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Non-invasive assessment in MASLD: from biomarker discovery to clinical pathway integration

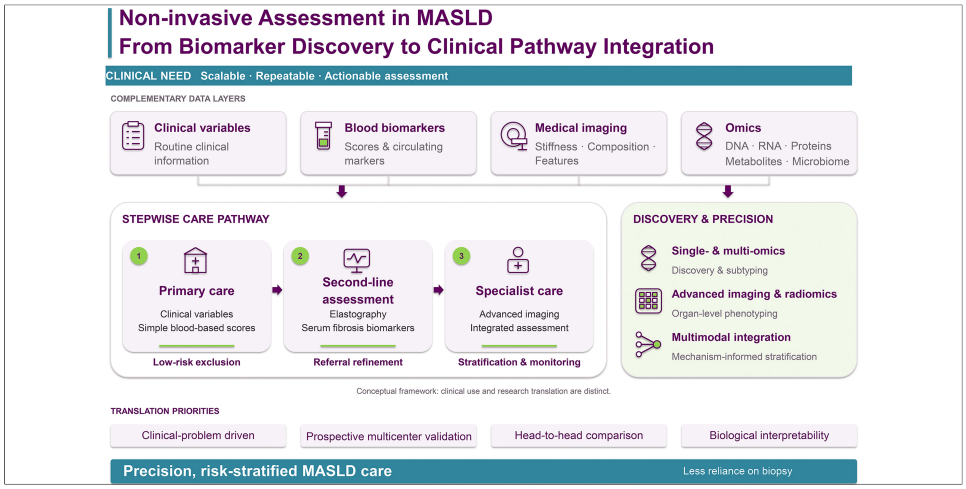
Qiuyi Shen[1], Hongjian Kang[1], Qianxue Shan[1], Ziqiang Yu[1], Dawei Yang[2,3], Zhenghan Yang[2,3], Weitian Chen[1]

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the leading causes of chronic liver disease worldwide. Although liver biopsy remains the histological reference standard for assessing steatohepatitis, fibrosis stage, and therapeutic response, its invasiveness, sampling variability, and limited suitability for repeated monitoring have driven the development of non-invasive approaches. Clinical scores based on routine variables, omics-derived biomarkers, quantitative imaging techniques, and multimodal integrative models have substantially expanded the landscape of MASLD assessment. This review summarizes current progress in non-invasive evaluation of MASLD from a clinically oriented perspective, covering traditional blood-based and clinical tools, omics approaches, quantitative imaging, and multimodal integration. Particular attention is given to how these tools may serve different clinical purposes, including targeted screening or case-finding, specialist referral, fibrosis stratification, prognostic assessment, longitudinal monitoring, and precision, risk-stratified care. Major translation barriers remain, including the predominance of technology-driven instead of clinically driven study designs, the imperfect nature of biopsy-based reference standards, insufficient head-to-head comparisons across modalities, limited external validation of high-dimensional models, and uncertainty regarding real-world implementation. We argue that the future of non-invasive assessment

[1]Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Hong Kong SAR, China.
[2]Department of Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China.
[3]State Key Laboratory of Digestive Health, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China.

Correspondence to: Prof. Weitian Chen, Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Hong Kong SAR, China. E-mail: wtchen@cuhk.edu.hk

in MASLD lies not in identifying a universally superior single modality, but in developing a clinical-context-specific, stepwise, and biologically interpretable framework that aligns non-invasive tools with distinct clinical needs and decision points.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide, affecting approximately 32% of adults[1]. Its prevalence continues to increase, imposing a substantial and growing burden on healthcare systems globally[2-5]. A multicountry modeling study projected that the number of MASLD cases across eight countries could increase by up to 30% between 2016 and 2030[6]. Clinical assessment of MASLD focuses primarily on three key disease features: steatosis, inflammatory activity, and fibrosis. Among these features, fibrosis stage is the strongest histological predictor of liver-related outcomes and mortality, with the greatest risks observed in patients with advanced fibrosis or cirrhosis. This prognostic importance is further highlighted by the rapidly increasing contribution of MASLD to the global burden of hepatocellular carcinoma (HCC)[7]. Although MASLD-related HCC most commonly develops in patients with advanced fibrosis or cirrhosis, it can also occur before cirrhosis in a subset of patients[8]. Early identification of high-risk individuals and dynamic risk stratification across the disease spectrum are therefore essential. Accordingly, the primary objective of non-invasive assessment extends beyond detecting steatosis to identifying clinically significant fibrosis and predicting disease progression[9-11]. Evidence demonstrating the prognostic value of fibrosis stage in patients with MASLD, including those with metabolic dysfunction-associated steatohepatitis (MASH), further supports its use as a surrogate endpoint in clinical assessment[9].

Liver biopsy remains the reference standard for histological assessment of MASLD. However, biopsy is associated with invasive risks, including internal bleeding, complications, and even life-threatening events, making it unsuitable as a tool for long-term, real-time monitoring of disease progression[12]. In addition, each biopsy samples only about 1/50,000 of the liver, and such a limited specimen cannot adequately represent the condition of the entire organ, thereby leading to sampling error[13-15]. Finally, liver fibrosis is a dynamic process, whereas fibrosis staging based on biopsy is only semi-quantitative and cannot satisfactorily capture disease progression[16-19]. Because of these limitations, together with the substantial clinical demand, there is an urgent need for non-invasive assessment methods, as biopsy is not suitable for large-scale, repeated, dynamic use in clinical management. Over the past several decades, a wide range of non-invasive approaches has emerged. The analysis of omics and imaging data has led to the development of numerous techniques with promising diagnostic performance to assist clinicians in the evaluation of MASLD.

Rather than seeking a single best-performing tool, the key to non-invasive assessment of MASLD lies in building a stratified, interpretable, and clinically translatable framework that aligns with different clinical scenarios and management goals. In this context, this article reviews non-invasive assessment strategies for MASLD with emphasis not only on diagnostic performance, but also on their utility in screening, risk stratification, prognosis, and long-term monitoring. Because primary care and specialist liver centers differ substantially in clinical goals and available resources, this review focuses on what each of these settings actually needs. It also emphasizes methods that are interpretable and translatable, rather than covering end-to-end deep learning models in detail. The following sections are organized accordingly, beginning with current clinical tools, then progressing to emerging omics and imaging approaches, and finally exploring their future applications in the precision management of MASLD.

Unlike most previous reviews that focus on diagnostic accuracy and comparison of individual non-invasive tests, this review focuses on the clinical positioning of non-invasive tools across different MASLD care pathways. We emphasize how blood-based scores, omics-derived biomarkers, quantitative imaging, and

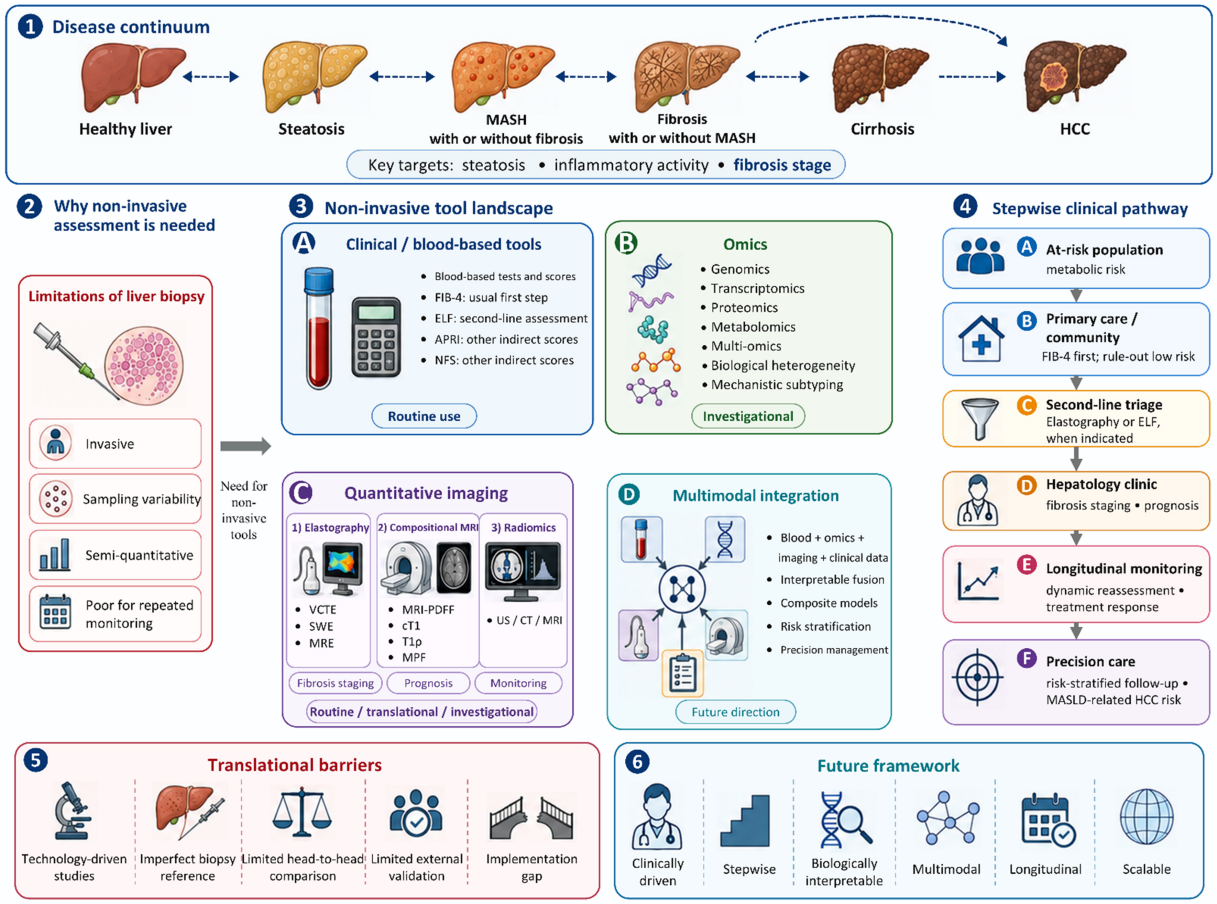


Figure 1. Non-invasive assessment across the MASLD disease continuum. The figure shows the limitations of liver biopsy, the roles of established and emerging tools in a stepwise clinical pathway, and key barriers and future directions for clinical translation. The pathway is conceptual. APRI: Aspartate aminotransferase-to-platelet ratio index; CT: computed tomography; cT1: corrected T1; ELF: enhanced liver fibrosis; FIB-4: fibrosis-4 index; HCC: hepatocellular carcinoma; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; MPF: macromolecular proton fraction; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging; MRI-PDFF: MRI-derived proton density fat fraction; NFS: nonalcoholic fatty liver disease fibrosis score; SWE: shear wave elastography; T1ρ: spin-lattice relaxation time in the rotating frame; US: ultrasound; VCTE: vibration-controlled transient elastography.

multimodal models may be deployed differently for population screening, referral prioritization, fibrosis stratification, prognostic assessment, longitudinal monitoring, and precision management[7,10,11,20-23]. We further discuss the potential for integrating complementary tools within the same clinical task into multimodal strategies, with the aim of developing a comprehensive, high-performance, and interpretable precision-medicine pathway. We also distinguish tools with current clinical readiness from those that remain largely investigational. Figure 1 summarizes the MASLD disease continuum, the clinical roles of established and emerging non-invasive tools, their positions in a stepwise care pathway, and the main barriers to translation. Table 1 further compares their evidence-supported uses and boundaries of interpretation.

Literature search and study selection

This narrative review was informed by a targeted search of PubMed and Web of Science for relevant studies published through January 2026, without a formal lower publication-date limit. We focused primarily on studies published between 2005 and 2026, while retaining earlier foundational publications where relevant. Search terms included combinations of "MASLD" or "NAFLD", "fibrosis", "non-invasive test", "magnetic resonance elastography", "PDFF", "radiomics", and "omics". Additional relevant studies were identified by

Table 1. Potential application of the MASLD non-invasive assessment tools in different clinical tasks

Tool category	Representative approaches	Clinical question/setting	What the evidence supports	Boundary of interpretation
Blood-based scores	AST/ALT ratio, APRI, BARD, FIB-4, NFS; ELF, PRO-C3	Primary care and diabetology triage; specialist prognostication	Reliable for ruling out, not confirming; FIB-4 is a widely used first-line test; both prognostic for decompensation and mortality; two-step pathways reduce unnecessary referral[7,10,11,20]	Large indeterminate zone; no discrimination of individual stages; age confounds indirect scores[10,11,21,22]
Single-omics	Genomics, transcriptomics, proteomics, metabolomics and metagenomics for biomarker discovery and diagnosis	Research and selected cohorts	Risk variants robustly replicated but of modest effect; credible replicated circulating candidates; potential metabolomic and microbiome markers of disease activity and fibrosis[7,10,11]	Evidence strength differs by layer; genotype adds marginally over routine clinical data; mostly exploratory, cross-sectional, and optimistic in single-cohort pilots[10]
Multi-omics integration	Multi-omics models for disease classification, fibrosis stratification	Research and selected cohorts	Adding a molecular layer improves within-cohort discrimination; panels for at-risk steatohepatitis can outperform simple indirect scores; microbiome-derived predicted metabolites support a feasible blood test[7,10]	Within-cohort discrimination gain is not incremental clinical utility; needs external validation; non-routine assays and limited cost-effectiveness; each modality's contribution must be shown[7,11]
Elastography	VCTE, 2D-SWE, MRE; stiffness-containing composites	Specialist care after triage: refine fibrosis risk, prognosis	VCTE the most validated and superior to simple blood panels; MRE more accurate; both prognostic, with serial rise carrying independent risk[7,10,11]	Confounded by necroinflammation, cholestasis, congestion, food intake and (for MRE) iron; serial change is not histological regression; MRE limited by cost and access[10,11,20,21]
Quantitative imaging	MRI-PDFF; iron-corrected T1, T1ρ, MPF	Trials and specialist care: quantify hepatic fat and assess fibrosis	MRI-PDFF the most accurate and reproducible fat measure; fibrosis-oriented parameters remain exploratory[7,10,11,21]	Require external validation[7,11,22]
Radiomics	Radiomics models based on ultrasound, CT or MRI for fibrosis or steatosis assessment	Research: image-derived features add beyond existing clinical, biochemical and imaging measures	Rationale is images as mineable data feeding decision support[24,25]	Limited by reproducibility; segmentation the most contentious step; studies underpowered, single-centre, externally unvalidated; interpretability gap *vs.* radiographic features[24-26]

2D-SWE: Two-dimensional shear wave elastography; ALT: alanine aminotransferase; APRI: aspartate aminotransferase-to-platelet ratio index; AST: aspartate aminotransferase; BARD: body mass index, aspartate aminotransferase-to-alanine aminotransferase ratio, and diabetes score; CT: computed tomography; ELF: enhanced liver fibrosis; FIB-4: fibrosis-4 index; MASLD: metabolic dysfunction-associated steatotic liver disease; MPF: macromolecular proton fraction; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging; MRI-PDFF: MRI-derived proton density fat fraction; NFS: nonalcoholic fatty liver disease fibrosis score; PRO-C3: N-terminal propeptide of type III collagen; T1: longitudinal relaxation time; T1ρ: spin-lattice relaxation time in the rotating frame; VCTE: vibration-controlled transient elastography.

screening the reference lists of relevant articles, review articles, and clinical guidelines. Priority was given to large prospective or multicenter studies, meta-analyses, studies using histological or clinically meaningful outcome reference standards, and studies with direct relevance to clinical risk stratification, prognostic assessment, or longitudinal monitoring in MASLD. Studies included in the tables were selected as representative examples based on study design, sample size, methodological quality, and clinical relevance; they were not intended to constitute an exhaustive systematic evidence synthesis.

Clinical parameter-based non-invasive tools

Clinical application of non-invasive tools differs between primary care and hepatology specialist settings. In primary care, the main goal is to identify low-risk patients who can be managed without much intervention and high-risk patients who need further tests or specialist referral. In contrast, hepatology clinics focus on more refined diagnostic assessment, fibrosis staging, prognostic stratification, treatment selection, and longitudinal monitoring[20]. These tasks demand more from non-invasive tools, requiring them to be reliable, robust, and consistent. Assessment based on routine laboratory parameters and simple clinical variables is

the common non-invasive strategy in MASLD. These tools are inexpensive, accessible, and scalable, making them particularly suitable for first-line triage and population-level risk stratification. Existing evidence indicates that non-invasive tools such as Fibrosis-4 index (FIB-4), Nonalcoholic fatty liver disease fibrosis score (NFS) and Aspartate aminotransferase-to-platelet ratio index (APRI) are clinically useful in the assessment of patients with MASLD[27-30]. Because these parameters are derived from routine clinical indicators and the calculations are simple and inexpensive, these methods are highly accessible in large-scale population screening and primary care settings. As a result, they have become the most commonly used first-line screening tools and have been incorporated into clinical guidelines[22,23].

Studies have moved beyond comparing these models to fibrosis stages and now focus more on their ability to predict liver-related events, HCC, and overall mortality[29-31]. For example, Tayob *et al.* validated the epatocellular carcinoma early detection screening (HES) algorithm, which integrates alpha-fetoprotein (AFP), age, alanine aminotransferase (ALT), platelet count, and longitudinal changes in AFP, and demonstrated that it improved the detection of early-stage HCC within 6 months compared with AFP alone in a community-based cirrhosis cohort[32]. Fujii *et al.* further showed that, among patients with biopsy-proven MASLD, a baseline platelet count was associated with an increased risk of HCC development[33]. Collectively, these findings suggest that routinely available laboratory parameters may contribute not only to fibrosis assessment, but also to HCC screening and prognostic stratification.

Most conventional scoring systems are based on indirect indicators such as age, aminotransferase levels, platelet count, and metabolism-related parameters. Although they are clinically useful, they remain limited in their ability to capture biological heterogeneity and individualized disease trajectories[27,34,35]. Ioannou *et al.* developed a prediction model using seven routinely available variables - age, sex, diabetes, body mass index, platelet count, serum albumin, and the aspartate aminotransferase (AST)-to-ALT ratio - in patients with MASLD and alcohol-related liver disease[29]. The model achieved an area under the curve (AUC) of 0.75 in the validation cohort, indicating moderate discriminative performance and suggesting that the integration of conventional clinical parameters may support HCC risk stratification. Particularly in the context of dynamic monitoring, repeated measurement of indices such as FIB-4 has shown some prognostic value in several large population-based studies[34], but its ability to identify true histological progression in individual patients is not stable, and findings have even differed across studies[27,35].

Unlike indirect scores derived from routine clinical variables, the Enhanced Liver Fibrosis (ELF) test reflects extracellular-matrix turnover through hyaluronic acid, amino-terminal propeptide of type III procollagen, and tissue inhibitor of metalloproteinase-1. In MASLD, ELF has shown good diagnostic performance for advanced fibrosis (AUC 0.83), although its predictive value depends substantially on the underlying disease prevalence and selected threshold[36]. ELF also has prognostic relevance: higher ELF scores were independently associated with liver-related outcomes in patients with chronic liver disease, and this association has subsequently been confirmed in a large population-based cohort, particularly among individuals with obesity, diabetes, or elevated ALT[37,38]. Therefore, ELF is best positioned as a clinically validated complementary test for fibrosis risk refinement, rather than a stand-alone universal rule-in tool.

Routine clinical scores are easy to scale and access, but they do not reflect much of the underlying biology. By contrast, omics-driven integrative strategies are better for understanding disease mechanisms and supporting therapeutic development.

Table 2 summarizes the representative studies of blood-based biomarkers, conventional fibrosis scores, and clinically translatable composite models discussed in this section. Overall, routine clinical scores and blood-based markers work best as first-line tools for population-level risk stratification, primary care screening, and

Table 2. Representative studies of blood-based biomarkers and clinical scoring systems for non-invasive assessment of MASLD

Author(s)	Year	Study design	Sample size	Clinical task	Biomarker/Model
Srivastava *et al.*[28]	2019	Prospective	3,012	Screening	FIB-4
Siddiqui *et al.*[27]	2019	Retrospective	1,904	Diagnosis	APRI, FIB-4, AST/ALT ratio, NFS
Ioannou *et al.*[29]	2019	Retrospective	7,068	Prognosis	HCC risk prediction models
Hagstrom *et al.*[34]	2020	Retrospective	40,729	Prognosis	FIB-4
Balkhed *et al.*[35]	2022	Retrospective	135	Prognosis	FIB-4, NFS, APRI, dAAR
Labenz *et al.*[39]	2022	Prospective	11,859	Screening	SEAL algorithm
Younes *et al.*[31]	2021	Retrospective	1,173	Prognosis	APRI, BARD, FIB-4, NFS, HFS
Parkes *et al.*[37]	2010	Prospective	457	Prognosis	ELF
Saarinen *et al.*[38]	2023	Prospective	6,040	Prognosis	ELF
Tayob *et al.*[32]	2021	Retrospective	38,431	Screening	Updated HES algorithm, AFP
Fujii *et al.*[33]	2023	Retrospective	1,398	Prognosis	Platelet count

AFP: Alpha-fetoprotein; ALT: alanine aminotransferase; APRI: aspartate aminotransferase-to-platelet ratio index; AST: aspartate aminotransferase; BARD: body mass index, aspartate aminotransferase-to-alanine aminotransferase ratio, and diabetes score; dAAR: dynamic aspartate-to-alanine aminotransferase ratio; ELF: enhanced liver fibrosis; FIB-4: fibrosis-4 index; HCC: hepatocellular carcinoma; HES: hepatocellular carcinoma early detection screening; HFS: Hepamet fibrosis score; MASLD: metabolic dysfunction-associated steatotic liver disease; NFS: nonalcoholic fatty liver disease fibrosis score; SEAL: structured early detection of asymptomatic liver cirrhosis.

referral prioritization. Their main clinical value is in excluding advanced fibrosis among low-risk populations and identifying patients who require second-line assessment with elastography, ELF test, or specialist evaluation. However, because these scores are based largely on indirect variables such as age, aminotransferases, and platelet count, they are less suitable for refined fibrosis staging, precise individual-level monitoring, or mechanistic disease characterization. Therefore, these tools should be used as triage tools at the entry of a stepwise pathway rather than as standalone methods for comprehensive MASLD assessment.

OMICS-DRIVEN NON-INVASIVE ASSESSMENT

Single-omics assessment

Early omics research was limited to single-omics approaches, investigating MASLD separately from the perspectives of DNA, RNA, proteins, and metabolites. The research objectives ranged from pathological exploration, diagnosis, and prognostic evaluation to treatment monitoring[40-43]. Some studies have further extended the research to the identification of HCC-related risk, suggesting that single-omics strategies may contribute to disease subtyping and fibrosis assessment, and provide complementary information for identifying high-risk individuals with MASLD who are susceptible to liver cancer[44-46]. The major strength of omics-based research is its ability to interrogate MASLD biology at the molecular level. By characterizing genetic susceptibility, transcriptional regulation, protein expression, metabolic remodeling, and microbial interactions, omics approaches can identify candidate biomarkers, reveal mechanistic pathways, and support biologically informed patient stratification[47].

Genomics can help characterize genetic susceptibility to MASLD by providing relatively stable upstream biological information. Unlike dynamic biomarkers that reflect changes in disease activity, genetic markers are better suited for baseline and long-term risk stratification than real-time disease monitoring. From a clinical perspective, their potential value lies in complementing conventional clinical factors and fibrosis assessment models to identify individuals who may be more susceptible to MASLD progression, advanced fibrosis, or MASLD-related HCC. However, genomics should currently be regarded as an adjunctive risk-enrichment tool instead of a standalone approach for disease monitoring, treatment-response assessment, or

selection of populations for HCC surveillance[48,49]. In relation to HCC risk, genetic evidence supports an inherited susceptibility to MASLD-related HCC. The *PNPLA3* rs738409 variant has been consistently associated with steatotic liver disease severity, fibrosis progression, and an increased risk of HCC. In addition, polygenic risk scores incorporating multiple liver-disease-associated variants have shown promise for non-invasive risk stratification of individuals at higher risk of severe liver outcomes, although their predictive performance remains under investigation. Collectively, these findings suggest that genetic background influences not only hepatic steatosis and fibrosis progression, but also susceptibility to liver cancer[45,50,51]. Representative studies on variants such as *PNPLA3*, *TM6SF2*, *GCKR*, and *MBOAT7* have shown that host genetic background affects inter-individual heterogeneity in disease severity and clinical outcomes[45,48,52-54]. However, because genomic information is largely static and cannot directly reflect short-term changes in inflammation, fibrotic remodeling, or treatment response, its role in MASLD should therefore be more appropriately viewed as complementary to dynamic biomarkers rather than as a replacement for them.

Transcriptomics shows how molecular processes change and drive MASLD progression, beyond just genetic risk. Its principal contribution lies in providing information on steatosis, inflammation, and fibrosis, thereby bridging upstream risk factors and downstream clinical phenotypes. Transcriptomic studies have also identified pathway-level drivers of disease progression, highlighting their value in mechanistic stratification and therapeutic target discovery[55]. However, RNA signals may vary according to disease stage, sample type, and cellular context, and the multicellular architecture of the liver further complicates their interpretation. Transcriptomics is useful for understanding mechanisms and finding biomarkers, but its clinical use will need better standardization, validation, and integration with other non-invasive methods.

Proteomics reveals the functional effector layer of MASLD by detecting proteins involved in hepatocellular injury, inflammatory signaling, and matrix remodeling. Because proteins are more directly linked to biological functions, and many proteins can be detected in blood, proteomics has strong clinical applicability for the development of non-invasive biomarkers. Sanyal *et al.* developed proteomic models for selected histological components of NAFLD, with training/paired-validation AUCs of 0.95/0.79 for steatosis, 0.83/0.72 for inflammation, 0.87/0.83 for ballooning, and 0.92/0.85 for fibrosis. The combined model for at-risk NASH achieved AUCs of 0.93/0.85, respectively[56]. Nevertheless, issues such as technical variability, lack of standardization, and limited external validation continue to constrain its routine application.

Metabolomics captures the downstream dynamic layer of disease biology by reflecting the persistent metabolic disturbances closely associated with steatosis, inflammation, and fibrosis in MASLD. Compared with genomics, metabolomics is more sensitive to the current physiological state and may therefore be better suited for identifying active disease processes, monitoring disease progression, or assessing treatment-related changes[57-60]. This is also what gives metabolomics its translational appeal for blood- or urine-based biomarkers, particularly for large-scale screening and repeated assessment[57,61,62].

In the field of MASLD-related HCC, serum metabolomics and lipidomics have shown considerable potential for clinical translation. Lewinska *et al.* reported that patients with MASLD-HCC exhibited serum lipid profiles that clearly differed from those of patients with non-malignant MASLD and healthy controls[63]. Based on these differences, they developed a MASLD-HCC Diagnostic Score, which could distinguish MASLD-HCC from non-malignant MASLD, healthy controls, and HCC of other etiologies, with better diagnostic performance than AFP[63]. Lu *et al.* further identified a circulating metabolite signature in multicenter MASLD and MASLD-HCC cohorts that could predict the presence of HCC in the setting of MASLD[64]. Model performance was further improved when cirrhosis status was incorporated, and the metabolite signature was also associated with overall survival in patients with MASLD-HCC[64]. Overall, these

studies suggest that serum metabolic signatures may not only facilitate HCC detection but also reflect a high-risk state during the progression from MASLD to HCC. Its potential value lies in identifying metabolic reprogramming associated with disease progression and high-risk states[58,60]. However, because metabolic profiles are highly susceptible to environmental influences, reproducibility across populations and the standardization required for clinical use remain important challenges.

Table 3 summarizes representative single-omics studies. Across these studies, genomics appears most relevant to relatively stable susceptibility and long-term risk assessment, whereas transcriptomic, proteomic, and metabolomic approaches provide more dynamic biological information but remain largely investigational because of limited standardization and external validation.

Multi-omics assessment

Each individual omics layer shows one part of MASLD biology and therefore provides an incomplete representation of this multifactorial disease. For example, genomics cannot capture the influence of dietary and environmental factors on MASLD. By integrating multi-level biological information and combining it with artificial intelligence (AI), multi-omics enables the construction of models from large-scale datasets and diverse data modalities to extract and identify disease-related information. This approach improves model performance as well as helps establish a more complete mechanistic chain of disease development[40]. In multifactorial diseases such as MASLD, any single dimension is insufficient to directly characterize the origins and progression of the disease. In contrast, the integration of multidimensional information makes it possible to build more complex and interpretable models that illustrate the interactions and transformations among various biomolecules. The integration may enhance the biological interpretability of multi-omics models, particularly when coupled with experimental validation, and could help move the field beyond descriptive association studies towards research on mechanistic hypotheses. For diseases such as HCC, cross-layer integration is important, as HCC risk is unlikely to be determined by a single molecular layer alone. It reflects the combined effects of multiple factors, including genetic susceptibility, inflammation and fibrotic progression, metabolic dysregulation, and host-microbiome interactions[44,83,84].

Several studies have systematically compared the diagnostic performance of single-omics strategies with that of multi-omics integration, consistently confirming the superiority of integrative approaches within specific study cohorts. Wood *et al.* and Zhou *et al.* developed diagnostic models and found that model performance was optimal after integrating all omics data[85,86]. Beyond diagnosis, this integrative strategy is also applicable to the identification of severe clinical outcomes, particularly cirrhosis and HCC, because a multi-omics framework is more likely to simultaneously capture the genetic background preceding tumorigenesis, high-risk inflammatory and fibrosis stage, and their associated molecular information[44,87].

The integration of different omics datasets can significantly improve diagnostic performance. The likely reason is that different omics datasets carry complementary information, and this complementarity represents a major advantage of multi-omics. Compared with the relatively narrow and task-specific applications typically seen in single-omics studies, multi-omics may offer broader clinical and biological utility. Some multi-omics studies have established a workflow of exploring pathological mechanisms, building diagnostic models, and validating clinical performance, moving from descriptive association to mechanistic inference and, in selected cases, experimental causal testing. Both Caussy, Loomba and Oh *et al.* used microbial features to reveal the influence of the gut microbiota on liver pathology and subsequently validated this relationship in predictive models[87,88]. Quesada-Vázquez *et al.* further advanced mechanistic research toward functional validation: after integrating metabolomic, transcriptomic, and microbial data and identifying a negative association between plasma histidine and steatosis, they verified the therapeutic effect of histidine supplementation in multiple animal models, thereby completing a closed loop from association

Table 3. Representative studies of single-omics approaches for non-invasive assessment of MASLD

Author(s)	Year	Study design	Sample size	Clinical task	Omics
Liu *et al.*[45]	2014	Retrospective	375	Prognosis	Genomics
De Vincentis *et al.*[65]	2022	Retrospective	266,687	Prognosis	Genomics
Eslam *et al.*[66]	2016	Retrospective	1,992	Diagnosis	Genomics
Dongiovanni *et al.*[48]	2018	Retrospective	9,414	Prognosis	Genomics
Verweij *et al.*[67]	2022	Retrospective	542,904	Prognosis	Genomics
Bianco *et al.*[46]	2021	Retrospective	367,041	Prognosis	Genomics
Chen *et al.*[68]	2023	Retrospective	54,773	Prognosis	Genomics
Abul-Husn *et al.*[51]	2018	Retrospective	46,544	Prognosis	Genomics
Jamialahmadi *et al.*[49]	2021	Retrospective	425,671	Screening	Genomics
Valenti *et al.*[53]	2010	Retrospective	824	Prognosis	Genomics
Baselli *et al.*[50]	2022	Retrospective	301	Prognosis	Genomics
Walker *et al.*[52]	2020	Retrospective	27,744	Prognosis	Genomics
Emdin *et al.*[69]	2021	Retrospective	4,829	Prognosis	Genomics
Grimaudo *et al.*[70]	2020	Prospective	471	Prognosis	Genomics
Govaere *et al.*[71]	2020	Retrospective	403 (381 NAFLD + 22 controls); discovery *n* = 206, validation *n* = 175	Diagnosis/Prognosis	Transcriptomics
Sun *et al.*[44]	2024	Retrospective	546	Prognosis	Transcriptomics
Conway *et al.*[72]	2023	Retrospective	1,208	Prognosis	Transcriptomics
Baboota *et al.*[55]	2022	Retrospective	58	Diagnosis/Prognosis	Transcriptomics
Tobaruela-Resola *et al.*[73]	2025	Retrospective	100	Diagnosis	Transcriptomics
Starmann *et al.*[74]	2012	Retrospective	87	Diagnosis	Transcriptomics
Bell *et al.*[75]	2010	Retrospective	85	Diagnosis	Proteomics
Feng *et al.*[76]	2023	Retrospective	285	Diagnosis	Proteomics
Yuan *et al.*[77]	2020	Retrospective	56	Diagnosis	Proteomics
Luo *et al.*[78]	2021	Retrospective	216	Diagnosis	Proteomics
Govaere *et al.*[79]	2023	Retrospective	306	Diagnosis	Proteomics (*n* = 306); hepatic transcriptomics in paired subset (*n* = 52)
Jiang *et al.*[80]	2023	Retrospective	2,236 overall; 80 in the proteomic subset	Diagnosis	Proteomics
Sanyal *et al.*[56]	2023	Retrospective	636	Diagnosis/Treatment	Proteomics
Rodríguez-Suárez *et al.*[81]	2010	Retrospective	18	Diagnosis	Proteomics
McGlinchey *et al.*[58]	2022	Retrospective	627	Diagnosis	Metabolomics
Zhu *et al.*[57]	2022	Retrospective	83	Diagnosis	Metabolomics
Perakakis *et al.*[59]	2019	Retrospective	80	Diagnosis	Metabolomics
Chen *et al.*[60]	2024	Retrospective	250	Diagnosis	Metabolomics
Khusial *et al.*[62]	2019	Retrospective	559	Screening	Metabolomics
Moolla *et al.*[61]	2020	Retrospective	275	Diagnosis	Metabolomics
Kalhan *et al.*[82]	2011	Retrospective	60	Diagnosis	Metabolomics
Lu *et al.*[64]	2023	Retrospective	113	Diagnosis	Metabolomics

Omics categories were assigned according to the actual assay platforms rather than the terminology used in the original articles. Although MASLD is used throughout this review, NAFLD is retained when referring to studies conducted under the previous nomenclature to reflect their original diagnostic criteria and study populations. NAFLD: Nonalcoholic fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease.

to causality[89]. Therefore, the strengths of multi-omics research should not be interpreted solely as improvements in predictive performance. Rather, its added value may lie in generating biologically meaningful hypotheses and identifying candidate pathways that can be tested in longitudinal and experimental studies. This approach may enhance the translational relevance of multi-omics research, but it should not be regarded as a mature tool for clinical prognostication or selection of patients for surveillance at present. Although multi-omics offers many advantages over single-omics approaches, most current studies on multi-omics remain at the research stage. Owing to factors such as testing costs, the complexity of clinical analytical workflows, and insufficient standardization, few studies have been used in real-world clinics. At the same time, most existing studies have been conducted in specific centers or selected populations, while multicenter external validation remains inadequate, resulting in limited reproducibility and generalizability.

Table 4 summarizes representative multi-omics studies. The main potential advantage of multi-omics over single-omics lies in integrating complementary biological layers and generating mechanistic hypotheses; however, most evidence remains retrospective and exploratory, with limited readiness for routine clinical implementation. In summary, omics-based approaches give a useful biological insight into MASLD heterogeneity and may support biomarker discovery, molecular subtyping, prognostic modeling, and treatment-response research. For MASLD-related HCC, multi-omics approaches may be valuable for risk enrichment and mechanistic discovery, as they can identify molecular changes linking metabolic dysfunction, inflammation, fibrosis, and hepatocarcinogenesis. At present, however, most omics tools remain insufficiently standardized and externally validated for routine clinical screening, referral decisions, or longitudinal monitoring. Their most appropriate current role is therefore in mechanistic investigation, discovery of candidate biomarkers, and research-oriented precision stratification, with promise for future translation into clinically deployable panels once analytical reproducibility, cost-effectiveness, and real-world validity are established. In contrast to omics approaches, which characterize molecular changes, quantitative imaging provides organ-level information on steatosis, stiffness, tissue composition, and architectural heterogeneity.

NON-INVASIVE IMAGING ASSESSMENT

At the organ and tissue levels, non-invasive assessment of MASLD depends mainly on imaging-based biomarkers. Once liver fibrosis progresses to cirrhosis, patients face an increased risk of portal hypertension, hepatic decompensation, and HCC. Previous studies have demonstrated that patients with steatohepatitis are at substantial risk of developing HCC in the presence of advanced fibrosis or cirrhosis[95]. Among patients with biopsy-confirmed MASLD, fibrosis stage is one of the strongest predictors of liver-related mortality and the risk of HCC[96,97]. Advanced fibrosis and cirrhosis remain the most important risk substrate for MASLD-related HCC; however, HCC risk is not determined solely by fibrosis stage. Therefore, non-invasive imaging-based assessment of fibrosis should be regarded as an important component of HCC risk enrichment, rather than as a tool that directly measures hepatocarcinogenesis.

Numerous imaging-based methods have been reported for the evaluation of liver fibrosis; however, a comprehensive review of all available techniques is beyond the scope of this article. The methods discussed in this review can broadly fall into three groups. The first group uses the mechanical properties of liver tissue, taking liver stiffness itself as the imaging biomarker. This includes Vibration-controlled transient elastography (VCTE), Shear wave elastography (SWE), and Magnetic resonance elastography (MRE). The second group involves leveraging endogenous contrast mechanisms to acquire information on tissue composition through specifically designed composition imaging sequences, followed by post-processing to derive quantitative compositional indices, such as T1, T1ρ, and quantitative magnetization transfer (MT). The third group consists of approaches based on image post-processing and quantitative modeling, in which quantitative features are extracted from routine imaging and liver fibrosis is indirectly assessed through mathematical analysis or diagnostic models; representative methods include radiomics.

Table 4. Representative studies of multi-omics integration strategies for MASLD assessment

Author(s)	Year	Study design	Sample size	Clinical task	Omics
Wood *et al.*[85]	2017	Retrospective	576[a] (training 443; validation 133)	Diagnosis	Genomics, Proteomics, Phenomics (clinical variables)
Oh *et al.*[87]	2020	Retrospective	163	Diagnosis	Microbiomics, Metabolomics
Younossi *et al.*[90]	2005	Retrospective	98	Biomarker discovery	Transcriptomics, Proteomics
Atabaki-Pasdar *et al.*[91]	2020	Retrospective	1,514	Diagnosis	Genomics, Transcriptomics, Proteomics, Metabolomics
Zhou *et al.*[86]	2016	Retrospective	318	Diagnosis	Metabolomics, Genomics
Wen *et al.*[92]	2026	Retrospective	166	Diagnosis	Transcriptomics, Epigenomics
Quesada-Vázquez *et al.*[89]	2023	Retrospective	651	Treatment	Metabolomics, Transcriptomics, Microbiomics
Leung *et al.*[93]	2022	Prospective	180	Prognosis	Microbiomics, Metabolomics
Sveinbjornsson *et al.*[84]	2022	Retrospective	36,116	Diagnosis/Prognosis	Genomics, Transcriptomics, Proteomics
Li *et al.*[83]	2025	Retrospective	61	Diagnosis	Transcriptomics, Metabolomics, Proteomics
Anspach *et al.*[94]	2026	Retrospective	8 (multi-omics discovery); 424 TCGA-LIHC samples (transcriptomic validation)	Association discovery study	Transcriptomics, Metabolomics, Lipidomics

Omics categories were assigned according to the actual assay platforms rather than the terminology used in the original articles. [a]Sample size is reported as stated in the Abstract of the original article. The Methods, Results, and Table 1 instead report 134 participants in the validation set, which, together with 443 in the discovery set, would total 577 rather than the reported 576. This internal discrepancy cannot be resolved from the published report. This internal discrepancy cannot be resolved from the published report. TCGA-LIHC: The Cancer Genome Atlas-Liver Hepatocellular Carcinoma; MASLD: metabolic dysfunction-associated steatotic liver disease.

Owing to its availability and lower cost, VCTE remains one of the most widely used non-invasive techniques for the clinical assessment of liver fibrosis[7]. Although MRE generally outperforms VCTE in terms of diagnostic performance and reproducibility, its use is limited by higher costs, less accessibility, and the need for specialized equipment. Assessment methods based on elastography or other mechanical parameters generally require dedicated equipment, specialized functional modules, or compatible probes. In contrast, compositional imaging methods based on endogenous contrast mechanisms and radiomics do not require additional standalone examination devices, thereby offering practical advantages in clinical implementation and application flexibility.

Assessment based on stiffness

Elastography has become a key non-invasive tool in the clinical management of MASLD. Its clinical use spans primary screening of high-risk populations, accurate diagnosis of advanced fibrosis, longitudinal monitoring of disease progression, and prognostic evaluation of liver-related outcomes[98]. VCTE, SWE, and MRE are currently the main elastography-based methods used for fibrosis assessment in MASLD; however, their value lies not so much in their technical differences as in their distinct positions within the clinical pathway. In many clinical pathways, FIB-4 is used for initial risk assessment, followed by VCTE when further evaluation is needed. SWE provides an ultrasound-based alternative with good feasibility within routine imaging workflows, whereas MRE is generally reserved for settings requiring higher precision and reproducibility. Rather than viewing these modalities as competing technologies, it may be more useful to regard them as complementary tools with different levels of accessibility, accuracy, and resource needs. It should be emphasized that elastography-based techniques use liver stiffness as a surrogate marker of fibrosis.

Table 5. Representative studies of elastography approaches for MASLD assessment

Author(s)	Year	Study design	Sample size	Clinical task	Technique
Boursier *et al.*[107]	2022	Retrospective	1,057	Prognosis	VCTE
Wong *et al.*[105]	2012	Prospective	193	Diagnosis	VCTE
Petta *et al.*[106]	2021	Retrospective	1,039	Prognosis	VCTE
Shili-Masmoudi *et al.*[104]	2020	Prospective	2,245	Prognosis	VCTE
Wong *et al.*[100]	2010	Prospective	246	Diagnosis	VCTE
Braude *et al.*[103]	2023	Retrospective	7,079	Prognosis	VCTE
Boursier *et al.*[101]	2016	Retrospective	452	Diagnosis	VCTE
Serra-Burriel *et al.*[108]	2019	Prospective	6,295	Screening	VCTE
Mendoza *et al.*[116]	2022	Prospective	104	Diagnosis	VCTE, SWE
Ozturk *et al.*[114]	2020	Retrospective	116	Diagnosis	SWE
Lee *et al.*[110]	2021	Prospective	102	Diagnosis	SWE
Pierce *et al.*[117]	2024	Prospective	40	Diagnosis	SWE, VCTE
Jang *et al.*[109]	2022	Prospective	132	Diagnosis	SWE
Imajo *et al.*[120]	2016	Retrospective	142	Diagnosis	MRE
Park *et al.*[121]	2017	Prospective	104	Diagnosis	MRE
Gidener *et al.*[122]	2021	Retrospective	829	Prognosis	MRE

MRE: Magnetic resonance elastography; SWE: shear wave elastography; VCTE: vibration-controlled transient elastography.

They do not directly measure extracellular matrix composition or interrogate the molecular pathophysiology underlying MASLD progression.

Among elastography-based techniques, VCTE is still one of the most widely used non-invasive tools in routine clinical practice because of its ease of operation, rapid acquisition, and established role in fibrosis triage[99-107]. A cohort study of 6,295 individuals from Europe and Asia found VCTE-based fibrosis screening in primary care to be cost-effective[108]. SWE can be integrated into conventional ultrasound platforms, offering practical advantages in workflow flexibility, and has demonstrated good reproducibility in several MASLD cohorts[109-116]. A study evaluating the repeatability and reproducibility of SWE and VCTE showed that, in patients with MASLD, SWE had superior interday and interoperator reproducibility to VCTE and achieved the prespecified performance threshold[117]. MRE generally provides higher diagnostic accuracy and reproducibility, particularly in obese patients and specialist care settings, although its broader application is limited by cost, availability, and examination complexity[118,119]. Overall, these techniques have become central to non-invasive fibrosis assessment, although all of them are susceptible to confounding by factors other than fibrosis itself, such as inflammation, congestion, and cholestasis[11].

Table 5 summarizes representative elastography studies. Collectively, VCTE has the broadest evidence base for scalable fibrosis triage and prognostic assessment, SWE offers an ultrasound-integrated alternative, and MRE provides higher diagnostic precision in specialist settings.

Assessment based on non-invasive compositional imaging

The pathological hallmark of liver fibrosis is excessive deposition of collagen-rich extracellular matrix[97]. This remodeling expands the extracellular matrix compartment and often shifts tissue water distribution as well. These tissue alterations provide a biological basis for compositional magnetic resonance imaging (MRI) sensitive to relaxation and MT. Quantitative MRI methods, including T1 mapping[123-125] and T1ρ mapping[126-130], have been investigated as potential non-invasive approaches for assessing liver fibrosis. Both T1 and T1ρ values have been reported to increase with fibrosis severity.

However, both T1 mapping and T1ρ mapping are sensitive to hepatic iron content, which can confound fibrosis assessment. To address this limitation, iron-corrected T1 mapping[123-125] has been introduced for liver fibrosis evaluation, and iron correction strategies for hepatic T1ρ mapping[131] have also been reported. In addition to iron deposition, inflammation may also influence T1 and T1ρ measurements. Furthermore, reliable quantification requires close agreement between the assumed signal model and the acquired data. Careful sequence design, acquisition optimization, and post-processing can therefore help minimize possible sources of bias and improve measurement robustness.

Because collagen forms a gel-like macromolecular network, it is expected to exhibit a strong MT effect. Although the liver contains other proteins, these molecules are generally more mobile than collagen and are therefore expected to contribute less to MT. Triglycerides and lipids are hydrophobic and have limited MT effects. These properties suggest that quantitative MT imaging may provide a means to evaluate collagen deposition in the liver and thereby assess liver fibrosis. This concept has been demonstrated in both animal[132] and human studies[133-135]. Importantly, quantitative MT-based methods appear to be relatively less affected by hepatic iron deposition, which is an advantage for compositional imaging of the liver.

Conventional quantitative MT methods typically require T1 information and relatively long acquisition times, posing challenges for robust clinical imaging of the liver. In contrast, spin-lock radiofrequency-based methods[136,137] have shown advantages for quantitative MT imaging because they can be designed to achieve higher saturation efficiency with reduced direct water saturation, enabling rapid mapping of macromolecular proton fraction (MPF) in the liver.

Compared with stiffness-based methods, compositional imaging approaches that more directly interrogate collagen-related tissue properties provide a distinct physical mechanism for fibrosis assessment. These methods do not require exogenous contrast agents or additional hardware and may have potential for detecting early-stage fibrosis. In early fibrosis, liver stiffness may not change substantially, whereas direct imaging of collagen-associated tissue alterations may provide greater sensitivity to early extracellular matrix remodeling. Such capability could be important for the development of antifibrotic therapies, patient stratification, and treatment monitoring. By introducing complementary biophysical mechanisms, compositional imaging may help address current limitations in non-invasive liver fibrosis assessment. Nevertheless, despite their promise, these techniques should be regarded as research tools for tissue characterization rather than as tools for hepatocellular carcinoma risk prediction; further technical development, standardization, and large-scale clinical validation are required before routine clinical implementation.

Assessment based on radiomics

Radiomics is another imaging-based strategy that can often be applied to routinely acquired clinical images without requiring additional scanner hardware, although robust implementation requires standardized acquisition, segmentation, preprocessing, and analysis pipelines. The basic idea is to extract large numbers of quantitative features from medical images automatically, and then use those features to build models for diagnosis, prognosis, treatment-response assessment, or disease monitoring[24-26,138]. To improve reproducibility and comparability in radiomics research, Zwanenburg *et al.* standardized 169 radiomic features[139]. Because of their widespread clinical use, computed tomography (CT) and ultrasound have provided relatively large datasets for radiomics research, although their roles in MASLD care differ. Models developed by Zhang *et al.* and Meng *et al.* have both achieved encouraging results[140,141]. In comparison, although Chen *et al.* and Xu *et al.* reported good performance using T2- and T1-weighted MRI sequences, respectively, limitations in sample size may have constrained the generalizability of these models[142,143].

Table 6. Representative studies of radiomics-based models for MASLD assessment

Author(s)	Year	Study design	Sample size	Clinical task	Modality
Zhang *et al.*[141]	2025	Retrospective	840	Diagnosis	CT
Lubner *et al.*[145]	2017	Retrospective	289	Diagnosis	CT
Wang *et al.*[146]	2022	Retrospective	443	Diagnosis	CT
Dichtel *et al.*[147]	2023	Retrospective	16	Diagnosis	CT
Cui *et al.*[148]	2021	Retrospective	332	Diagnosis	CT
Tang *et al.*[144]	2023	Retrospective	227	Diagnosis	CT
Li *et al.*[149]	2025	Retrospective	254	Diagnosis	CT
Chen *et al.*[150]	2021	Retrospective	22	Diagnosis	PET/CT
Meng *et al.*[140]	2023	Retrospective	618	Prognosis	Ultrasound
Xia *et al.*[151]	2024	Retrospective	87 rats	Diagnosis	Ultrasound (Experimental animal study)
Chen *et al.*[143]	2022	Retrospective	203	Diagnosis	MRI
Xu *et al.*[142]	2021	Retrospective	53	Diagnosis	MRI
Cannella *et al.*[152]	2019	Retrospective	54	Diagnosis	MRI

CT: Computed tomography; MRI: magnetic resonance imaging; PET/CT: positron emission tomography/computed tomography.

However, most current radiomics studies in MASLD have focused mainly on diagnosis, whereas real-world clinical settings include both primary care clinics that require first-line screening tools and specialist clinics that address diagnosis, prognosis, and monitoring. Some clinical indicators currently used in primary care still play an important role in radiomics research. In a representative study, Tang *et al.* showed that a combined clinical-radiomics model achieved an AUC of 0.930 for the diagnosis of moderate-to-severe fatty liver, whereas the radiomics-only model reached only 0.807; notably, the clinical model alone had already achieved an AUC of 0.904, meaning that the addition of radiomics was only a modest absolute improvement of 0.026 in AUC[144]. This finding should not be interpreted as definitive evidence that radiomics has limited value in the management of MASLD. Rather, it suggests that radiomics may improve performance, but its incremental benefit over readily available clinical variables may be modest in some diagnostic settings. Many radiomics studies therefore still require large-scale, multicenter validation to establish model robustness, generalizability, and true clinical value. The future of radiomics in MASLD will depend on its ability to provide reliable and useful clinical information beyond existing low-cost tools, rather than just slightly improving diagnostic accuracy. Table 6 summarizes representative radiomics studies across CT, ultrasound, MRI, and positron emission tomography (PET)/CT. Despite encouraging diagnostic results, most studies remain retrospective and single-center, and the incremental clinical value of radiomics beyond conventional clinical and imaging variables remains uncertain.

In summary, imaging-based tools occupy different positions across the MASLD care pathway. VCTE fits best for second-line triage and fibrosis risk stratification after initial blood-based screening, particularly in primary care or referral pathways. SWE can provide similar elastography-based information within conventional ultrasound workflows. MRE offers higher accuracy and reproducibility and is useful in specialist settings, clinical trials, and cases with indeterminate or discordant first-line tests. MRI-derived proton density fat fraction (MRI-PDFF) is well suited for quantifying steatosis and monitoring treatment-related changes in liver fat, whereas emerging compositional MRI methods and radiomics are still mostly at the research stage. Thus, established elastography-based methods, MRE, and MRI-PDFF are clinically useful for staging, prognostic assessment, and longitudinal follow-up, whereas newer quantitative imaging and radiomics approaches require further standardization and external validation before routine implementation.

MULTI-MODALITY INTEGRATION

Over the past decades, non-invasive assessment of MASLD has evolved from reliance on isolated laboratory indices and conventional imaging measurements toward a broader framework incorporating blood-based biomarkers, elastography, advanced MRI techniques, AI, radiomics, and omics profiling. Different diagnostic approaches should not be viewed as being in simple competition with one another; rather, they reflect distinct layers of disease biology. Blood-based biomarkers and composite scores, such as FIB-4 and ELF, provide systemic surrogate indicators of liver injury, inflammation and fibrosis risk. Imaging-based methods, including VCTE, SWE, MRE, and MRI-PDFF, quantify hepatic fat content, liver stiffness, and fibrosis-related structural alterations at the organ level. Omics and radiomics approaches further capture molecular perturbations linking metabolic, genetic, transcriptomic, and proteomic layers, whereas radiomics quantifies image-derived phenotypes and tissue heterogeneity. Integrating these complementary data may help link molecular changes to organ-level manifestations of MASLD[153,154]. From this perspective, a more relevant clinical question is which combination of tests provides actionable information for a specific decision point in the MASLD care pathway.

In primary care and community settings, the priority is not detailed biological analysis, but scalable identification of individuals who are unlikely to have advanced disease and those who require referrals. Therefore, a sequential strategy using FIB-4 as a first-line screening tool, followed by VCTE-derived liver stiffness measurement or ELF testing in patients at intermediate or high risk, remains of substantial practical value[155,156]. In this framework, a low FIB-4 result supports rule-out of advanced fibrosis and continued management with metabolic risk-factor control and periodic reassessment in primary care. Intermediate results should prompt second-line testing because they do not reliably distinguish low- from high-risk disease, whereas persistently high-risk or abnormal second-line results should lead to specialist evaluation. This approach is supported by large multicenter longitudinal studies. In a cohort of 12,950 patients with MASLD, sequential assessment with FIB-4 followed by VCTE-derived liver stiffness measurement (VCTE-LSM) stratified patients into low-, intermediate-, and high-risk groups, with 5-year liver-related event rates of 0.5%, 1.0%, and 10.8%, respectively[155]. In a prospective real-world study of patients with type 2 diabetes, those with elevated FIB-4 underwent transient elastography and specialist assessment; 21.4% were subsequently identified as having previously unrecognized advanced MASLD, supporting the clinical yield of this sequential approach[157].

By contrast, specialist hepatology clinics face a different set of challenges, including refinement of fibrosis stage, identification of patients at risk of progression, selection of candidates for therapeutic intervention, and monitoring of longitudinal change. These tasks may benefit more from higher-resolution phenotyping, including elastography, advanced MRI-based methods, selected omics approaches, and composite non-invasive scores that combine imaging or elastography with laboratory variables, such as FibroScan-AST (FAST)[158], MRE combined with FIB-4 (MEFIB)[159], and MRI-aspartate aminotransferase (MAST)[160]. FAST combines FibroScan-derived parameters with AST to identify active MASH with significant fibrosis[158]. MEFIB integrates MRE with FIB-4 to enrich for patients with significant or advanced fibrosis and to support referral and risk stratification[159]. MAST further combines MRE, MRI-PDFF, and AST, enabling joint assessment of MASH activity and fibrosis burden[160]. Accordingly, the value of a non-invasive test should be judged not only by its aggregate diagnostic accuracy in heterogeneous cohorts, but also by its ability to inform specific clinical decisions.

Importantly, the value of multimodal integration lies both in the complementarity of data and in its potential to connect mechanistic understanding with clinical application[154,161,162]. Clinical biomarkers can help identify high-risk populations, imaging can localize and quantify organ-level injury, and omics can help explain why disease progression differs among individuals[154]. When interpreted together, these data may support a more

comprehensive model of MASLD and could facilitate patient stratification, individualized prognosis, treatment selection, and long-term follow-up.

Overall, the future of non-invasive MASLD assessment is unlikely to depend on one modality replacing another. Rather, the field is moving toward a layered, clinically contextualized framework in which blood-based biomarkers support broad triage, imaging refines phenotypic and prognostic assessment, and omics provides deeper biological resolution for mechanism-informed stratification. Such a strategy may ultimately provide a more practical, reproducible, and biologically meaningful framework for reducing reliance on biopsy, while preserving histology for selected cases in which diagnostic uncertainty or trial requirements justify invasive assessment.

CHALLENGES FROM BENCH TO BEDSIDE

Although omics, quantitative imaging, and AI have pushed the development of non-invasive assessment for MASLD, a stable, unified, and broadly generalizable strategy has yet to emerge. One reason is that much of the current literature remains technology-driven rather than clinically driven. Model development is often centered on maximizing AUC in retrospective datasets, whereas the intended use case, target population, clinical pathway, and downstream decision point are insufficiently specified. As a result, high-dimensional or technically sophisticated models may show impressive performance in selected cohorts yet add limited value in practice if they do not outperform simpler tools, cannot be reproduced across centers, or are difficult to implement at scale. For MASLD, where screening and longitudinal follow-up must be scalable and sustainable, parsimony, external validity, calibration, and deployability may matter more than marginal improvements in discrimination.

A second limitation is that the reference standard itself is imperfect. Although liver biopsy remains the conventional histologic reference standard, it samples only a very small fraction of hepatic parenchyma, inter-observer agreement for steatohepatitis activity components is only moderate, and fibrosis staging remains semi-quantitative. These inherent shortcomings of the "gold standard" restrict, to some extent, the optimization and validation of non-invasive assessment methods. Given sampling variability and interobserver disagreement, the apparent performance of non-invasive tests may be constrained by a practical ceiling imposed by biopsy-based classification itself. This suggests that the field may ultimately require more robust reference frameworks, including composite outcome-based endpoints, central pathology review, AI-assisted digital pathology tools for MASH histology assessment, and longitudinal outcomes instead of sole reliance on single-time-point histology.

Another structural problem is the relative lack of direct head-to-head evidence across modalities and populations. The European LITMUS and US NIMBLE consortia have begun to fill this gap by evaluating non-invasive tests in more standardized and collaborative frameworks. However, robust direct comparisons across biomarkers, imaging modalities, and composite models in unselected real-world populations remain limited. Evidence from collaborative and external-validation studies suggests that the apparent performance of many tools is lower in less-selected populations than in the enriched tertiary or case-control cohorts in which they were often developed. In addition, the relative ranking of tests may change when disease prevalence, spectrum effects, and cohort enrichment are considered. Therefore, studies or guidelines that rely mainly on derivation-cohort AUCs without adequately considering enrichment effects may overstate real-world performance.

Evidence also remains relatively limited for the precise identification and dynamic monitoring of early fibrosis, especially at potentially reversible stages of disease. This gap is particularly important because future disease-burden reduction will depend not only on detecting advanced fibrosis and cirrhosis, but also on

identifying high-risk individuals earlier in the disease course, thereby providing a critical window for intervention to delay fibrosis progression, reduce liver-related events, and lower the risk of HCC. Current evidence indicates that MASLD is emerging as a major cause of HCC, and that a proportion of cases can arise in the absence of cirrhosis, highlighting the clear limitations of the traditional strategy of defining surveillance candidates solely on the basis of cirrhosis status[163,164]. However, this observation does not imply that universal HCC surveillance should be implemented for all non-cirrhotic patients with MASLD. A more rational future direction is to develop validated non-invasive risk-enrichment frameworks that integrate fibrosis burden, metabolic risk factors, liver functional status, genetic susceptibility, longitudinal biomarker trajectories, and imaging phenotypes, thereby more precisely identifying patients who may require prioritization for HCC surveillance. At the quantitative imaging level, important practical limitations also remain. Liver stiffness-based methods are valuable for fibrosis assessment, but their implementation and interpretation are constrained by modality-specific limitations. Ultrasound-based elastography can be affected by operator dependence, body habitus, fasting status, and technical failure, whereas MRE is less widely available and more costly. Across stiffness-based approaches, liver stiffness may also be influenced by non-fibrotic processes such as inflammation, cholestasis, venous congestion, and edema. Elastography remains a cornerstone of fibrosis assessment because of its maturity and prognostic relevance, yet stiffness is still an indirect surrogate rather than a direct measurement of fibrotic architecture. MRI-based techniques may provide complementary phenotypic information. Although established methods such as MRI-PDFF and MRE are relatively well validated, many emerging MRI-based approaches still require broader standardization, cross-platform reproducibility assessment, and external validation. For advanced imaging to become clinically consequential, standardization, external validation, and workflow feasibility must be treated as primary endpoints.

Similarly, major translational challenges remain for high-dimensional approaches such as radiomics and multi-omics, as well as for AI models built upon them. Radiomics and other quantitative imaging signatures may capture tissue heterogeneity beyond conventional stiffness-based assessment, but their clinical utility remains constrained by variability in image acquisition, segmentation strategies, feature extraction, and cross-platform reproducibility. Multi-omics offers powerful opportunities for biological discovery, yet its translational gap remains substantial because molecular signatures are often affected by batch effects, platform heterogeneity, and differences in analytical pipelines. In both settings, high-dimensional signals may appear highly predictive in selected datasets while remaining difficult to reproduce, interpret biologically, or implement clinically. Moreover, AI can facilitate pattern recognition and multimodal integration, but it does not eliminate the fundamental risks of overfitting, shortcut learning, and hidden cohort-specific bias. Prospective validation, transparent reporting, calibration assessment, and evaluation across demographic and metabolic subgroups are therefore essential before such models can be adopted in clinical pathways. Therefore, the challenge is not simply to generate more features, but to identify which image- and molecular-derived signatures are robust, biologically meaningful, and actionable in real clinical pathways.

Future directions: toward precision and risk-stratified MASLD care

Future development of non-invasive assessment in MASLD should shift from a model-performance-driven paradigm to a clinical problem-driven paradigm. The goal is not to focus on incremental improvements in diagnostic accuracy or predictive performance; future studies should be designed around specific clinical tasks and clearly defined use cases. Study design should move from retrospective case-control comparisons toward prospective, multicenter, pathway-based evaluation. In parallel, endpoint selection should focus on clinical needs, encompassing histological stage and progression to advanced fibrosis, liver-related events such as hepatic decompensation and HCC, and treatment response. Compared with costly efforts to achieve increasingly fine-grained histopathological classification, clinical practice is often more concerned with disease progression, long-term prognosis, and the consequences of management decisions.

With the burden of MASLD-related end-stage liver disease continuing to increase, future research priorities should also shift further upstream toward early risk identification, targeted case-finding, and prevention. Rather than relying primarily on intervention at advanced stages, establishing robust, accurate, accessible, and scalable risk-identification tools in primary care and community healthcare settings has clear practical value for reducing disease burden and allocating resources sensibly. Therefore, the development of initial risk-identification strategies suitable for primary care, community settings, and high-risk populations has clear practical value for future non-invasive assessment systems. In this setting, simple and scalable tools are likely to remain the entry point of care pathways, with more advanced tests reserved for second-line refinement.

Children and adolescents represent an important special population in MASLD assessment because disease phenotype, histological patterns, growth-related physiology, and clinical decision thresholds may differ from those in adults. Adult-derived scores such as FIB-4 and NFS are strongly influenced by age and routine laboratory variables and therefore should not be directly extrapolated to pediatric MASLD without dedicated validation. In pediatric settings, the primary clinical tasks are usually identification of clinically significant steatosis, exclusion of advanced fibrosis, monitoring of cardiometabolic risk, and selection of patients who require specialist referral or biopsy. Imaging-based tools may be particularly attractive because they avoid invasive sampling and can support longitudinal follow-up. MRI-PDFF provides quantitative assessment of hepatic steatosis and is useful in clinical studies and treatment monitoring, whereas VCTE and other elastography methods may help stratify fibrosis risk when pediatric-specific protocols, probes, and cutoffs are available. However, evidence for longitudinal change thresholds, prognostic prediction, and treatment-response monitoring in children remains more limited than in adults. Therefore, pediatric MASLD requires age-appropriate validation of non-invasive tools rather than direct adoption of adult thresholds, and future studies should define pediatric-specific cutoffs, monitoring intervals, and clinically meaningful endpoints.

Multimodal integration will remain central to moving MASLD assessment toward precision medicine, but it should be pursued in a clinically disciplined manner. The goal is not to aggregate every available data type, but to determine which combinations of blood biomarkers, imaging, omics, pathology, and clinical variables provide actionable information at each stage of care. Early studies of composite models suggest that integrating clinical, laboratory, and imaging information can improve risk stratification. In the future, if digital pathology, electronic health records, and multi-omics data can be further incorporated, and if AI-based methods can be rigorously validated for integrating high-dimensional information, it may become possible to construct more precise risk-stratification systems, capture the heterogeneity of MASLD more fully, and support treatment decisions on a multimodal basis.

Longitudinal monitoring should receive much greater emphasis in future research. Repeated non-invasive assessment may be better suited than static single-time-point staging to capture dynamic changes in fibrosis, inflammatory activity, and treatment response. For longitudinal monitoring, available guidance and cohort data support a risk-adapted approach. In adults with MASLD, FIB-4 is commonly used as the first-line reassessment tool; it may be repeated every 2-3 years in lower-risk individuals and every 1-2 years in patients with prediabetes, type 2 diabetes, or multiple metabolic risk factors. A FIB-4 value below 1.3 generally supports continued follow-up in primary care, whereas values of 1.3 or higher should prompt second-line assessment with VCTE, ELF, or specialist evaluation; values above 2.67 indicate higher risk and usually warrant referral[22,23]. For VCTE, liver stiffness values below 8 kPa generally indicate low risk, values of 8 to 12 kPa require further evaluation, and values above 12 kPa suggest a high probability of advanced fibrosis or compensated advanced chronic liver disease, depending on the clinical context[107,165]. However, no universally accepted percentage-change threshold has been established for defining fibrosis progression or regression on serial VCTE, and longitudinal interpretation is therefore usually based on reproducible

changes across clinically relevant risk categories rather than small numerical fluctuations[107,166]. MRE-derived liver stiffness has shown good performance for fibrosis risk stratification in MASLD, and values around 3.5 to 3.6 kPa have been reported as useful thresholds for identifying advanced fibrosis in biopsy-proven MASLD cohorts[120,121,167,168]. For longitudinal follow-up, MRE remains a promising tool, but changes in liver stiffness should be interpreted in clinical context because inflammatory activity may increase stiffness and contribute to overestimation of early fibrosis stages[11,168,169]. Longitudinal monitoring is also important for assessing MASLD-related HCC risk. However, validated thresholds for dynamic HCC risk reclassification remain insufficient. Future studies should therefore focus on developing clinically meaningful monitoring strategies rather than relying on single time-point measurements. Therefore, longitudinal monitoring should integrate the magnitude and direction of change, baseline risk category, test reproducibility, and clinical context instead of relying on a single isolated measurement.

This is particularly relevant for identifying early fibrosis and potentially reversible disease states, as well as for evaluating therapeutic efficacy over time. A more dynamic assessment paradigm may ultimately prove more clinically meaningful than attempting to reproduce biopsy categories at a single time point.

Finally, in the long term, the MASLD field needs a more comprehensive and robust evaluation framework than liver biopsy alone. With deeper investigation into disease mechanisms and continued progress in multimodal data integration methods, it may become possible to develop a non-invasive assessment system that combines biological interpretability, clinical feasibility, reproducibility, and longitudinal relevance, thereby reducing, and in selected contexts partially replacing, the central role of liver biopsy in disease staging, risk stratification, and treatment-response assessment. This would not only help overcome the inherent sampling error and semi-quantitative limitations of biopsy but also facilitate drug development and therapeutic monitoring in MASLD. At the same time, implementation science should become an integral part of the research agenda, because a non-invasive tool is clinically meaningful only if it can be adopted, interpreted, acted upon, and sustained in real healthcare systems.

Limitations

This review has several limitations. First, because liver fibrosis is among the most prognostically important histological features in MASLD, we focused primarily on fibrosis, with more limited discussion of steatosis and inflammatory activity. Second, given the emphasis on interpretability and translational potential, this review does not systematically evaluate emerging technologies, such as deep learning approaches, or provide a comprehensive methodological comparison across techniques. Third, although we have strengthened the discussion of the increasing risk of MASLD-related HCC, this Review is not intended to provide a systematic overview of HCC surveillance, diagnosis, or treatment. Accordingly, the discussion of HCC-related evidence is focused primarily on the positioning of non-invasive tools for MASLD assessment. Finally, most of the evidence discussed derives from adult populations, with limited consideration of pediatric and other special populations.

Conclusion

The future of non-invasive assessment in MASLD lies not in identifying a universally superior single test, but in developing clinically driven, stepwise, and biologically interpretable frameworks that align different modalities with specific needs across the care pathway. Such an approach may provide a more practical and scalable alternative to biopsy-centered assessment for risk stratification, longitudinal monitoring, and precision, risk-stratified MASLD care.

DECLARATIONS

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Authors' contributions

Conceptualised the study: Shen Q
Performed the literature review: Shen Q
Led the drafting and revision of the manuscript: Shen Q
Contributed to the literature collection, organization of specific thematic sections, and critical revision of the manuscript: Kang H, Shan Q, Yu Z, Yang D, Yang Z
Supervised the overall study design and manuscript preparation: Chen W
All authors contributed to the article, reviewed the manuscript, and approved the final version for publication.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the authors used ChatGPT (OpenAI; GPT-5.4, released 2026-03-05) solely for language editing, including language polishing and improvements in clarity and readability. In addition, the image-generation feature within ChatGPT (OpenAI; GPT-6 Astra, released 2026-09-03) was used solely to generate illustrative elements for Figure 1, including the liver icon, based on the authors' instructions. These AI-generated elements were reviewed by the authors for scientific accuracy and incorporated into the final figure. These tools did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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