Noninvasive Assessment to Identify Patients With At-Risk Metabolic Dysfunction-Associated Steatohepatitis

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed nonalcoholic fatty liver disease, is a major global health issue and a leading cause of chronic liver disease. The prevalence of MASLD is increasing globally, with the disease in some patients progressing to metabolic dysfunction-associated steatohepatitis (MASH), which significantly raises the risk of fibrosis, cirrhosis, and adverse outcomes. Accurate identification of patients with at-risk MASH, defined as MASH with a fibrosis stage of 2 or higher, is critical for timely intervention and management. Although liver biopsy remains the gold standard for diagnosing MASH, its invasive nature, potential complications, and variability in interpretation necessitate the implementation of noninvasive tests (NITs). NITs hold the potential for reducing reliance on liver biopsies, enhancing early diagnosis, and improving patient management of chronic liver disease. Continued research and validation are essential to optimize these tools for clinical application. This article explores current NITs, including imaging biomarkers, combined imaging and serum biomarkers, advanced biomarkers and composite scores, as well as artificial intelligence–based approaches, which also show promise in improving the accuracy of noninvasive at-risk MASH detection.

Keywords
MASLD, MASH, noninvasive tests, biomarkers, composite scores

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is a significant global health challenge and a leading cause of chronic liver disease.[1] The change in terminology from NAFLD to MASLD, as recommended by the Delphi consensus process,[2] aims to better reflect the metabolic aspects of the disease, reduce stigmatization, and improve disease classification. In the United States, the prevalence of MASLD is estimated to be 32.5% among adults.[3] Globally, the prevalence has risen from 25.3% in 1990 to 2006 to 38.2% in 2016

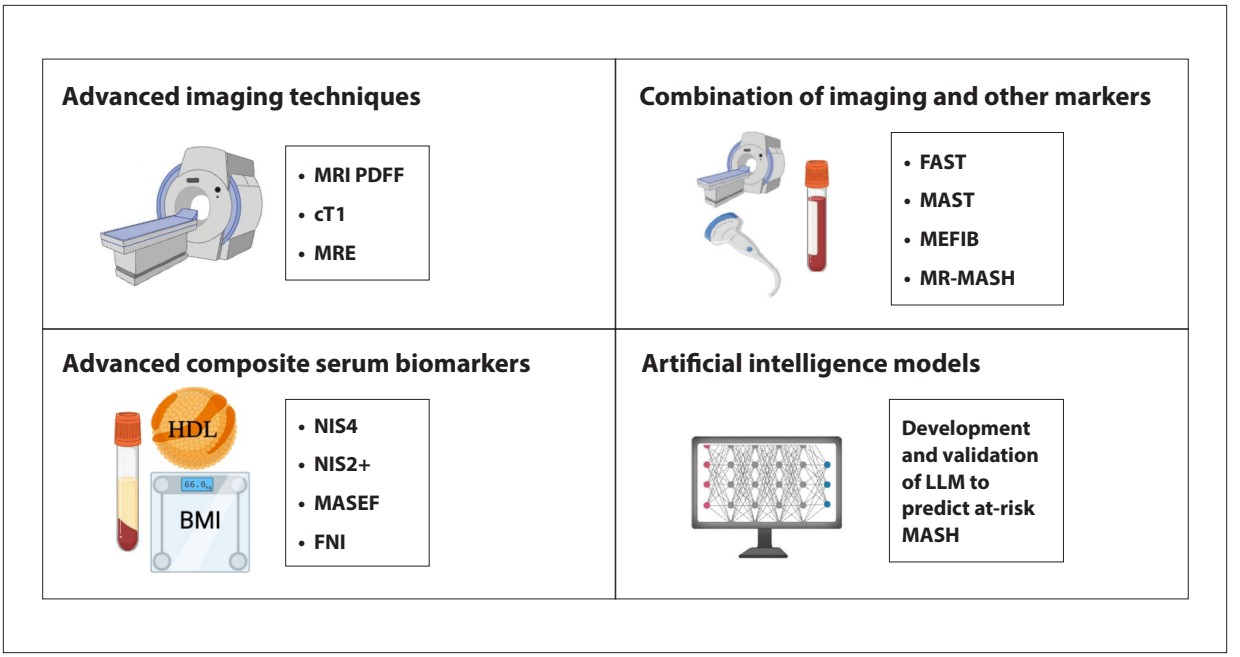

Figure. Noninvasive tests to identify patients with at-risk MASH (NAS ≥4 and fibrosis ≥ stage 2). The Figure was created with Biorender.com.

AST, aspartate aminotransferase; BMI, body mass index; cT1, iron-correct T1; FAST, FibroScan-AST; FNI, Fibrotic NASH Index; HDL, high-density lipoprotein; LLM, large language model; MASEF, metabolomics-advanced steatohepatitis fibrosis; MASH, metabolic dysfunction-associated steatohepatitis; MAST, magnetic resonance imaging and AST; MEFIB, magnetic resonance elastography with Fibrosis-4; MRE, magnetic resonance elastography; MRI PDFF, magnetic resonance imaging proton density fat fraction; MR-MASH, MRI-based composite biomarker for MASH; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NIS, NASH and Inflammation Score.

to 2019, highlighting the increasing impact of metabolic dysfunction on public health.[4] A subset of MASLD patients will develop metabolic dysfunction-associated steatohepatitis (MASH), which carries an increased risk of developing fibrosis and cirrhosis and is associated with adverse outcomes.[4] Histologic evaluation of MASH activity, typically assessed through the NAFLD activity score (NAS), combines histologic scores for steatosis, hepatocellular ballooning, and lobular inflammation.[5] Patients with MASH and a fibrosis stage of 2 or higher are at greater risk for liver-related complications and progression to cirrhosis.[6] Identifying MASH patients with a fibrosis stage of 2 or higher is critical, as timely intervention through lifestyle changes, pharmacotherapy, or clinical trial enrollment can alter the natural course of the disease.[7] The recent US Food and Drug Administration approval of resmetirom (Rezdiffra, Madrigal), a thyroid hormone receptor–ß agonist, as the first treatment for MASH highlights the importance of early identification of the disease with the potential for reversal.[8]

Although liver biopsy is the gold standard for diagnosing MASH and fibrosis, its invasive nature, associated complications, sampling, and interobserver variability necessitate the development of validated, accurate, and cost-effective noninvasive tests (NITs).[9] However, most noninvasive blood biomarkers and imaging tests have been developed to assess the presence and severity of liver fibrosis and steatosis. These are comprehensively reviewed in the recent American Association for the Study of Liver Diseases (AASLD) guidelines for the noninvasive diagnosis of fibrosis and steatosis.[10,11] In recent years, progress has been made in the development and validation of NITs for diagnosing patients with at-risk MASH, which is defined as a NAS of 4 or higher and significant fibrosis of stage 2 or higher. These NITs, which include imaging techniques, biomarkers, and composite scores combined with various clinical parameters, offer promising tools for identifying at-risk MASH patients.[12] This article examines the current NITs available for assessing at-risk MASH (Figure).

Imaging Biomarkers

Proton Density Fat Fraction

Magnetic resonance imaging (MRI)-based techniques have been evaluated for their potential in diagnosing at-risk MASH. MRI proton density fat fraction (PDFF) is one such technique that has been effective in quantifying

liver fat noninvasively. MRI PDFF is a reliable and accurate measure for identifying patients with MASLD, correlating strongly with histologic steatosis.[13] However, the ability of MRI PDFF to stage disease severity or identify MASH with significant fibrosis may be limited owing to the decrease in liver fat as fibrosis progresses. Early studies revealed that MRI PDFF is weakly associated with ballooning of hepatocytes and is not linearly related to either inflammation or fibrosis.[14,15] A study by Andersson and colleagues, which included 543 patients with suspected MASLD, found that the area under the receiver operating characteristic curve (AUROC) for identifying MASH patients at high risk for progression was 0.69 (95% CI, 0.64-0.74) with MRI PDFF.[16]

Iron-corrected T1

Iron-corrected T1 (cT1) is a promising MRI-based technique that measures fibroinflammatory activity in the liver. In the aforementioned study by Andersson and colleagues, the authors reported that cT1 correlates well with fibroinflammatory markers and has high diagnostic accuracy for identifying patients with at-risk MASH. The study found an AUROC of 0.78 (95% CI, 0.74-0.82) for cT1, indicating superior performance compared with PDFF. The sensitivity and specificity for cT1 at the optimal cutoff value of 825 ms were 78% and 67%, respectively, with a negative predictive value (NPV) of 88%. The combination of cT1 with other MRI metrics did not significantly improve diagnostic performance, underscoring the standalone value of cT1 in clinical practice.[16] The diagnostic ability of cT1 to predict at-risk MASH and its low-indeterminate range makes it a promising tool in the noninvasive assessment of at-risk MASH, potentially reducing the need for invasive liver biopsies. However, cost and accessibility remain issues, and the AASLD guidance indicated that this tool needs further validation.[7]

Magnetic Resonance Elastography

Magnetic resonance elastography (MRE) is an imaging technique that accurately measures liver stiffness as a biomarker of fibrosis.[17] MRE has also been evaluated for identifying patients with at-risk MASH. In a prospective clinical trial of 89 patients with a prior diagnosis of MASLD or suspected MASLD, Li and colleagues compared the diagnostic accuracy of identifying at-risk MASH using MRE liver stiffness measurements, PDFF, and T1 relaxation time. MRE showed the highest diagnostic accuracy for at-risk MASH, with an AUROC of 0.89 (95% CI, 0.82-0.95) and an optimal cutoff value of 3.3 kPa, providing 79% sensitivity and 82% specificity. However, reliability of the study is unproven because this was a single-center study, with a low number of participants having histologically proven at-risk MASH (n=28) and without external validation.[18]

Combination of Imaging and Serum Biomarkers

FAST Score

The FAST score integrates FibroScan (Echosens; transient elastography) measurements with aspartate aminotransferase (AST) levels to identify individuals with at-risk MASH. This scoring method combines the liver stiffness measurement and the controlled attenuation parameter from FibroScan with AST values. In their prospective study, Newsome and colleagues enrolled 350 patients with a suspected diagnosis of MASLD. In the derivation cohort, the FAST score exhibited an AUROC of 0.80 (95% CI, 0.76-0.85), whereas in the pooled external validation cohort (n=1026), the AUROC was 0.85 (95% CI, 0.83-0.87).[19] The FAST score was also evaluated in a meta-analysis of 12 observational studies with 5835 patients with biopsy-proven MASLD and a fibrotic MASH prevalence of 28%. The FAST score's pooled sensitivity was 89% (95% CI, 82%-93%), and the pooled specificity was 89% (95% CI, 83%-94%), according to the rule-out (≤0.35) and rule-in (≥0.67) cutoffs. In addition, the FAST score demonstrated an NPV of 92% (95% CI, 91%-95%) and a positive predictive value (PPV) of 65% (95% CI, 53%-68%).[20]

MEFIB Score

The MEFIB score integrates MRE with the Fibrosis-4 (FIB-4) score, combining imaging with clinical data to enhance diagnostic accuracy. The MEFIB score was initially described as a means to diagnose stage 2 or higher liver fibrosis rather than inflammation.[21] Jung and colleagues initially described this score in a cohort of 238 patients and subsequently validated it in an external cohort of 222 patients. MRE alone had an AUROC of 0.93 for detecting fibrosis stage 2 or higher. The combination with FIB-4 further improved its diagnostic power, achieving a high PPV of 97.1% in the primary cohort and 91.0% in the validation cohort.[21]

The authors of the aforementioned study also evaluated the MEFIB score for identifying at-risk MASH and found that the MEFIB score had an AUROC of 0.768 (95% CI, 0.728-0.808) for diagnosing at-risk MASH.[22] However, these results might have been impacted by the high prevalence of fibrosis in that patient cohort (51.2%), which in turn might have impacted the PPV of the MEFIB score in diagnosing at-risk MASH.[23] In a study by Qi and colleagues that included 108 patients with biopsy-proven MASLD, the MEFIB score had an AUROC of 0.729 (95% CI, 0.619-0.838),[24] while in a study by

Castera and colleagues that included 330 outpatients with diabetes and biopsy-proven MASLD, the MEFIB score had an AUROC of 0.68 (95% CI, 0.62-0.74).[25]

MAST Score

The MAST score is a diagnostic tool that integrates MRI-based PDFF and MRE with AST values to identify patients with fibrotic MASH.[26] This score was developed and validated using cohorts from tertiary care centers. In the derivation cohort, the MAST score had a high AUROC of 0.858, with a sensitivity of 94.4% and a specificity of 72.9%. These values indicated a PPV of 42.5% and an NPV of 98.4%. The validation cohort confirmed the robustness of the MAST score, with an even higher AUROC of 0.929, with a sensitivity of 89.3%, specificity of 73.1%, PPV of 30.1%, and NPV of 98.1%. The MAST score also had a higher AUROC compared with the FAST score, which had an AUROC of 0.868 in the validation cohort.[26] Compared with the FAST score, the MAST score has shown similar or superior accuracy for identifying at-risk MASH[22]; in a recently published prospective study in patients with type 2 diabetes, the FAST and MAST scores had similar accuracy for diagnosing fibrotic MASH with an AUROC of 0.81 and 0.79, respectively (P=.41).[25] Importantly, the MAST score has been shown to predict clinical liver events, which further strengthens the utility of this NIT.[27]

MR-MASH Score

The MR-MASH score is an MRI-based composite biomarker developed to identify patients with MASH noninvasively. This score incorporates PDFF and waist circumference measurements to assess liver and body fat distribution. In a prospective multicenter study involving 317 patients with biopsy-confirmed MASLD, the MR-MASH score was derived and validated. The derivation cohort, including patients from Portugal and Spain, demonstrated a MASH prevalence of 51%. The AUROC for identifying at-risk MASH was 0.77 (95% CI, 0.69-0.84), indicating moderate diagnostic accuracy. The MR-MASH score also yielded 84% sensitivity, 57% specificity, 49% PPV, and 88% NPV. In the validation cohort, which included patients from the United States and Spain with different MRI protocols, the MR-MASH score showed a similar diagnostic accuracy in diagnosing at-risk MASH with an AUROC of 0.76 (95% CI, 0.67-0.84), 88% sensitivity, 56% specificity, 52% PPV, and 90% NPV.[28]

Advanced Serum Biomarkers and Composite Scores

NASH and Inflammation Score 4 Algorithm

This blood-based test is designed to identify patients with at-risk MASH among those with metabolic risk factors such as type 2 diabetes, obesity, dyslipidemia, and hypertension.[29] The nonalcoholic steatohepatitis (NASH) and Inflammation Score 4 (NIS4) algorithm combines 4 biomarkers: miR-34a-5p, alpha-2 macroglobulin, YKL-40, and glycated hemoglobin (A1C). Each of these biomarkers has a strong biological basis and association with MASH and fibrosis. The derived algorithm had an AUROC of 0.80 (95% CI, 0.73-0.85) in the initial cohort. The NIS4 was subsequently validated in the RESOLVE-IT diagnostic cohort and the Angers cohort, with AUROCs of 0.83 (95% CI, 0.79-0.86) and 0.76 (95% CI, 0.69-0.82), respectively. In the pooled validation cohort, patients with NIS4 values below 0.36 were classified as not having at-risk MASH, with a sensitivity of 81.5% (95% CI, 76.9-85.3) and specificity of 63.0% (95% CI, 57.8-68.0), resulting in an NPV of 77.9% (95% CI, 72.5-82.4). Conversely, those with NIS4 values above 0.63 were identified as having at-risk MASH, with a specificity of 87.1% (95% CI, 83.1-90.3) and sensitivity of 50.7% (95% CI, 45.3-56.1), leading to a PPV of 79.2% (95% CI, 73.1-84.2).[29] Nevertheless, the NIS4 has been recently replaced by the NIS2+.

NASH and Inflammation Score 2+

The NASH and Inflammation Score 2+ (NIS2+) is an enhanced version of the NIS4 algorithm designed to improve the detection of at-risk MASH. Developed by the creators of NIS4, the optimized NIS2+ algorithm incorporates two biomarkers, miR-34a-5p and YKL-40, while also adjusting for sex. This optimization aimed to simplify the test by using fewer biomarkers, addressing technical challenges such as the need for large sample volumes, and mitigating the limitations of NIS4, such as confounding factors like A1C values in patients undergoing diabetes treatment. NIS2+ demonstrated better performance compared with NIS4, with an AUROC of 0.813 (95% CI, 0.795-0.832) vs 0.792 (95% CI, 0.772-0.811) for NIS4.[30] One of the main goals of developing NITs for at-risk MASH is to reduce the rates of liver biopsy failure, where histology does not confirm the clinical suspicion of at-risk MASH, and the overall screening costs associated with inclusion in MASH trials. In another study by the same investigator group, NIS2+ was compared with traditional methods like FIB-4 for identifying at-risk MASH patients. The authors found that NIS2+ reduced liver biopsy failure rates by 39% and could lead to cost savings of approximately $2.3 million for every 1000 patients screened. In addition, NIS2+ reduced the number of unnecessary liver biopsies and reduced bias in the demographic and clinical profiles of the included patients. However, more head-to-head comparisons with other NITs designed to identify at-risk MASH are needed.[31]

Metabolomics-Advanced Steatohepatitis Fibrosis Score

The metabolomics-advanced steatohepatitis fibrosis (MASEF) score is a novel diagnostic tool also designed to identify patients with at-risk MASH. Developed with a combination of 12 lipid biomarkers, body mass index, AST, and alanine aminotransferase, the MASEF score uses machine learning models to provide a logistic probability score for at-risk MASH. In the derivation and validation cohorts, the MASEF score had robust diagnostic performance, with an AUROC of 0.76 and 0.79, respectively. The sensitivity, specificity, PPV, and NPV in the validation cohort were 0.78, 0.65, 0.48, and 0.88, respectively. Compared with the FAST score, the MASEF score had similar overall performance, providing an effective alternative for identifying patients at high risk for progression of liver disease.[32] The implementation of the MASEF score in clinical practice could enhance the efficiency of patient screening and management, particularly in settings where access to advanced imaging techniques is limited.

Fibrotic NASH Index

The Fibrotic NASH Index (FNI) was developed to provide a simple, noninvasive method for identifying patients with at-risk MASH, using routine laboratory tests, namely, AST, high-density lipoprotein cholesterol, and A1C. The original study involved a derivation cohort of 264 morbidly obese individuals undergoing bariatric surgery who underwent liver biopsies in Italy. The performance of the FNI in predicting fibrosis yielded an AUROC of 0.78 (95% CI, 0.80-0.95) in the derivation cohort, indicating good predictive accuracy.[33] The FNI was further validated using 3 independent European cohorts: 370 individuals from Finland, 947 from Italy, and 5368 from England, all at high risk for MASLD. In these validation cohorts, the AUROC ranged from 0.80 to 0.95. For the rule-out cutoff of 0.10, sensitivity ranged from 0.87 to 1, with an NPV between 0.99 and 1. For the rule-in cutoff of 0.33, specificity ranged from 0.73 to 0.94, with a PPV between 0.12 and 0.49. These results demonstrate that the FNI could be a valuable tool for identifying individuals at risk for fibrotic MASH.[33] Although further validation and comparison with other available NITs are needed, FNI, given its affordability and noninvasive nature, might be used in primary health care to screen for fibrotic MASH.

The Potential Role of Artificial Intelligence

Artificial intelligence (AI) has emerged as a tool in identifying at-risk MASH. Lee and colleagues developed a machine learning algorithm that significantly improves the detection of MASH. This algorithm utilizes a gradient-boosting machine model to analyze various clinical and laboratory parameters, providing a noninvasive method to identify patients with MASH. The study demonstrated that the AI model achieved an AUROC of 0.83 (95% CI, 0.80-0.86), indicating high diagnostic accuracy. In comparison, the FAST score had an AUROC of 0.77 (95% CI, 0.73-0.81).[34] Although further studies are needed, incorporating AI could help health care providers accurately and cost-effectively identify patients with at-risk MASH.[35]

Conclusion

Identifying at-risk MASH patients is crucial for timely intervention and effective management of the disorder. Noninvasive liver tests offer promising alternatives to liver biopsy, with advanced imaging techniques, integrated biomarker approaches, composite diagnostic scores, and AI-based models all contributing to the evolution of NITs for diagnosing at-risk MASH. Continued research and validation are essential to refine these tools and enhance their clinical utility.

Disclosures

Dr Kalligeros and Dr Danpanichkul have no relevant conflicts of interest to disclose. Dr Noureddin has been on the advisory board for 89bio, Gilead, Intercept, Pfizer, Novo Nordisk, Blade, Echosens, Fractyl Health, Terns, Siemens, and Roche Diagnostics; has received research support from Allergan, Bristol Myers Squibb, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking Therapeutics, and Zydus; and is a minor shareholder or has stocks in Anaetos, Rivus, and Viking Therapeutics.

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