***Invited Review***

***Title:* Noninvasive Tests of Fibrosis in the Management of MASLD: Revolutionizing Diagnosis, Progression, and Regression Monitoring**

***Short Title:* NITs for fibrosis in MASLD**

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**ABSTRACT**

With the recent conditional approval of resmetirom by the U.S. Food and Drug Administration, the treatment of metabolic-associated steatotic liver disease (MASLD) has entered a new era, necessitating a comprehensive understanding of the strengths and weaknesses of non-invasive tools for diagnosing and monitoring MASLD-related fibrosis. This article focuses on F2/F3 liver fibrosis and summarizes the current application status of non-invasive tests (NITs), including serum biomarkers, imaging methods, and their combined use in the management of MASLD. The article emphasizes the application of NITs in several areas: diagnosis and baseline stratification, monitoring fibrosis progression, and predicting liver-related clinical outcomes, as well as assessing disease regression, remission, and long-term liver-related outcomes. Furthermore, we critically compare the advantages and limitations of NITs and propose practical strategies for integrating them into clinical practice. Additionally, we highlight the key challenges currently faced in applying these NITs and potential future research avenues. We suggest that future studies prioritize validating NITs across diverse patient populations. Moreover, we consider that exploring their role in dynamic monitoring and integrating multi-omics technologies, artificial intelligence, and personalized risk models is essential to enhance diagnostic accuracy and treatment planning.

**Keywords:** metabolic dysfunction-associated steatotic liver disease, metabolic-associated fatty liver disease, metabolic dysfunction-associated steatohepatitis, non-invasive tests, fibrosis

**1. Introduction**

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease globally.[1, 2] The disease burden of MASLD extends beyond liver-related complications, encompassing a range of extrahepatic cardiometabolic and oncologic complications.[3, 4] The global prevalence of MASLD in the adult population is approximately 30-35%.[5] As an important part of the MASLD disease spectrum, metabolic dysfunction-associated steatohepatitis (MASH) is closely related to a faster progression of the disease to advanced fibrosis. Patients with MASLD may further progress from MASH to fibrotic MASH (also known as at-risk or high-risk MASH).[6] Fibrotic MASH is closely related to the occurrence of adverse liver-related events (LREs), such as hepatic decompensation and hepatocellular carcinoma (HCC).[7, 8] The severity of liver fibrosis is the strongest histological risk factor for LREs and all-cause mortality.[9] Therefore, early diagnosis and effective liver fibrosis management are crucial.[10]

Stages F2/F3 liver fibrosis represent an important threshold for clinical intervention in individuals living with MASLD.[11] After the approval of resmetirom by the Food and Drug Administration (FDA) in the United States, the treatment and monitoring of MASLD/MASH have entered a new era[12]. Resmetirom treatment increased the rates of both MASH resolution and fibrosis improvement in adults with MASH and F2/F3 fibrosis. [12, 13] Moreover, the phase 3 placebo-controlled ESSENCE trial showed that in patients with MASH and fibrosis stages 2 or 3, once‐weekly subcutaneous semaglutide 2.4 mg for 72 weeks led to a 39.9% rate of liver fibrosis improvement without MASH worsening, whereas 62.9% experienced MASH resolution without worsening in fibrosis (vs 20.3% and 34.3% in the placebo group, respectively, both P < 0.001).[14] Consequently, improved identification of patients, long-term follow-ups, and accurate patient monitoring are crucial for optimizing care for this patient group.[15, 16]

Although liver biopsy remains the “gold standard” for diagnosing different stages of MASLD-related fibrosis, traditional liver biopsy carries potential risks and complications and may also have sampling errors.[17, 18] Quantitative analysis methods based on digital pathologies, such as qFibrosis and qFIBS technologies, have provided more accurate means for diagnosing and monitoring liver diseases.[19, 20] Although digital pathology can provide powerful technical support for pathology, it does not address the inherent drawbacks of liver biopsy.

In contrast, non-invasive tests (NITs) are becoming increasingly important for diagnosing and managing MASLD-related fibrosis, especially in evaluating the stages liver fibrosis, tracking disease progression, and assessing treatment effects.[21, 22] The FDA has approved that candidates for treatment with resmetirom do not need confirmation by liver biopsy.[11, 23] Therefore, we aimed to evaluate the current status of NITs in MASLD-related fibrosis, primarily regarding stages F2/F3 liver fibrosis, and explore their prospects and challenges for future clinical practice.

**2.** **NITs for diagnosis and baseline stratification**

Biomarkers play a crucial role in disease diagnosis, predicting future disease progression and outcomes, as well as identifying the optimal therapy for specific patients.[24] This review article will categorize the NITs into serum-based, imaging-based, and combined (serum and imaging) biomarkers (**Figure 1).** The accuracy of NITs for MASH with clinically significant fibrosis or MASLD with significant fibrosis are summarized in **Supplementary Table 1.**

***2.1*** ***Serum-based biomarkers***

***2.1.1 Traditional serum tests***

Traditional serum scores include the fibrosis-4 index (FIB-4), the nonalcoholic fatty liver disease fibrosis score (NFS), and the aspartate aminotransferase-to-platelet ratio index (APRI). [25] When FIB-4 index is below 1.3, it helps exclude advanced fibrosis (stage F ≥ 3), and when FIB-4 index is greater than 2.67, the test result suggests a high probability of advanced fibrosis.[26, 27] However, it should be noted that FIB-4 index has only moderate accuracy for diagnosing advanced fibrosis, has a low positive predictive value, and is easily affected by factors such as age (**Table 1**).[28] When the patient's age exceeds 65 years, the cut-off value of FIB-4 index for excluding advanced fibrosis should be set at 2.0 (instead of 1.3). In addition, FIB-4 index performs poorly in people under 35 years of age.[29]

***2.1.2 Enhanced liver fibrosis (ELF) score***

A meta-analysis indicates that when the ELF score < 7.7, it has a high sensitivity of 93%, but its specificity is limited. When the ELF score exceeds 9.8, its specificity reaches 86%, requiring even higher cut-off values to achieve greater specificity. The area under the receiver operating characteristic curve (AUROC) of the ELF score for advanced fibrosis is 0.83 (0.71-0.90).[30] Although the dual cutoff value method results in the ELF score demonstrating high sensitivity and specificity in excluding and confirming advanced fibrosis, the constituent indicators of the ELF score are challenging to measure in many hospital laboratories, which limits its utility. In addition, when the disease prevalence is low (such as in the primary care population), the positive predictive value (PPV) of the ELF score is low, which also leads to false-positive results (**Table 1**).[30]

***2.1.3 A PRO-C3-based score (ADAPT)***

The ADAPT score includes age, pre-existing diabetes, serum procollagen type III N-terminal peptide (PRO-C3), and platelet count.[31] The AUROC of the ADAPT score for advanced fibrosis is 0.86 (95% CI 0.79-0.91) in the derivation cohort and 0.87 (95% CI 0.83-0.91) in the validation cohort.[31] By integrating serum PRO-C3 levels with clinical parameters, the ADAPT score significantly improves diagnostic accuracy and has the potential for clinical translation.[31, 32] In Asian individuals with MASLD, Tang et al. also found that the ADAPT score had an AUROC of 0.865 (95% CI 0.829-0.901) for advanced fibrosis, which can reliably exclude advanced fibrosis.[33] Among the various combinations tested for identifying advanced fibrosis (stage F≥3), the stepwise algorithm that combines ADAPT and Agile 4 yielded the highest diagnostic accuracy.[34] However, the detection of PRO-C3 depends on specialized laboratory equipment and technical support, which makes it challenging to obtain in some medical institutions with limited resources.

***2.1.4*** ***NIS2+™***

NIS2+™ is an optimized blood biomarker detection technology designed to identify individuals with high-risk MASH. [35] Harrison et al. showed that in the training cohort, the low cut-off value of NIS2+™ was 0.4564, which may be used to exclude high-risk MASH, achieving a sensitivity of 80%; the high cut-off value was 0.6815, which may be used to identify high-risk MASH, achieving a specificity of 90%. In the test cohort, the AUROC of NIS2+™ was 0.813, surpassing than that of NIS4® (0.792, *p* = 0.0002), FIB-4 (0.653, *p*<0.0001), and serum ALT (0.699, *p*<0.0001). Compared to NIS4®, NIS2+™ exhibited a higher AUC value (0.813 vs 0.792) in detecting high-risk NASH, indicating improved diagnostic accuracy. The results of NIS2+™ are not significantly influenced by patient characteristics such as age, sex, body mass index (BMI), or pre-existing type 2 diabetes, allowing it to maintain consistent diagnostic performance in various subgroups.[35] Unlike traditional serum or blood biomarkers, the detection of miR-34a-5p requires relatively complex laboratory equipment and a high level of operational skills.[36] This may limit its application in primary hospitals or regions with limited resources.

***2.1.5*** ***MACK-3***

MACK-3 was validated in a multicenter cohort consisting of 1924 patients with biopsy-proven MASLD[37]. The AUROC for fibrotic MASH is 0.79.[37] MACK-3 has a high sensitivity (91%) and specificity (85%). However, MACK-3 uses CK-18 as one of its biomarkers, and the detection of CK18 may not be available in some clinical laboratories, which limits its widespread adoption. In addition, the proportion of patients with MASLD in the gray zone is relatively high, and combining other tests or clinical data for further evaluation is needed.[37]

***2.1.6*** ***Fibrotic NASH index (FNI)***

FNI combines serum AST, high-density lipoprotein cholesterol, and glycated hemoglobin levels. When FNI < 0.10, it is used to exclude high-risk MASH.[38] An FNI index ≥ 0.33 is used to identify high-risk MASH.[38] The AUROC of FNI in the derivation cohort is 0.78 (0.71–0.85), and in three external validation cohorts, the AUROCs are 0.83 (0.72–0.95), 0.95 (0.92–0.98), and 0.80 (0.75–0.83) respectively. FNI is based on routine and widely used laboratory indicators, so it is especially suitable for primary medical institutions. The PPV of FNI is low, especially in populations with a low risk of fibrotic MASH. Additionally, the FNI index has mainly been validated in individuals with metabolic diseases and further validation in a more diverse population may be required.

***2.2 Imaging-based methods***

***2.2.1 Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE)***

An individualized meta-analysis showed that the AUROCs of LSM-VCTE, FIB-4, NFS, APRI, and AST/ALT in identifying advanced fibrosis were 0.85, 0.76, 0.73, 0.70, and 0.64 respectively. LSM-VCTE showed the best performance with the highest AUROC (*p*<0.001).[39] Sequential or combined application of the FIB-4 index and LSM can improve diagnostic accuracy. When the FIB-4 index of a patient with MASLD falls between 1.3 and 2.67, and the LSM value ranges from 8 to 12 kPa, this indicates the presence of significant fibrosis. Conversely, a FIB-4 index exceeding 2.67, along with an LSM greater than 12 kPa, suggests advanced fibrosis. Furthermore, a FIB-4 score exceeding 3.48 and an LSM of 20 kPa or greater indicate cirrhosis. In contrast, a FIB-4 index below 1.3 and an LSM below 8 kPa exclude advanced fibrosis.[39] However, the technical performance of VCTE is influenced by the patient's body weight, particularly in severely obese individuals, where its accuracy is reduced. The success rate and accuracy of VCTE examinations greatly depend on the operator's technical proficiency, and poor technique may lead to examination failure or unreliable results.[40]

***2.2.2 Magnetic Resonance Elastography (MRE)***

A meta-analysis that included eight independent cohorts to explore the cut-off values of MRE for MASLD-related fibrosis found that the AUROC of MRE for detecting significant liver fibrosis was 0.92 (sensitivity 79%; specificity 89%, with a cut-off value of 3.14 kPa). [41] For advanced fibrosis, the AUROC was 0.92 (sensitivity 87%; specificity 88%), with a cut-off value of 3.53 kPa. For cirrhosis, the AUROC was 0.94 (sensitivity 88%; specificity 89%, with a cut-off value of 4.45 kPa). [41]

Meanwhile, increased hepatic inflammatory activity and gamma-glutamyl transferase levels may affect the diagnostic accuracy of MRE, potentially leading to an overestimation of early-stage liver fibrosis (stages F0-F1). Although MRE performs efficiently in evaluating liver fibrosis in MASLD, it is more expensive and harder to obtain than VCTE.[27, 42]

***2.2.3 Shear-wave elastography (******SWE)***

SWE is another NITs based on ultrasound. It measures the liver stiffness in real-time by evaluating the velocity of shear waves generated by ultrasonic pulses. There are two main types of SWE: point SWE (pSWE) and two-dimensional SWE (2D-SWE). Due to differences in technology and methodology, the cut-off values of most SWE platforms may vary. Additionally, the cut-off values used by SWE to diagnose advanced fibrosis have not been as widely validated as those of VCTE.10

***2.2.4 Corrected T1 (cT1)***

cT1 is a quantitative index derived from magnetic resonance imaging (MRI) that evaluates both liver inflammation and fibrosis. It reflects the pathological state of the liver by measuring the T1 relaxation time of liver tissue. The cT1 value will increase due to extracellular edema or fibrosis in chronic diseases, making cT1 a valuable non-invasive biomarker for identifying patients with MASH who have fibrosis. Andersson et al. indicated that the AUROC of cT1 for identifying patients with high-risk MASH (NAS ≥4 and fibrosis ≥2) was 0.78 (95%CI, 0.74-0.82).[43] A cT1 value of ≥825 ms was used to exclude high-risk MASH (NAS ≥4 and fibrosis ≥2), with a high negative predictive value (NPV = 88%), indicating that patients were less likely to be high-risk MASH below this threshold. A cT1 value of ≥925 ms was used to confirm high-risk MASH, with a positive predictive value (PPV = 60%) and specificity (90%). [43]

**2.3 Combination** **serum and imaging-based biomarkers**

***2.3.1 FibroScan-AST (FAST)***

The FAST score is a comprehensive measure that combines the LSM obtained by VCTE, the controlled attenuation parameter (CAP), and serum AST levels to assess the presence of fibrotic MASH. [44] In a recent meta-analysis, Ravaioli et al. reported that the sensitivity, specificity, negative predictive value, and positive predictive value (PPV) of the FAST score in identifying fibrotic MASH were 89%, 89%, 92%, and 65% respectively.[45] The FAST score displayed good sensitivity, specificity, and negative predictive value. However, with a PPV of 65%, it indicates that even if the FAST score is positive, there remains a relatively high likelihood of a false positive. This may result in some patients without fibrotic MASH receiving unnecessary liver biopsies or drug treatments. Additionally, the CAP value and serum AST levels may be influenced by various factors (such as obesity, diabetes, or fluctuations in serum liver enzyme levels), which may impact the accuracy and consistency of the FAST score, especially in certain populations (**Table 1**).

***2.3.2 acFibroMASH index***

The acFibroMASH index comprises the acMASH index and LSM, while the acMASH index consists of serum AST and creatinine (SCr) levels.[46] In the derivation cohort, the AUROC of acFibroMASH was 0.808 (95% CI: 0.748–0.869), accurately identifying fibrotic MASH. In the validation cohort, the AUROC was 0.800 (95% CI: 0.758–0.839). An acFibroMASH value <0.15 can be used to exclude fibrotic MASH whereas an acFibroMASH value >0.39 can be used to diagnose fibrotic MASH.[46] The acFibroMASH combines the MASH status and fibrosis stage, enabling accurate diagnosis of fibrotic MASH with a high negative predictive value. However, SCr level in the acFibroMASH index may be influenced by renal diseases or other non-liver conditions, potentially affecting the accuracy of the acFibroMASH index in certain patient groups.[46]

***2.3.3 Agile 3+ and Angle 4***

The Agile 3+ score is mainly used for diagnosing advanced fibrosis (F ≥3) and comprises LSM, AST/ALT ratio, PLT count,, sex, and diabetes status.[47] The AUROC of Agile 3+ was 0.90 (95% CI 0.88–0.91) in the training set and 0.90 (95% CI 0.88–0.92) in the internal validation set. The low cut-off value (0.451) is suitable for excluding patients with advanced fibrosis, while the high cut-off value (0.679) is suitable for diagnosing those with advanced fibrosis.[47] Compared to FIB-4 and LSM, Agile 3+ demonstrates superior diagnostic specificity and PPV and while reducing the proportion of the uncertain interval. As the Agile 3+ score requires VCTE to obtain LSM data, it may face constrains due to equipment and resource limitations in certain countries (**Table 1**). [Sanyal](https://pubmed.ncbi.nlm.nih.gov/?term=%22Sanyal%20AJ%22%5BAuthor%5D) et al. developed and validated Agile 4 score by combining LSM with routine biomarkers to identify the presence of cirrhosis. They found that Agile 4 outperformed FIB-4 and LSM in terms of AUROC, and percentage of patients with indeterminate results.[47] In the context of Resmetirom, excluding MASLD-related cirrhosis is crucial for identifying eligible patients. An Agile 4 score below 2.251 has a NPV of .98 and .96 in two external validation cohorts, respectively, making it an effective tool for excluding cirrhosis. [47]

***2.3.4 MAST***

The MAST score combines MRI-proton density fat fraction (MRI-PDFF), MRE, and serum AST levels.[48]. In the validation cohort, the AUC of the MAST score was 0.93 (95% CI 0.88-0.97), showing a very high diagnostic ability.[48] MAST outperforms both the NFS and FIB-4 and has a higher AUC value than the FAST score (0.93 vs. 0.87). [48] The low cut-off value (0.165) effectively excludes patients with high-risk MASH, while the high cut-off value (0.242) is suitable for diagnosing patients with high-risk MASH.[48] The MAST score requires MRI-PDFF and MRE examinations, which have high equipment requirements for equipment and may limit its utility in certain clinical settings. Additionally, the MAST score has limited negative predictive ability for significant fibrosis[49]. In this study, the authors compared the diagnostic performance of three NITs (MEFIB, MAST, and FAST) for identifying significant fibrosis in MASLD, showing that the NPV of MEFIB was 90.1%, surpassing that of both MAST (69.6%) and FAST scores (71.8%).[49]

***2.3.5 MRE combined with FIB-4 (MEFIB index)***

MEFIB index combines MRE, and the FIB-4 score and is used to identify patients with MASH-related fibrosis of stage ≥2 who require drug treatment. When MRE ≥3.3 kPa and FIB-4 ≥1.6, the AUC of the MEFIB index was 0.90 (in the training cohort) and 0.84 (in the Japan-MASLD cohort).[50] MEFIB index demonstrates an extremely high PPV, with a PPV of 97.1% in the Training cohort and 91.0% in the Japan cohort.[50] The high PPV of the MEFIB index aids in identifying patients with stage ≥2 fibrosis who require treatment , although it lacks an effective exclusion mechanism. MEFIB index performs excellently for high-risk groups but may not fully fulfill its role for low-risk populations.[50] If only patients who meet the criteria are included without effectively excluding low-risk patients, it may lead to inaccurate patient management. Additionally, MRE equipment is expensive and may not be available in some regions and medical institutions.

**3.** **NITs for monitoring fibrosis progression** **and predicting clinical outcomes**

The accuracy of NITs for fibrosis progression in MASLD are summarized in **Supplementary Table 2.**

***3.1*** ***Serum markers***

In a longitudinal study involving paired liver biopsies, the progression of APRI, FIB-4, and NFS over time was strongly correlated with one-stage fibrosis advancement, demonstrating cross-validated C-statistics greater than 0.80.[51] A retrospective cohort study of 202,319 patients with MASLD, with a median follow-up duration of 8.2 years, showed that at baseline, 74.7%, 21.4%, and 3.9% of the patients had FIB-4 scores categorized as low-risk (2.67), respectively. After three years of follow-up, 20.9% of the low-risk patients progressed to moderate or high-risk, while 55.3% of the high-risk patients remained in the high-risk category. Compared to patients who maintained a low-risk status, those who remained at high risk exhibited a significantly higher incidence of HCC (4.56 vs. 0.05 per 1000 person-years, adjusted subdistribution hazard ratio (sHR) 57.7, 95% CI 40.5-82.2). Furthermore, the risk of the composite endpoint of liver cirrhosis and HCC was significantly increased (sHR: 28.6, 95% CI 24.6-33.2). The study confirmed that the longitudinal increase in the FIB-4 score is dose-dependently associated with the risks of developing HCC and liver cirrhosis.[52] As new therapies emerge, long-term follow-up will be essential not only to monitor fibrosis progression but also to evaluate the sustainability of treatment effects over time.

***3.2 Imaging-based tools***

Loomba et al. reported that the optimal baseline LSM threshold for predicting the progression of patients with F3 fibrosis to liver cirrhosis was ≥16.6 kPa, with a C-statistic of 0.72.[53] At this threshold, the sensitivity, specificity, PPV, and negative predictive value were found to be 58%, 76%, 31%, and 91%, respectively. To predict the risk of LREs in patients with cirrhosis (F4 fibrosis), the optimal baseline LSM threshold was determined to be ≥30.7 kPa, with a C-statistic of 0.77. The corresponding sensitivity, specificity, PPV, and negative predictive value at this threshold were 70%, 79%, 11%, and 99%, respectively.[53] In addition, an increase in LSM of ≥5 kPa (and ≥20% from baseline) was associated with an increased risk of progression to liver cirrhosis in patients with F3 fibrosis.[53] Furthermore, Gawrieh et al. suggested that change in LSM by VCTE over time is independently and bi-directionally associated with risk of LRE and is a non-invasive surrogate for clinical outcomes in patients with MASLD.[54] Additionally, the non-invasive two-step approach of FIB-4 followed by LSM is effective in classifying patients at different risks of LREs.[55]

Studies have shown that liver stiffness measured by MRE is closely related to the risk of developing LREs. [56] A meta-analysis involving 1,707 patients with longitudinal data and a median follow-up period of three years indicated that, compared to those with an MRE score of less than 5 kPa, patients with an MRE score between 5 and 8 kPa had an HR of 11.0 (95% CI: 7.03 - 17.1, *P* < 0.001) for the occurrence of the primary hepatic outcome, which included ascites, hepatic encephalopathy, and treatable varices. Furthermore, patients with an MRE score exceeding 8 kPa exhibited an HR of 15.9 (95% CI: 9.32 - 27.2, P < 0.001).[56] The 3-year risk of developing incident HCC in patients with an MRE < 5 kPa, 5 - 8 kPa, and ≥ 8 kPa was 0.35%, 5.25%, and 5.66%, respectively.[56]

***3.3 Combination serum and imaging biomarkers***

A multicenter cohort study showed that the time-dependent AUROC of the Agile 3+ and Agile 4 scores for predicting LREs reached 0.89, surpassing most traditional non-invasive fibrosis indices (such as FIB-4, NFS), with risk stratification being more accurate (only 10.2%-14.3% of patients were in the moderate-risk range).[57] These findings indicate that a single or sequential Agile score has a high degree of accuracy in predicting long-term LREs in patients with MASLD, making it a suitable alternative to liver biopsy in clinical practice and in phase 2b and phase 3 clinical trials of MASLD/MASH.[55, 57]

A meta-analysis showed that the MEFIB index, defined as positive when MRE is greater than or equal to 3.3 kPa and FIB-4 is greater than or equal to 1.6, was significantly associated with the risk of LREs, with an HR of 20.6 (95% CI: 10.4 - 40.8, *P*<0.001).[56] The acFibroMASH developed by our team also demonstrated good predictive efficacy for long-term LREs. We found that regarding the prediction of the 5-year risk of LREs, the AUROC of the acFibroMASH index was 0.835 (95% CI 0.786–0.882), which surpassed the FAST score of 0.750 (95% CI 0.693–0.800, *P* < 0.01). Compared to patients with an acFibroMASH < 0.15, those with an acFibroMASH > 0.39 had a higher risk of long-term LREs (adjusted HR: 11.23, 95% CI 3.98–31.66).[46]

**4.** **NITs for monitoring regression or remission and long-term outcomes**

In recent years, the use of NITs to predict histological changes in the liver after intervention has become a critical area of research.[58, 59] Although various NITs have been developed, research on NITs specifically for assessing disease improvement/remission remains relatively scarce. A meta-analysis showed that patients exhibiting a relative reduction in MRI-PDFF of ≥30% (responders) demonstrated a significantly higher histological response rate—defined as an improvement of the NAS by ≥2 points without any worsening of fibrosis—compared to those who did not meet this criterion (non-responders), with rates of 51% versus 14% (OR=6.98, 95% CI 2.38–20.43, *P*<0.001). Furthermore, the remission rate of MASH, characterized by the disappearance of ballooning and a lobular inflammation score of 0 to 1, was also significantly higher among responders (41% vs. 7%, OR=5.45, 95% CI 1.53–19.46, *P*=0.009).[60] A post hoc analysis of the 72-week obeticholic acid treatment trial for non-cirrhotic MASH indicated that the optimal cutoff point for the relative decline in MRI-PDFF for histologic response was 30%.[61]

Loomba et al. constructed the first MASH resolution prediction model based on paired MASLD data from two liver biopsies, which incorporated baseline MRI-PDFF, changes in MRI-PDFF, and parameters related to histological response to evaluate the histological remission of MASH[62]. Another study found that changes in the baseline MASLD activity score, baseline serum triglyceride levels, and serum ALT levels were associated with histological response in MASLD.[63] Specifically, ALT decrease at week 24 (17 U/L vs <17 U/L) was associated with histologic response in multivariable analysis.[63] It is important to mention that the existing data are largely from natural history cohorts and cannot represent the situation in treated patients. For example, although a reduction in the FAST score correlated with histological improvements in the phase 2 semaglutide trial, patients who did not achieve the histological endpoints also had significant reduction in FAST score due to the impact of weight reduction on NITs.[64]

**5. Integrating NITs into Clinical Practice**

***5.1*** ***Clinical practice protocols based on NITs***

Most current guidelines suggest that a stepwise diagnostic approach that utilizes scores based on routine blood laboratory indicators (such as FIB-4) and imaging techniques (such as liver transient elastography) to exclude or assess advanced fibrosis in MASLD patients and predict long-term LREs.[26, 27, 65] FIB-4 index can initially assess the risk of advanced fibrosis in MASLD. For patients with FIB-4 ≥ 1.3, LSM by transient elastography is necessary for fibrosis risk stratification. [26, 27, 65] MASLD patients with FIB-4 ≥ 1.3 and LSM ≥ 8 kPa should be further diagnosed and evaluated by a specialist.[27] In addition, alternative detection tools to VCTE include MRE, SWE, and ELF.[27]

Exploring the cut-off values of these alternative options is a crucial and valuable task. In the patient group with a FIB-4 score in the indeterminate range of 1.3 to 2.7, the ELF score is recommended as a second-line testing option, with a suggested cut-off value of 9.8 for the ELF score. Patients who achieve this score should be referred to a specialist for further evaluation. This strategy results in a relatively small proportion of patients with an ELF score exceeding 9.8 requiring subsequent referral to a specialist, at only 14%. Additionally, when predicting LSM that exceed 8 kPa, the false negative rate remains low, at just 8%.[66] In a series of practical applications in primary care in the UK, performing FIB-4 testing first and then the ELF test has quadrupled the number of confirmed cases of advanced liver fibrosis and cirrhosis, while reducing the number of unnecessary referrals by ~80%, showing remarkable results.[67] However, in clinical practice, relatively few centres in the UK have access to ELF measurements.

The EASL–EASD–EASO Clinical Practice Guidelines recommend the use of blood biomarker-derived scores and elastography to rule out advanced fibrosis, with elastography being particularly suitable for predicting its presence.[27] In addition, sequential evaluation using NITs can aid in ruling out fibrosis progression in patients with MASLD and may also help predict the risks of LREs and all-cause mortality.[27] Similarly, the clinical practice guidelines of the Asian Pacific Association for the Study of the Liver recommend that patients with significant fibrosis should be monitored annually through a combination of NITs and liver stiffness measurement.[26] Notably, although current guidelines provide well-established recommendations for diagnosis and risk stratification, they remain insufficient in guiding fibrosis progression monitoring and assessment of therapeutic response. With emerging therapies such as resmetirom and semaglutide entering clinical practice, future updates of clinical guidelines should emphasize the role of NITs in longitudinal disease monitoring and treatment response evaluation.

***5.2 Challenges in real-world practice***

***5.2.1 Technical and methodological limitations***

Currently, widely used liver stiffness detection technologies, such as ultrasound elastography and MRE, exhibit significant prominent device-dependent differences.[68] The test results for the same patient may vary due to different device models, thus increasing the complexity of diagnosis and posing obstacles to comparing data across centers. Although some NITs have been included in the guidelines, a lack of unified standards for their cut-off values used in longitudinal monitoring persists. Biological interfering factors are the key factors affecting the accuracy of NITs.[69, 70] A key challenge is effectively excluding these interfering factors to ensure the accuracy and clinical applicability of the measurement results. Additionally, inter-test variability is a critical issue, particularly for imaging-based modalities like transient elastography. The issue of test-retest reliability, particularly in modalities like FibroScan, is vital for ensuring consistency in diagnostic results.

***5.2.2 Clinical implementation barriers***

Although advanced imaging technologies, their accessibility in many medical settings is limited. MRE demands costly MRI equipment and skilled operators. Due to resource constraints, high costs, and technical limitations in numerous areas, MRE is not widely available.[71, 72] Additionally, the majority of patients with MASLD are seen at primary care, where accessibility to ultrasound scan and ultrasound elastography can also be an issue. Improving the availability of these technologies in primary medical institutions or developing more accessible and cost-effective alternative solutions remains a significant challenge in promoting non-invasive detection.[73] Conversely, some doctors may lack an understanding of these tools or have insufficient knowledge of how to reasonably interpret the test results properly and make clinical decisions.[74, 75, 76]

***5.2.3 Research and validation gaps***

Several NITs, such as LSM and FIB-4, have been widely used for diagnosing and monitoring liver fibrosis. However, their long-term effects on evaluating fibrosis regression and predicting prognosis have not been fully verified.[15, 77] After patients receive treatment, accurately evaluating the regression of fibrosis and assessing the durability of the treatment effect remains a gap in clinical research.[78, 79] In addition, the key factors for predicting histological response vary across different intervention measures. The performance data for most NITs are derived from specific populations. However, there are ethnic differences in the epidemiological characteristics of fibrosis and MASH, and there are also varying degrees of deviation in the influence of the detection tools by different age groups, sexes, and comorbid conditions.[80] The effectiveness and reliability of NITs in diverse populations, such as African ethnic groups, have not been thoroughly studied.[81, 82]

**6. Suggested future directions for development**

***6.1*** ***The application of*** ***multi-omics and multi-modal fusion***

Future NITs need to integrate multi-omics data, such as genomics, proteomics, and metabolomics, with imaging technologies, to construct more accurate diagnostic models.[83, 84] The combination of multi-dimensional information is expected to overcome the limitations of a single technology and provide personalized diagnostic and treatment plans for patients. For example, Chen et al. proposed a new method for diagnosing MASLD that combines a comprehensive clinical dataset with a prediction method based on multimodal learning.[85] A multimodal learning-based prediction method (DeepFLD) is proposed, which incorporates several modalities and demonstrates excellent diagnostic performance (**Figure 2)**.[85] Additionally, with the interdisciplinary integration of nanomaterials science, biomedical engineering and molecular imaging, nanosensing technology is expected to revolutionize the diagnosis and treatment model of MASLD, providing new key technical support for global liver disease prevention and control.

***6.2 Artificial intelligence (AI) and digital health applications for dynamic tracking***

With the rapid development of AI and digital health technologies, more advanced devices and algorithms will be applied to dynamically monitor liver diseases in the future.[86] Using AI algorithms for real-time analysis and predicting non-invasive detection results can assist doctors in promptly identifying changes in patients' conditions, adjusting treatment plans, and improving treatment outcomes. For example, AI-driven smartphone applications and wearable devices can track patients' physiological indicators in real-time and provide accurate disease warnings and management suggestions, significantly improving the convenience and effectiveness of disease monitoring (**Figure 2)**.[87, 88, 89] In recent years, point-of-care testing (POCT), as an emerging diagnostic platform, has made significant progress in enhancing on-site disease management and monitoring.[90] In the future, the development of portable POCT detection devices based on NITs will bring new changes to the screening and stratified management of MASLD.

***6.3 Non-invasive surrogate endpoints in clinical trials***

In therapeutic MASH trials, identifying appropriate surrogate endpoints is essential for accelerating the approval of new drugs.[21, 89, 91] Relying on NITs enables the assessment the impact of drugs on MASH and liver fibrosis, without resorting to a liver biopsy, thus expediting the clinical research process, and reducing costs.[92]

***6.4*** ***Global standardization efforts***

Global standardization efforts are particularly crucial with the ongoing development of diagnostic criteria for MASLD.[93] Establishing international cooperative organizations, such as the MASLD working group, can promote unified standards for MASLD and fibrosis worldwide, and facilitate the sharing of clinical data and the verification of methods across various countries and regions. These efforts will provide valuable opportunities for comparative studies of NITs in other populations and enhance the optimization of diagnostic and treatment methods for fibrosis.

***6.5 Update the pharmacotherapeutic protocols***

In addition to resmetirom, new pharmacotherapies and combination treatment strategies are emerging as promising approaches for treating MASLD.[13, 94] Combining drug treatment with non-invasive monitoring can achieve comprehensive management of patients' conditions, timely evaluate the treatment effect, and facilitate adjustments to the treatment plan. [13, 95] Resmetirom expands the medication options available to treat patients with MASH and can be administered alongside other medications to optimize cardiometabolic factors, such as incretin receptor agonists and statins.[96]

***6.6*** ***Toward personalized fibrosis monitoring***

With the development of personalized medicine, future fibrosis monitoring will focus on individual differences among patients.[97, 98] By utilizing dynamic risk models and combining factors such as the patient's age, sex, and comorbid conditions, it is possible to customize the most suitable non-invasive detection path for each patient. This personalized monitoring strategy helps improve the early detection rate of diseases, avoids excessive screening, or missed diagnoses, and improves the precision and effectiveness of treatment (**Figure 2)**.

**7. Conclusions**

NITs have demonstrated great potential in the managing MASLD/MASH fibrosis and are promoting innovation in the diagnosis, monitoring, and treatment of liver disease. The advancement of NITs, such as serum biomarkers, and imaging technologies, has significantly enhanced our ability to evaluate liver fibrosis in MASLD. However, despite the considerable promise of these tools, challenges remain in practical applications, including technical and methodological limitations, accessibility of medical equipment, and barriers in the clinical practice process. To tackle these challenges and fully realize the potential of NITs, future research should emphasize long-term verification, assess performance across different populations, and develop standardized implementation protocols. Integrating multi-omics methods, AI-driven tracking systems, and personalized risk models will lead to breakthroughs in more dynamic, accurate, and customized fibrosis monitoring for individuals with MASLD/MASH.

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**Table legend**

**Table 1.** Non-invasive tests for identifying the severity of fibrosis in MASLD/MASH (focusing on stages F2/F3) in the post-Resmetirom Era.

**Figure legends**

**Figure 1.** Non-invasive tests of fibrosis in the management of MASLD in the Resmetirom era based on updated MASLD natural history.

**Figure 2.** Prospects for non-invasive tests of fibrosis in the management of MASLD.

**Supplementary Tables**

**Supplementary Table 1.** The accuracy of NITs for MASH with clinically significant fibrosis or MASLD with significant fibrosis.

**Supplementary Table 2.** The accuracy of NITs for progression or regression of MASLD.