials and may aid in identifying patients who need more aggressive strategies.[56,57]

Vali et al use serum proteomics to develop a dichotomous protein phenotype model (SomaSignal), with similar accuracy to FIB-4 for significant liver fibrosis. For detecting advanced fibrosis, it demonstrates superior performance compared to other diagnostic tools such as ADAPT and FibroScan demonstrating an AUROC of 90% (95% CI 86–94%), indicating its high diagnostic efficacy.[58] The ability of SomaSignal to detect advanced fibrosis helps in the timely and accurate staging of the disease, thereby providing critical insights that can guide more effective management and treatment strategies, which are crucial for optimizing therapeutic approaches and improving long-term patient outcomes.

These diagnostic panels offer high accuracy for identifying high-risk MASH and advanced fibrosis, with NIS4 being unaffected by common confounders, but they are complex, costly, and not yet standardized for widespread clinical use.

FibroScan-AST

FibroScan-AST score is diagnostic tool used to grade steatosis and identify patients with MAFLD who are at an increased risk of disease progression. This method employs simultaneous transient elastography to measure liver fat attenuation using several predictors, including liver stiffness measurement, controlled attenuation parameter, AST, and ALT. The predictive performance of FibroScan-AST in the identification, calibration and diagnostic accuracy is satisfactory.[59] Newsome et al have demonstrated that FibroScan-AST performs well, featuring a negative likelihood ratio of 0.2 and a positive likelihood ratio of 5. This score is particularly effective in identifying risk groups among patients with progressive MASH, indicating its utility in clinical settings for stratifying patient risk and guiding management decisions.[60] The FAST score combines liver stiffness, CAP, and AST to identify patients with progressive MASH, providing good risk stratification, but it requires specialized equipment and may not be suitable for all clinical settings, particularly primary care.

miRNAs and Endocan

MicroRNAs (miRNAs) are promising markers for the diagnosis and severity stratification of MAFLD. A previous study suggests that miRNA-34a, miRNA-122 and miRNA-192 can serve as potential diagnostic markers for separating steatosis and MASH. Serum miRNA-122 is useful for differentiating between MAFLD patients and healthy controls, while miRNA-34a is effective for differentiating between steatosis and MASH. Both miRNAs demonstrate moderate diagnostic accuracy, suggesting their potential utility in clinical settings for the assessment and management of liver diseases.[61,62] Johnson et al

find that miR-193a-5p shows an increase in the MAFLD cohort.[63] Moreover, serum miR-571 levels exhibit a strong correlation with liver fibrosis staging, and miRNA122a is associated with MASH and liver fibrosis.[64]

TGFB2 overlapping transcript 1, a newly discovered long noncoding RNA, is used to distinguish between patients with advanced fibrosis ($F \geq 3$) and those with significant fibrosis ($F \geq 2$) when combined with FIB-4 or liver stiffness measurement.[65] Endocan is a proteoglycan secreted by endothelial cells, which is independently associated with BARD and FLI. Klisic et al demonstrate that Endocan by itself is a poor discriminator of advanced fibrosis (AUROC = 0.667), but the addition of the endocan assay to the serologic model can increase the AUROC to 0.840, with a diagnostic specificity of 86.36% and a sensitivity of 72.41%.[66] miRNAs and endocan show promise as novel blood-based biomarkers for MASH and fibrosis, with potential for non-invasive diagnosis, but their diagnostic accuracy is moderate, and they lack validation in large cohorts and standardized assays.

Artificial Intelligence Models

Artificial intelligence (AI) technologies are significantly enhancing diagnostic performance by integrating multimodal data.[67] In the field of imaging, deep learning algorithms combined with multiparametric ultrasound (eg, liver viscosity, elastography) enable objective quantification of steatosis, inflammation, and fibrosis, thereby improving the accuracy of MASH identification.[68,69] AI models based on ultrasound images, such as the VAS-MASH-US score, have demonstrated promising diagnostic performance (AUROC = 0.75, sensitivity 79.0%), facilitating the identification of high-risk patients requiring biopsy and reducing unnecessary invasive procedures. At the biomarker level, machine learning integrates clinical parameters, metabolomics, and proteomics data to develop various tools, including the SomaSignal proteomic model, the MASHRisk blood-based score, and novel non-invasive tests (NITs) targeting F2–F3 fibrotic MASH, which significantly outperform traditional serum biomarkers (the latter showing sensitivities of only 62–66%).[70–72]

Furthermore, dynamic monitoring parameters (eg, changes in ALT, MRI-PDFF) have been integrated into the MASH resolution index for non-invasive assessment of histological improvement.[73] In the field of molecular imaging, PET tracers targeting CCR2/CD163, combined with AI analysis, enable non-invasive visualization of hepatic macrophage infiltration, reflecting inflammatory activity. In pathological assessment, AI-assisted systems such as AIM-MASH have demonstrated high reproducibility and scoring consistency in clinical trials, supporting pathologists in enhancing the reliability of histological interpretation.[74,75] Collectively, these AI-driven strategies not only optimize patient stratification and improve the efficiency of clinical trial enrollment,[76–78] but also facilitate precise risk stratification, disease monitoring, and individualized patient management.[79]

Identifying F2-F3 Fibrotic MASH

Patients with MASH and F2-F3 liver fibrosis represent the current treatment-eligible population as defined by the U.S. Food and Drug Administration, and accurate non-invasive identification of this subgroup is critical for clinical management and prognostic improvement. However, systematic evaluation and optimization of existing NITs specifically for this population remain insufficient.[80] Multiple studies have indicated that although traditional serum-based models (eg, FIB-4, enhanced liver fibrosis score) and imaging techniques (eg, transient elastography, MRI-proton density fat fraction, magnetic resonance elastography are useful for fibrosis risk stratification, their accuracy in distinguishing F2-F3 fibrosis in MASH is limited, partly due to discordance between fibrotic and inflammatory activity.[81] To enhance diagnostic performance, researchers are actively developing novel strategies, including machine learning-based multiparameter algorithms (eg, the acFibroMASH index integrating serum creatinine and aspartate aminotransferase), metabolomics-driven scores targeting high-risk MASH with NAS ≥4 and fibrosis stage ≥F2,[69] multiparametric ultrasound combined with liver viscosity measurement,[82] and LiverMultiScan technology utilizing cT1 values and liver fat content for MASH severity stratification (eg, cT1 > 875 ms indicating advanced MASH).[83] Furthermore, two-step screening algorithms (eg, initial triage with FIB-4 followed by elastography or specific biomarkers) are recommended for precise referral of high-risk populations such as individuals with type 2 diabetes or obesity.[84,85] With the approval of targeted therapies such as resmetirom, optimizing NITs for the identification of F2/F3 fibrotic MASH has become a key direction for advancing personalized treatment and improving clinical trial efficiency.

For the identification of MASH, a sequential approach is advisable: To rule out high-risk MASH and avoid unnecessary invasive procedures, tests with high sensitivity and a high negative predictive value, such as the FAST score, are most useful. For confirming the presence of MASH, panels with high specificity, like CK-18 or MACK-3, are preferred to ensure accurate diagnosis. In cases where there is discordance between a screening test and a diagnostic panel, or between serology and imaging, second-line assessment with MRI-based scores or a referral to a specialist center for a potential liver biopsy is crucial for definitive management. The diagnostic models for MASH, including CK-18, PRO-C3, ADAPT, NIS4, MACK-3, SomaSignal, FAST, and MEFIB are presented in Table 2.

Table 2 Common Biomarker Models for MASH

Index	Algorithm	AUROC	Sensitivity	Specificity	Endpoint
CK-18[51]	–	0.75 (95% CI: 0.71–0.79)	0.55 (95% CI: 0.52–0.59)	0.87 (95% CI: 0.81–0.92)	MASH
PRO-C3[53]	–	0.70 (95% CI: 0.66–0.74)	0.45	0.86	MASH with F ≥ 2
		0.74 (95% CI: 0.69–0.78)	0.56	0.82	MASH
ADAPT[53]	ADAPT includes PRO-C3, T2DM, platelet count and age	0.76 (95% CI: 0.72–0.80)	0.64	0.75	MASH with F ≥ 2
		0.78 (95% CI: 0.74–0.82)	0.77	0.69	MASH
NIS4[54]	NIS4 incorporates microRNA-34a-5p, α2-macroglobulin, human chitinase-3-like protein 1 and glycated haemoglobin	0.83 (95% CI: 0.80–0.86)	0.77	0.76	MASH
MACK-3[58]	Includes AST, CK18, and homeostasis model assessment	0·76 (95% CI: 0.71–0.80)	0·41 (95% CI: 0.34–0.48)	0·89 (95% CI: 0.85–0.92)	MASH
SomaSignal[58]	SomaSignal is the net logistic regression models each component (ie, steatosis [containing 12 protein analytes], lobular inflammation [containing 14 protein analytes], hepato-cellular ballooning [containing five protein analytes], and fibrosis [containing eight protein analytes])	0·81 (95% CI: 075–0.86)	0·67 (95% CI: 0.59–0.75)	0·82 (95% CI: 0.59–0.75)	MASH
FibroScanAST[86]	–	0.929 (95% CI: 0.88–0.97)	0.66	0.87	MASH
MRI-AST[86]	–	0.868 (95% CI: 0.80–0.92)	0.89	0.72	MASH
MEFIB[87]	MRE combined with FIB-4	0.768 (95% CI: 0.72–0.80)	0.60	0.78	MASH

Abbreviations: AUROC, Area Under the Receiver Operating Characteristic curve; CK-18, Cytokeratin 18; PRO-C3, N-Terminal Propeptide of Type III Collagen; T2DM, Type 2 Diabetes Mellitus; NIS4, A diagnostic panel comprising miR-34a-5p, α2-macroglobulin, glycated haemoglobin, and human chitinase-3-like protein 1; AST, Aspartate Aminotransferase; MACK-3, A composite score including Homeostasis Model Assessment (HOMA), AST, and CK18; SomaSignal, A proteomics-based diagnostic mo MRI, Magnetic Resonance Imaging; FIB-4, Fibrosis-4 Index; MEFIB, A scoring system combining Magnetic Resonance Elastography (MRE) and FIB-4.

Non-Invasive Assessment of Fibrosis

HA, LN, PIIINP and C IV

The uptake and degradation of hyaluronic acid (HA) predominantly take place in the liver, where circulating HA is processed. This hepatic pathway is crucial for maintaining the balance and clearance of HA from the bloodstream. This increase is primarily due to heightened production by the body and a decreased ability of the liver to eliminate HA efficiently. Serum HA concentration increases and is positively correlated with the stage of liver fibrosis.

Elevated serum laminin (LN) serves as a valuable indicator of chronic liver injury, with impaired hepatic endothelial cell function leading to elevated serum LN concentrations. These elevated LN levels exhibit a direct correlation with the progression of liver fibrosis, thus indicating an augmented risk of fibrotic liver disease development.[88]

Type III collagen N-peptide (PIIINP) is synthesized by cells as a non-collagenous polysaccharide precursor. During the biosynthesis of type III collagen, the N-terminal pro-peptide is enzymatically cleaved from its precursor, pre-collagen type III. This process facilitates the release of PIIINP into the bloodstream.[89]

Type IV collagen (C IV) is another significant marker, reflecting basement membrane regeneration. In patients with MAFLD. C IV levels are considerably elevated and correlated with significant and advanced fibrosis and it is a valuable marker for assessing the severity of MASH.[89] Overall, serum markers such as HA, LN, PIIINP, and C IV are crucial serological indicators used in assessing the diagnosis, severity, and prognosis of liver fibrosis in patients with MAFLD.

These extracellular matrix markers reflect fibrogenesis and matrix remodeling, offering insights into fibrosis progression, but they are not fibrosis-specific, may be influenced by extrahepatic conditions, and lack standardized cut-offs.

AAR, APRI and the BARD Score

AAR and APRI are calculated simply and have acceptable accuracy for detecting advanced fibrosis (F3-4).[90] A previous study highlights that APRI is an independent variable for advanced fibrosis, with a sensitivity of 91.9% and a specificity of 90.3%.[91] Furthermore, research conducted by Amernia et al has underscored the superiority of APRI in differentiating the degree of liver fibrosis than FIB-4.[36]

The BARD score, which includes readily accessible clinical parameters, is calculated based on AAR, BMI and diabetes status. The BARD score has high applicability because these components are readily available to clinicians, and it is moderately accurate in detecting fibrosis. While the BARD score demonstrates only moderate accuracy in detecting fibrosis, its notable strength lies in its high negative predictive value. The BARD score plays a vital role in refining treatment strategies and improving patient outcomes by facilitating precise and effective management of liver conditions.[30,38]

Simple scores like AAR, APRI, and BARD are inexpensive and useful for excluding advanced fibrosis due to their high negative predictive value, yet they have only moderate accuracy for fibrosis staging and may underperform in certain populations such as diabetic patients.

NFS, FIB-4 and AGILE 3+

NAFLD fibrosis score (NFS) and FIB-4 are the extensively used tools for the screening of MAFLD patients. Comparative analyses indicate superior diagnostic accuracy of the FIB-4 index in detecting fibrosis, whereas NFS demonstrates reduced performance specifically within the diabetic cohort.[92] A large study has demonstrated that an increase in FIB-4 correlates with an increased risk of liver disease and repeated FIB-4 tests can help identify those at risk for serious liver diseases.[93] FIB-4 and NFS have good ability to identify advanced fibrosis, and they demonstrate an acceptable diagnostic accuracy for MAFLD patients with T2MD.[94]

Salomone et al find that NFS is more predictive of mortality than APRI and FIB-4 and is considered an accurate tool for risk stratification of mortality in MAFLD patients.[95] Moreover, the newly introduced AGILE 3+ score, which incorporates AAR, platelet count, T2DM, gender, age, and liver stiffness measurements, has been proposed for diagnosing advanced fibrosis in MAFLD and for forecasting liver-related events.[96,97] These widely validated tools are accessible for fibrosis risk stratification, with FIB-4 and AGILE 3+ showing superior performance, but they may

misclassify intermediate-risk patients and have reduced accuracy in specific subgroups like the elderly or those with T2DM.

LiverRisk Score and Hepascore

The LiverRisk score, derived from a prospective cohort, integrates demographic data (age, sex) with six routine laboratory parameters to estimate liver stiffness and predict long-term outcomes. It has shown superiority over traditional serum biomarkers of fibrosis and is valid in identifying individuals with increased risk for liver-related hospitalization and HCC. This tool enables the stratification of patients into distinct risk categories for liver-related outcomes.[98] The LiverRisk score offers prognostic capabilities for the future development of liver fibrosis and liver-related events, facilitating the stratification of individuals to optimize preventive healthcare strategies.

The Hepascore is derived from hepatitis C virus populations and is composed of α2-macroglobulin, HA, GGT, total bilirubin and biometric parameters (gender and age), and the ability to identify advanced fibrosis has been demonstrated in MAFLD.[99] Hepascore has excellent accuracy in predicting cirrhosis of all chronic liver diseases, with the sensitivity of 81% and specificity of 74% for advanced fibrosis. Hepascore is not suitable for precise staging of liver fibrosis in this population. Besides, Hepascore is accurate in ruling out advanced fibrosis and cirrhosis.[99,100] Hepascore has similar overall accuracy with Fibroscan and even higher accuracy than Fibroscan in obese patients for predicting advanced fibrosis.[101] LiverRisk predicts long-term liver-related outcomes and Hepascore shows good accuracy for advanced fibrosis, especially in obese patients, yet both require further validation in diverse MASLD cohorts and are not suitable for precise fibrosis staging.

ELF, SAFE and UP Fibrosis Model

The Enhanced Liver Fibrosis (ELF) panel, an analytical algorithm comprised HA, PIIINP and tissue inhibitor of metalloproteinase-1, demonstrates proficiency in the precise detection of advanced fibrosis in patients with MAFLD.[1,30] Inadomi et al show that diagnostic performance of the ELF panel in identifying advanced fibrosis in MAFLD is comparable to FibroScan.[102] A large prospective study suggests that the ELF test is an effective tool as a population screening tool for liver fibrosis, significantly reducing the incidence of false positives when compared to both FIB-4 and NFS.[103] The ELF panel's ability to deliver accurate diagnoses with fewer false positives makes it a promising option for both clinical and large-scale screening settings.

The steatosis-associated fibrosis estimator (SAFE) is a machine learning-derived model that incorporates various indicators including platelets, AST, ALT and globulin (total serum protein minus albumin), BMI, the presence of T2DM and age. The ability of SAFE to determine the grade is higher than FIB-4 and NFS in differentiating between F0/1 and ≥F2, and SAFE exhibits a negative predictive value of 92% in excluding fibrosis stages ≥F2. The performance of the SAFE model was superior to that of the NFS.[104] Overall, the SAFE model's utilization of machine learning to integrate multiple clinical indicators represents a significant advancement in accurately diagnosing and effectively excluding significant fibrosis.

The UP fibrosis model and UP significant fibrosis model have been established for patients with MAFLD based on urinary protein biomarkers, demonstrating strong diagnostic capabilities with an AUROC exceeding 0.90. This indicates high accuracy and promising potential for diagnosis of liver fibrosis.[105] While urine biomarkers provide greater accessibility and are less invasive compared to blood tests, they present challenges due to the sophisticated technical skills required for their measurement and the relative scarcity of verification data compared to established serological biomarkers.

ELF offers high diagnostic accuracy with fewer false positives, while SAFE and UP models integrate novel biomarkers for enhanced detection, but these tests are costly, less accessible, and require further validation before routine clinical adoption.

Omics

Proteomics enables the semi-quantitative identification of differentially expressed proteins in MASLD, offering deeper insights into its underlying mechanisms. While the pathogenesis of MAFLD remains elusive, increasing evidence

suggests that the disease arises from the development of complex processes involving the modification of numerous proteins. Yu et al show that NAFL patients has a higher hemoglobin level, which is highly correlated with the risk of developing MAFLD and has a significant predictive value.[106] A previous multicenter study describes the transcriptional changes during disease progression within the context of MAFLD to identify potential circulating markers, revealing that AKR1B10 and GDF15 are strongly correlated with disease activity and stage.[107] Sveinbjornsson et al demonstrate that variants are significant for both phenotypes, and variants also increase the risk of MAFLD. Most variants with risk allele variants are associated with cholesterol and sex hormone binding globulin measurements.[108] There is a study that identified protein biomarkers associated with high-risk MASH by correlated proteomics and transcriptomic data and developed a composite panel that included AKR1B10, ADAMTSL2, CFHR4, and TREM2, BMI, and the presence of T2DM. The index had the potential to predict the progression of MAFLD in a non-invasive manner.[109] These finding suggests that these proteins could serve as valuable biomarkers for monitoring the progression and severity of MAFLD.

Table 3 Common Biomarker Models for Fibrosis

Index	Algorithm	AUROC	Sensitivity	Specificity	Endpoint
AAR[113]	AAR = AST: ALT ratio	0.64 (95% CI: 0.62–0.65)	0.75 (95% CI: 0.73–0.77)	0.47 (95% CI: 0.45–0.48)	F ≥ 3
APRI[113]	APRI = (AST level/AST upper limit of normal)/(platelet count [10^9/L]) × 100	0.70 (95% CI: 0.69–0.72)	0.67 (95% CI: 0.64–0.69)	0.63 (95% CI: 0.62–0.65)	F ≥ 3
The bard score[114]	0 – 4 scale, BMI ≥ 28 kg/m2 = 1 point, AAR ≥ 0.8 = 2 points, T2DM = 1 point	0.70 (95% CI: 0.67–0.72)	–	–	F ≥ 2
		0.70 (95% CI: 0.67–0.71)	–	–	F = 3
		0.70 (95% CI: 0.66–0.73)	–	–	F = 4
NFS[113]	NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × (IFG/diabetes: yes = 1, no = 0) + 0.99 × (AST/ALT ratio) – 0.013 × platelet count (×10^9/L) – 0.66 × albumin (g/dL)	0.73 (95% CI: 0.71–0.75)	0.75 (95% CI: 0.72–0.78)	0.63 (95% CI: 0.61–0.65)	F ≥ 3
AGILE 3 +[97]	AGILE 3 + incorporates age, sex, AST, ALT, platelet, diabetes status, and liver stiffness measurement	0.88	0.91 (95% CI: 0.87–0.93)	0.66 (95% CI: 0.58–0.73)	F ≥ 3
FIB-4[113]	FIB-4 = (age [years] * AST [U/L])/([platelets (109 /L)] * ALT $^{1/2}$ [U/L])	0.76 (95% CI: 0.74–0.77)	0.69 (95% CI: 0.67–0.72)	0.70 (95% CI: 0.69–0.72)	F ≥ 3
MRE (kPa)[115]	–	0.87 (95% CI: 0.80–0.94)	0.71 (95% CI: 0.60–0.81)	0.85 (95% CI: 0.78–0.91)	F ≥ 1
	–	0.91 (95% CI: 0.80–0.97)	0.78 (95% CI: 0.67–0.85)	0.89 (95% CI: 0.83–0.94)	F ≥ 2
	–	0.92 (95% CI: 0.88–0.95)	0.83 (95% CI: 0.77–0.88)	0.89 (95% CI: 0.86–0.92)	F ≥ 3
	–	0.90 (95% CI: 0.81–0.95)	0.81 (95% CI: 0.66–0.90)	0.90 (95% CI: 0.85–0.94)	F ≥ 4

Abbreviations: AAR, AST to ALT Ratio; APRI, AST to Platelet Ratio Index; AUROC, Area Under the Receiver Operating Characteristic curve; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BMI, Body Mass Index; NFS, NAFLD Fibrosis Score; FIB-4, Fibrosis-4 Index; MRE, Magnetic Resonance Elastography; CI, Confidence Interval; T2DM, Type 2 Diabetes Mellitus.

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From steatosis to MASH and MASH to cirrhosis, branched-chain amino acids, phenylalanine and taurocholic acid increase with the disease severity, whereas glutathione decreased with disease severity.[110] An analysis of cross-sectional data from prospective cohorts reveals that eight lipids (5 α-androstane-3-monosulfate, androstenedione sulfate, pregnanediol-3-glucuronide, palmitoleate, epiandrosterone sulfate, 5 α-androsterone-3-disulfate, dehydroepiandrosterone sulfate and glucuronide), one amino acid (taurine), and one carbohydrate (caramel) are significantly associated with late-stage fibrosis, with higher diagnostic accuracy than both FIB-4 index and NFS.[111] Compared to patients with steatosis, free radical-mediated linoleic acid oxidation products are significantly higher in MASH patients.[112]

These observations suggest a shift towards more reliable diagnostic tools, which could significantly improve patient management and outcomes, which also underscore the need for further validation studies to confirm these findings and explore their implications in broader clinical practices. This analytical approach is vital for unraveling the intricate biochemical pathways implicated in MAFLD, potentially leading to more effective targeted therapies.

Omics technologies such as proteomics and metabolomics uncover novel biomarkers and disease mechanisms, enabling precision diagnostics, but they are complex, expensive, and require extensive validation and standardization before clinical implementation.

To effectively manage liver fibrosis, a clear diagnostic pathway is essential: For excluding advanced fibrosis, highly sensitive tests with a strong negative predictive value, such as the AGILE 3+ score or the SAFE score, are the best initial step. To accurately identify patients with significant or advanced fibrosis, highly specific tools like MRE or the ELF test should be utilized. If there is discordance between first-line serological tests (like FIB-4) and elastography findings, second-line imaging with MRE or a referral to a hepatologist for consideration of a liver biopsy is recommended to resolve the uncertainty and guide treatment decisions. Table 3 outlines fibrosis staging tools, including AAR, APRI, BARD, NFS, FIB-4, AGILE 3+, and MRE.

Conclusions

The increasing global burden of MASLD necessitates accurate, accessible, and non-invasive diagnostic tools to replace or reduce reliance on liver biopsy. Significant progress has been made in the development of non-invasive tests for steatosis, MASH, and fibrosis. Serum biomarkers such as FLI, FIB-4, NFS, and ELF, along with imaging techniques like FibroScan and MRI, enable effective risk stratification and disease staging. Multi-marker panels and emerging technologies such as omics and artificial intelligence offer promising improvements in diagnostic accuracy and personalized management. However, challenges remain, including the need for standardization, validation across diverse populations, and integration into clinical workflows. Future efforts should focus on refining these tools, establishing stepwise diagnostic pathways, and enabling early intervention to halt disease progression and improve patient outcomes.

Viewpoints

MASLD is increasingly recognized as a significant global public health concern.

Liver biopsy is traditionally considered the gold standard for diagnosing and assessing the severity of MASLD. Due to its inherent heterogeneity and complexity, accurate diagnosis of MASLD through liver biopsy remains challenging.

Early identification of patients with MASLD and liver fibrosis may help improve patient outcomes through timely intervention.

There is a pressing need for further research to establish an effective surveillance strategy for the early diagnosis and staging of MASLD.

Abbreviations

ALT, alanine aminotransferase; APRI, AST, platelet ratio index; AST, aspartate aminotransferase; AAR, AST: ALT ratio; AUROC, the area under the receiver operating characteristic curve; BMI, body mass index; C IV, type IV collagen; CT, computed tomography; CK-18, cytokeratin 18; FIB-4, fibrosis 4 score; FLI, fatty liver index; GGT, γ-glutamyltransferase; HA, hyaluronic acid; HSI, hepatic steatosis index; LAP, lipid accumulation product; LN, laminin; MASH, metabolic-associated steatohepatitis; MAFLD, metabolic associated fatty liver disease; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; miRNAs, microRNAs; MRI, magnetic resonance imaging; NAFLD,

nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; PIIINP, type III collagen N-peptide; PRO-C3, N-terminal type III collagen pro-peptide; SAFE, steatosis-associated fibrosis estimator; T2DM, diabetes mellitus type 2.

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Disclosure

The authors report no conflicts of interest in this work.

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