Review

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]

[1]Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Hong Kong, China.

[2]Department of Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China.

[3]State Key Laboratory of Digestive Health, China.

Correspondence to: Dr. Weitian Chen, Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Hong Kong, China. Email: wtchen@cuhk.edu.hk

Received: 26 May 2026 | Approved: 04 June 2026 | Online: 04 June 2026

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.

At the same time, major translational 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 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.

Keywords: MASLD, non-invasive assessment, blood-based biomarkers, omics, quantitative imaging, multimodal models, precision medicine

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently one of the leading causes of chronic liver disease worldwide, affecting approximately 32% of adults[1]. Numerous studies have confirmed that the incidence of MASLD continues to rise, placing a substantial burden on healthcare systems globally[2-5]. A study based on

cohorts from eight countries projected that the total number of MASLD cases would increase by as much as 30% between 2016 and 2030[6]. At present, the three most important features in the assessment of MASLD are steatosis, inflammatory activity, and fibrosis stage. Among the histological characteristics of MASLD, the degree of liver fibrosis is the feature most closely associated with liver-related outcomes and mortality risk. Therefore, the central goal of non-invasive evaluation is not merely to identify steatosis, but to achieve accurate stratification of high-risk fibrosis and disease progression[7-9].

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[10]. 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[11-13]. Finally, liver fibrosis is a dynamic process, whereas fibrosis staging based on biopsy is only semi-quantitative and cannot satisfactorily capture disease progression[14-17]. 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 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 multimodal models may be deployed differently for population screening, referral prioritization, fibrosis stratification, prognostic assessment, longitudinal monitoring, and precision management. A summary of the potential roles of these tool categories across major clinical tasks is provided in Table 1.

Table 1. The potential application of the MASLD non-invasive assessment tool in different clinical tasks.

Tool category	Screening	Diagnosis/Staging	Risk stratification/Prognosis	Treatment monitoring
Clinical scores / blood-based assessment	FIB-4, NFS, APRI	FAST, MEFIB, MAST, Pro-C3-based or other blood-based models	FIB-4 and related blood-based models for liver-related outcomes and mortality risk	Repeated measurement of FIB-4 and related blood-based markers, although value for individual histological monitoring remains inconsistent
Single omics	Not established	Genomics, transcriptomics, proteomics, and metabolomics for biomarker discovery and diagnosis	Genomics for long-term risk stratification; other omics for progression and outcome prediction	Potential for treatment-response monitoring, especially for dynamic molecular changes, but not yet implemented in routine clinical practice

Multi-omics integration	Not established	Multi-omics models for disease classification, fibrosis stratification, and mechanistic subtyping	Potential for prognostic stratification and disease progression prediction	Potential for dynamic monitoring, but clinical implementation remains limited
Elastography	US, VCTE	VCTE, SWE, MRE	VCTE, MRE	Repeated liver stiffness measurement but clinical implementation remains limited
Quantitative imaging	Exploratory	MRI-PDFF, corrected T1, T1rho, MPF	MRE, MPF and other advanced MRI-based markers with potential prognostic value	Longitudinal MRI-based assessment of steatosis and fibrosis-related change
Radiomics	Not established	Radiomics models based on US, CT, or MRI for fibrosis or steatosis assessment	Exploratory; clinical utility remains uncertain	Exploratory

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[19]. 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[20-23]. 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[24,25].

Studies have moved beyond comparing these models to fibrosis stages and now focus more on their ability to predict liver-related events, hepatocellular carcinoma, and overall mortality[22,23,26]. However, 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[20,27,28]. 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[27], but its ability to identify true histological progression in

individual patients is not stable, and findings have even differed across studies[20,28]. Therefore, conventional non-invasive scores are more suitable for population-level screening and stratification, whereas their utility for precise monitoring and individualized management still requires further improvement.

The assessment of traditional clinical variables has gradually evolved from the use of single diagnostic tools toward multimodal, multilevel integration. On the one hand, the integration of traditional clinical variables with mechanistic information derived from proteomics, metabolomics, and spatial transcriptomics holds promise not only for improving diagnostic and prognostic performance, but also for supporting patient stratification, therapeutic target identification, and treatment response monitoring, thereby promoting the evolution of non-invasive assessment from a clinical adjunct to a precision medicine decision-making platform[26,28]. On the other hand, composite models represented by FAST, MEFIB, and MAST are more clinically translatable[29-31]. The FAST model (FibroScan + AST) focuses on identifying active Metabolic Dysfunction-Associated Steatohepatitis (MASH) with significant fibrosis[29]. The MEFIB model (MRE + FIB-4) is intended to optimize specialist referral for patients with significant fibrosis[30]. The MAST model further integrates MRE, MRI-PDFF, and AST to enable joint assessment of high-risk MASH activity and fibrosis risk[31]. Compared with omics-based integrative approaches, these elastography-based composite models are cheaper, easier to use, and more practical for clinics and trial screening; by contrast, omics-driven integrative strategies are better for understanding disease mechanisms and supporting therapeutic development.

Routine clinical scores are easy to scale and access, but they don’t reflect much of the underlying biology. Table 2 summarizes the representative studies of blood-based biomarkers, conventional fibrosis scores, and clinically translatable composite models discussed in this section.

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 A, *et al.*[21]	2019	Prospective	3,012	Screening	FIB-4
Siddiqui MS, *et al.*[20]	2019	Retrospective	1,904 / 292	Diagnosis	APRI, FIB-4, AST/ALT ratio,NFS
Ioannou GN, *et al.*[22]	2019	Retrospective	7,068 / 16,175	Prognosis	HCC risk prediction models
Hagstrom H, *et al.*[27]	2020	Retrospective	40,729	Prognosis	FIB-4
Balkhed W, *et al.*[28]	2022	Retrospective	135	Prognosis	FIB-4, NFS, APRI, dAAR
Labenz C, *et al.*[108]	2022	Prospective	11,859 / 349,570	Screening	SEAL algorithm
Younes R, *et al.*[26]	2021	Retrospective	1,173	Prognosis	APRI, BARD, FIB-4, NFS, Hepamet fibrosis score (HFS)

Overall, routine clinical scores and blood-based markers work best as first-line tools for population-level risk stratification, primary care screening, and referral prioritization. Their main clinical value is in excluding advanced fibrosis and identifying patients who require second-line assessment with elastography, ELF, 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-based approaches have become a useful tool for identifying molecular signatures of disease susceptibility, activity, and progression.

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[32-35]. 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.

Genomics helps identify genetic risks for MASLD, focusing more on baseline risk than changes in disease activity, and provides the most upstream biological information for MASLD by characterizing genetic susceptibility. From a clinical perspective, its principal value lies in identifying individuals with genetic risk for progressing to steatosis, advanced fibrosis, or hepatocellular carcinoma, thereby supporting long-term risk assessment over real-time disease monitoring[36,37]. 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[36,38-41]. 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 be understood more appropriately as a foundational risk layer that complements, not replaces, dynamic biomarkers.

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[42]. 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 have strong clinical applicability for the development of non-invasive biomarkers. Sanyal developed models that could diagnose steatosis (AUC 0.95), inflammation (AUC 0.83), ballooning (AUC 0.87), and fibrosis (AUC 0.92), while a combined model achieved an AUC of 0.93 for identifying high-risk MASH[43]. 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[44-47]. This is also what gives metabolomics its translational appeal for blood- or urine-based biomarkers, particularly for large-scale screening and repeated assessment[44,48,49]. However, because metabolic profiles are highly susceptible to environmental influences, reproducibility across populations and the standardization required for clinical use remain important challenges. Representative studies of genomics, transcriptomics, proteomics, and metabolomics approaches for MASLD assessment are summarized in Table 3.

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 Y *et al.*[38]	2014	Retrospective	375	Prognosis	Genomics
De Vincentis *et al.*[109]	2021	Retrospective	266,687	Prognosis	Genomics
Eslam M *et al.*[110]	2015	Retrospective	1,992 / 1,242	Diagnosis	Genomics
Dongiovanni P *et al.*[36]	2018	Retrospective	9,414	Prognosis	Genomics
Verweij N *et al.*[111]	2022	Retrospective	542,904	Prognosis	Genomics
Bianco C *et al.*[112]	2021	Retrospective	367,041	Prognosis	Genomics
Chen VL *et al.*[113]	2023	Retrospective	54,773	Prognosis	Genomics
Sun J *et al.*[114]	2024	Retrospective	546	Prognosis	Transcriptomics, Genomics
Abul-Husn NS *et al.*[115]	2018	Retrospective	46,544 / 12,527	Prognosis	Genomics

					Transcriptomics
Jamialahmadi O *et al.*[37]	2021	Retrospective	425,671 / 2,621	Screening	Genomics
Valenti L *et al.*[40]	2010	Retrospective	824	Prognosis	Genomics Transcriptomics
Baselli GA *et al.*[116]	2022	Retrospective	301	Prognosis	Genomics Transcriptomics
Walker RW *et al.*[39]	2020	Retrospective	27,744	Prognosis	Genomics
Govaere O *et al.*[117]	2020	Retrospective	206 / 175	Diagnosis / Prognosis	Transcriptomics
Conway J *et al.*[118]	2023	Retrospective	1,208 / 186	Prognosis	Transcriptomics
Baboota RK *et al.*[42]	2022	Retrospective	58	Diagnosis / Prognosis	Transcriptomics
Tobaruela-Resola AL *et al.*[119]	2024	Retrospective	100	Diagnosis	Transcriptomics
Starmann J *et al.*[120]	2012	Retrospective	87	Diagnosis	Transcriptomics

Govaere *et al.*[121]	2023	Retrospective	306	Diagnosis	Transcriptomics
Bell LN *et al.*[122]	2010	Retrospective	85	Diagnosis	Proteomics
Feng G *et al.*[123]	2023	Retrospective	285	Diagnosis	Proteomics
Yuan X *et al.*[124]	2020	Retrospective	56	Diagnosis	Proteomics
Luo Y *et al.*[125]	2021	Retrospective	216	Diagnosis	Proteomics
Govaere O *et al.*[121]	2023	Retrospective	306	Diagnosis	Proteomics, Transcriptomics
Govaere O *et al.*[117]	2020	Retrospective	403	Diagnosis	Transcriptomics, Proteomics
Jiang Y *et al.*[126]	2023	Retrospective	2,236 / 80	Diagnosis	Proteomics
Sanyal AJ *et al.*[43]	2023	Retrospective	636	Diagnosis / Treatment	Proteomics
Rodríguez-Suárez E *et al.*[127]	2010	Retrospective	18 / 45	Diagnosis	Proteomics

McGlinchey AJ *et al.*[45]	2022	Retrospective	627	Diagnosis	Metabolomics
Zhu Q *et al.*[44]	2022	Retrospective	83	Diagnosis	Metabolomics
Perakakis N *et al.*[46]	2019	Retrospective	80	Diagnosis	Metabolomics
Chen J *et al.*[47]	2024	Retrospective	250	Diagnosis	Metabolomics
Khusial RD *et al.*[49]	2019	Retrospective	559	Screening	Metabolomics
Moolla A *et al.*[48]	2020	Retrospective	275	Diagnosis	Metabolomics
Kalhan SC *et al.*[128]	2011	Retrospective	60	Diagnosis	Metabolomics
Oh TG *et al.*[52]	2020	Retrospective	163 / 237 / 49	Diagnosis	Microbiomics

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, 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[32]. 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. This may enhance the clinical and biological interpretability of multi-omics models and, when combined with experimental validation, may help move the field from descriptive associations toward mechanistic inference and causal testing.

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. Wood *et al.* and Zhou *et al.* developed diagnostic models and found that model performance was optimal after integrating all omics data[50,51]. 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 *et al.* 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[52,53]. Quesada-Vazquez *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 to causality[54]. Therefore, the strengths of multi-omics studies lie not only in improved predictive performance, but also in their function to advance research from descriptive correlation to mechanistic interpretation and even causal validation. Such a research pathway gives multi-omics stronger scientific explanatory power in addition to its clinical utility.

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.

Representative multi-omics integration studies for MASLD assessment are summarized in Table 4. In summary, omics-based approaches give a useful biological insight into MASLD heterogeneity and may support biomarker discovery, molecular subtyping, prognostic modelling, and treatment-response research. 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.

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

Author(s)	Year	Study design	Sample size	Clinical Task	Omics
Wood GC *et al.*[50]	2017	Retrospective	576	Diagnosis	Genomics, Proteomics
Oh TG *et al.*[52]	2020	Retrospective	163	Diagnosis	Microbiomics, Metabolomics
Younossi ZM *et al.*[129]	2005	Retrospective	98	Screening	Transcriptomics, Proteomics
Atabaki-Pasdar N *et al.*[130]	2020	Retrospective	1,514	Diagnosis	Genomics, Transcriptomics, Proteomics, Metabolomics
Zhou Y *et al.*[51]	2016	Retrospective	318	Diagnosis	Metabolomics, Genomics
Wen W *et al.*[131]	2026	Retrospective	166	Diagnosis	Transcriptomics, Epigenomics
Perakakis N *et al.*[46]	2019	Retrospective	80	Diagnosis	Lipidomics, Glycomics
Quesada-Vazquez S *et al.*[54]	2023	Retrospective	651	Treatment	Metabolomics, Transcriptomics, Microbiomics
Leung H *et al.*[132]	2022	Prospective	180	Prognosis	Microbiomics, Metabolomics

Sveinbjornsson G *et al.*[133]	2022	Retrospective	36,116 / 9,491 / 4,809/ 35,559/ 47,151	Diagnosis / Prognosis	Genomics, Transcriptomics, Proteomics
Li Z *et al.*[134]	2025	Retrospective	61	Diagnosis	Transcriptomics, Metabolomics, Proteomics

Non-invasive imaging assessment

At the organ and tissue levels, non-invasive assessment of MASLD depends mainly on imaging-based biomarkers. 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.

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[55]. 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. Owing to its simplicity and broad availability, VCTE is well suited for first-line triage. 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. They do not directly measure extracellular matrix composition or interrogate the molecular pathophysiology underlying MASLD progression.

Among elastography-based techniques, VCTE is still the most widely used non-invasive tool in routine clinical practice because of its ease of operation, rapid acquisition, and established role in fibrosis triage[56-64]. A cohort study of 6,295 individuals from Europe and Asia found VCTE-based fibrosis screening in primary care to be cost-effective[65]. SWE can be integrated into conventional ultrasound platforms, offering practical advantages in workflow flexibility, and has demonstrated good reproducibility in several MASLD cohorts[66-73]. 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[74]. MRE generally provides the highest diagnostic accuracy and reproducibility, particularly in obese patients and specialist care settings, although its broader application is limited by cost, availability, and examination complexity[75,76]. 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[18]. Representative studies of VCTE, SWE, and MRE in MASLD are summarized in Table 5.

Table 5. Representative studies of elastography approaches for MASLD assessment.

Author(s)	Year	Study design	Sample size	Clinical Task	Biomarker / Model
Boursier J *et al.*[64]	2022	Retrospective	1,057	Prognosis	VCTE
Wong VWS *et al.*[62]	2012	Prospective	193	Diagnosis	VCTE
Petta S *et al.*[63]	2020	Retrospective	1,039	Prognosis	VCTE
Shili-Masmoudi S *et al.*[61]	2020	Prospective	2,245	Prognosis	VCTE
Wong VWS *et al.*[57]	2010	Prospective	246	Diagnosis	VCTE
Karlas T *et al.*[59]	2017	Retrospective	2,735	Diagnosis	VCTE
Braude M *et al.*[60]	2023	Retrospective	7,079	Prognosis	VCTE
Boursier J *et al.*[58]	2016	Retrospective	452 / 360	Diagnosis / Prognosis	VCTE
Serra-Burriel M *et al.*[65]	2019	Prospective	6,295	Screening	VCTE
Mendoza YP *et al.*[73]	2022	Prospective	104	Diagnosis	VCTE, SWE
Indre M-G *et al.*[70]	2025	Retrospective	2,223	Diagnosis	SWE

Ozturk A *et al.*[71]	2020	Retrospective	116	Diagnosis	SWE
Lee DH *et al.*[67]	2020	Prospective	102	Diagnosis	SWE
Herrmann E *et al.*[68]	2018	Retrospective	1,134	Diagnosis	SWE
Pierce TT *et al.*[74]	2024	Prospective	40	Diagnosis	SWE, VCTE
Jang JK *et al.*[66]	2022	Prospective	132	Diagnosis	SWE
Gidener T *et al.*[135]	2021	Retrospective	829	Prognosis	MRE
Imajo K *et al.*[104]	2016	Retrospective	142	Diagnosis	MRE
Park CC *et al.*[105]	2017	Prospective	104	Diagnosis	MRE

Assessment based on non-invasive compositional imaging

The pathological hallmark of liver fibrosis is excessive deposition of collagen-rich extracellular matrix[77]. This remodelling expands the extracellular matrix compartment and often shifts tissue water distribution as well. These tissue alterations provide a biological basis for compositional MRI sensitive to relaxation and MT. Quantitative MRI methods, including T1 mapping[77-79] and T1ρ mapping[80-84], have been investigated as 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[77-79] has been introduced for liver fibrosis evaluation, and iron correction strategies for hepatic T1ρ mapping[85] 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[86] and human studies[87-89]. 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[90,91] 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 the promise of these techniques, 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[92-94]. To improve reproducibility and comparability in radiomics research, Zwanenburg *et al.* standardized 169 radiomic features[95]. Because of their widespread clinical use, 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[96,97]. 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 have constrained the generalizability of these models[98,99].

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. A study by 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 added value of radiomics was only 2.6%[100]. These findings suggest that, although radiomics may improve performance, 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. Representative radiomics-based studies discussed in this section are summarized in Table 6.

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

Author(s)	Year	Study design	Sample size	Clinical Task	Modality
Zhang H *et al.*[97]	2025	Retrospective	840	Diagnosis	CT
Lubner MG *et al.*[136]	2017	Retrospective	289	Diagnosis	CT
Wang J *et al.*[137]	2022	Retrospective	443	Diagnosis	CT
Dichtel LE *et al.*[138]	2023	Retrospective	16	Diagnosis	CT
Cui E *et al.*[139]	2021	Retrospective	332	Diagnosis	CT
Tang S *et al.*[100]	2023	Retrospective	227	Diagnosis	CT
Chen ZW *et al.*[140]	2021	Retrospective	22	Diagnosis	PET/CT
Meng F *et al.*[96]	2023	Retrospective	618	Prognosis	Ultrasound
Xia F *et al.*[141]	2024	Retrospective	87	Diagnosis	Ultrasound
Chen ZW *et al.*[99]	2022	Retrospective	203	Diagnosis	MRI

Xu X *et al.*[98]	2021	Retrospective	53	Diagnosis	MRI
Li N *et al.*[142]	2024	Retrospective	254	Diagnosis	CT
Cannella R *et al.*[143]	2019	Retrospective	54	Diagnosis	MRI
Li F *et al.*[144]	2025	Retrospective	146	Diagnosis	MRI

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-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 and MRI-based biomarkers 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

In the past decade, non-invasive MASLD assessment has expanded from focusing mainly on imaging and lab tests to including blood biomarkers, imaging, AI, and omics profiling in research. These approaches interrogate different levels of disease biology. Blood-based biomarkers provide accessible systemic surrogates of liver injury, inflammation, and fibrogenesis; omics approaches capture molecular perturbations across biological layers; and imaging characterizes organ-level phenotypes of the liver and related tissues. VCTE, SWE, and MRE occupy different positions in the MASLD assessment pathway because they differ in accessibility, reproducibility, diagnostic

performance, cost, and suitability for repeated follow-up. 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. From the perspective of translational medicine, multimodal integration should not be viewed merely as a strategy to improve predictive performance. More importantly, it provides a framework for linking non-invasive assessment with real-world clinical decision-making. 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. In this context, low-cost and widely available blood-based tools such as FIB-4, together with sequential strategies incorporating second-line tests such as VCTE or ELF, remain attractive because they fit the practical demands of population-level triage and resource allocation. 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 FAST, MEFIB, and MAST. The value of a non-invasive tool should be measured by how well it supports decision-making in specific clinical situations, rather than just its overall accuracy in a mixed group of patients. For longitudinal management, repeated acquisition of blood biomarkers and imaging features is also more feasible than serial biopsy for monitoring disease progression and treatment response, although clinically meaningful change thresholds and standardized acquisition protocols remain important.

Importantly, the value of multimodal integration lies both in the complementarity of data and in its potential to connect mechanistic understanding with clinical application. 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. 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. In this sense, multimodal integration is not simply a means of aggregating information, but a way to bridge disease mechanism, phenotypic heterogeneity, and clinical utility.

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 AUROC 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.

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 over 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, artificial intelligence 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 to 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[24,25]. 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[64,101]. 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[64,102]. 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[103-106]. 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[18,106,107].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.

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

Availability of data and materials

Data is available on request.

Financial support and sponsorship

This study was supported by a grant from the Innovation and Technology Commission of the Hong Kong SAR (Project MRP/046/20X) and a grant from the Research Grants Council of the Hong Kong SAR (Project GRF 14213322). We would like to thank Dr. Vincent Wong from the Chinese University of Hong Kong for his valuable comments on this review.

Conflict of interest

Not applicable.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Teng ML, Ng CH, Huang DQ, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. *Clin Mol Hepatol*.

2023;29(Suppl):S32-42.[DOI:10.3350/cmh.2022.0365]

2. Le MH, Le DM, Baez TC, et al. Global incidence of non-alcoholic fatty liver disease: A systematic review and meta-analysis of 63 studies and 1,201,807 persons. *J Hepatol*. 2023;79(2):287-95.[DOI:10.1016/j.jhep.2023.03.040]

3. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2023;8(1):20-30.[DOI:10.1016/S2468-1253(22)00317-X]

4. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*. 2018;67(1):123-33.[DOI:10.1002/hep.29466]

5. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatol Baltim Md*. 2023;77(4):1335-47.[DOI:10.1097/HEP.0000000000000004]

6. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol*. 2018;69(4):896-904.[DOI:10.1016/j.jhep.2018.05.036]

7. Wong VWS, Adams LA, de Lédinghen V, Wong GLH, Sookoian S. Noninvasive biomarkers in NAFLD and NASH — current progress and future promise. *Nat Rev Gastroenterol Hepatol*. 2018;15(8):461-78.[DOI:10.1038/s41575-018-0014-9]

8. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. *N Engl J Med*. 2021;385(17):1559-69.[DOI:10.1056/NEJMoa2029349]

9. Taylor RS, Taylor RJ, Bayliss S, et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Gastroenterology*. 2020;158(6):1611-25.e12.[DOI:10.1053/j.gastro.2020.01.043]

10. Castéra L, Nègre I, Samii K, Buffet C. Patient-Administered Nitrous Oxide/Oxygen

Inhalation Provides Safe and Effective Analgesia for Percutaneous Liver Biopsy: A Randomized Placebo-Controlled Trial. *Am J Gastroenterol*. 2001;96(5):1553-7.[DOI:10.1111/j.1572-0241.2001.03776.x]

11. Bravo AA, Sheth SG, Chopra S. Liver Biopsy. *N Engl J Med*. 2001;344(7):495-500.[DOI:10.1056/NEJM200102153440706]

12. Davison BA, Harrison SA, Cotter G, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. *J Hepatol*. 2020;73(6):1322-32.[DOI:10.1016/j.jhep.2020.06.025]

13. Ratziu V, Charlotte F, Heurtier A, et al. Sampling Variability of Liver Biopsy in Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2005;128(7):1898-1906.[DOI:10.1053/j.gastro.2005.03.084]

14. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol*. 1995;22(6):696-9.[DOI:10.1016/0168-8278(95)80226-6]

15. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology*. 1996;24(2):289-93.[DOI:10.1053/jhep.1996.v24.pm0008690394]

16. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease†. *Hepatology*. 2005;41(6):1313.[DOI:10.1002/hep.20701]

17. Bedossa P, Consortium the FP. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. *Hepatology*. 2014;60(2):565.[DOI:10.1002/hep.27173]

18. Sanyal AJ, Castera L, Wong VWS. Noninvasive Assessment of Liver Fibrosis in NAFLD. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2023;21(8):2026-39.[DOI:10.1016/j.cgh.2023.03.042]

19. Wong VWS, Zelber-Sagi S, Cusi K, et al. Management of NAFLD in primary care settings. *Liver Int*. 2022;42(11):2377-89.[DOI:10.1111/liv.15404]

20. Siddiqui MS, Yamada G, Vuppalanchi R, et al. Diagnostic Accuracy of Noninvasive Fibrosis Models to Detect Change in Fibrosis Stage. *Clin Gastroenterol Hepatol Off*

Clin Pract J Am Gastroenterol Assoc. 2019;17(9):1877-85.e5.[DOI:10.1016/j.cgh.2018.12.031]

21. Srivastava A, Gailer R, Tanwar S, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *J Hepatol*. 2019;71(2):371-8.[DOI:10.1016/j.jhep.2019.03.033]

22. Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. *J Hepatol*. 2019;71(3):523-33.[DOI:10.1016/j.jhep.2019.05.008]

23. Lee J, Vali Y, Boursier J, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. *Liver Int*. 2021;41(2):261-70.[DOI:10.1111/liv.14669]

24. Kanwal F, Shubrook JH, Adams LA, et al. Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2021;161(5):1657-69.[DOI:10.1053/j.gastro.2021.07.049]

25. Tacke F, Horn P, Wai-Sun Wong V, et al. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81(3):492-542.[DOI:10.1016/j.jhep.2024.04.031]

26. Younes R, Caviglia GP, Govaere O, et al. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. *J Hepatol*. 2021;75(4):786-94.[DOI:10.1016/j.jhep.2021.05.008]

27. Hagström H, Talbäck M, Andreasson A, Walldius G, Hammar N. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. *J Hepatol*. 2020;73(5):1023-9.[DOI:10.1016/j.jhep.2020.06.007]

28. Balkhed W, Åberg FO, Nasr P, Ekstedt M, Kechagias S. Repeated measurements of non-invasive fibrosis tests to monitor the progression of non-alcoholic fatty liver disease: A long-term follow-up study. *Liver Int*. 2022;42(7):1545-56.[DOI:10.1111/liv.15255]

29. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study.

Lancet Gastroenterol Hepatol. 2020;5(4):362-73.[DOI:10.1016/S2468-1253(19)30383-8]

30. Jung J, Loomba RR, Imajo K, et al. MRE combined with FIB-4 (MEFIB) Index in detection of candidates for pharmacologic treatment of NASH related fibrosis. *Gut*. 2021;70(10):1946-53.[DOI:10.1136/gutjnl-2020-322976]

31. Noureddin M, Truong E, Gornbein JA, et al. MRI-based (MAST) score accurately identifies patients with NASH and significant fibrosis. *J Hepatol*. 2022;76(4):781-7.[DOI:10.1016/j.jhep.2021.11.012]

32. Perakakis N, Stefanakis K, Mantzoros CS. The role of omics in the pathophysiology, diagnosis and treatment of non-alcoholic fatty liver disease. *Metabolism*. 2020;111:154320.[DOI:10.1016/j.metabol.2020.154320]

33. Bourganou MV, Chondrogianni ME, Kyrou I, et al. Unraveling Metabolic Dysfunction-Associated Steatotic Liver Disease Through the Use of Omics Technologies. *Int J Mol Sci*. 2025;26(4):1589.[DOI:10.3390/ijms26041589]

34. Vitorino R. Transforming Clinical Research: The Power of High-Throughput Omics Integration. *Proteomes*. 2024;12(3):25.[DOI:10.3390/proteomes12030025]

35. Ghosh S, Zhao X, Alim M, Brudno M, Bhat M. Artificial intelligence applied to 'omics data in liver disease: towards a personalised approach for diagnosis, prognosis and treatment. *Gut*. 2025;74(2):295-311.[DOI:10.1136/gutjnl-2023-331740]

36. Dongiovanni P, Stender S, Pietrelli A, et al. Causal relationship of hepatic fat with liver damage and insulin resistance in nonalcoholic fatty liver. *J Intern Med*. 2018;283(4):356-70.[DOI:10.1111/joim.12719]

37. Jamialahmadi O, Mancina RM, Ciociola E, et al. Exome-Wide Association Study on Alanine Aminotransferase Identifies Sequence Variants in the *GPAM* and *APOE* Associated With Fatty Liver Disease. *Gastroenterology*. 2021;160(5):1634-46.e7.[DOI:10.1053/j.gastro.2020.12.023]

38. Liu YL, Patman GL, Leathart JBS, et al. Carriage of the *PNPLA3* rs738409 C > G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. *J Hepatol*.

2014;61(1):75-81.[DOI:10.1016/j.jhep.2014.02.030]

39. Walker RW, Belbin GM, Sorokin EP, et al. A common variant in PNPLA3 is associated with age at diagnosis of NAFLD in patients from a multi-ethnic biobank. *J Hepatol*. 2020;72(6):1070-81.[DOI:10.1016/j.jhep.2020.01.029]

40. Valenti L, Al-Serri A, Daly AK, et al. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease†. *Hepatology*. 2010;51(4):1209-17.[DOI:10.1002/hep.23622]

41. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology*. 2011;53(6):1883-94.[DOI:10.1002/hep.24283]

42. Baboota RK, Rawshani A, Bonnet L, et al. BMP4 and Gremlin 1 regulate hepatic cell senescence during clinical progression of NAFLD/NASH. *Nat Metab*. 2022;4(8):1007-21.[DOI:10.1038/s42255-022-00620-x]

43. Sanyal AJ, Williams SA, Lavine JE, et al. Defining the serum proteomic signature of hepatic steatosis, inflammation, ballooning and fibrosis in non-alcoholic fatty liver disease. *J Hepatol*. 2023;78(4):693-703.[DOI:10.1016/j.jhep.2022.11.029]

44. Zhu Q, Li H, Ao Z, et al. Lipidomic identification of urinary extracellular vesicles for non-alcoholic steatohepatitis diagnosis. *J Nanobiotechnology*. 2022;20(1):349.[DOI:10.1186/s12951-022-01540-4]

45. McGlinchey AJ, Govaere O, Geng D, et al. Metabolic signatures across the full spectrum of non-alcoholic fatty liver disease. *JHEP Rep*. 2022;4(5):100477.[DOI:10.1016/j.jhepr.2022.100477]

46. Perakakis N, Polyzos SA, Yazdani A, et al. Non-invasive diagnosis of non-alcoholic steatohepatitis and fibrosis with the use of omics and supervised learning: A proof of concept study. *Metabolism*. 2019;101:154005.[DOI:10.1016/j.metabol.2019.154005]

47. Chen J, Lu RS, Diaz-Canestro C, et al. Distinct changes in serum metabolites and lipid species in the onset and progression of NAFLD in Obese Chinese. *Comput Struct*

Biotechnol J. 2024;23:791-800.[DOI:10.1016/j.csbj.2024.01.007]

48. Moolla A, De Boer J, Pavlov D, et al. Accurate non-invasive diagnosis and staging of non-alcoholic fatty liver disease using the urinary steroid metabolome. *Aliment Pharmacol Ther*. 2020;51(11):1188-97.[DOI:10.1111/apt.15710]

49. Khusial RD, Cioffi CE, Caltharp SA, et al. Development of a Plasma Screening Panel for Pediatric Nonalcoholic Fatty Liver Disease Using Metabolomics. *Hepatol Commun*. 2019;3(10):1311-21.[DOI:10.1002/hep4.1417]

50. Wood GC, Chu X, Argyropoulos G, et al. A multi-component classifier for nonalcoholic fatty liver disease (NAFLD) based on genomic, proteomic, and phenomic data domains. *Sci Rep*. 2017;7(1):43238.[DOI:10.1038/srep43238]

51. Zhou Y, Orešič M, Leivonen M, et al. Noninvasive Detection of Nonalcoholic Steatohepatitis Using Clinical Markers and Circulating Levels of Lipids and Metabolites. *Clin Gastroenterol Hepatol*. 2016;14(10):1463-72.e6.[DOI:10.1016/j.cgh.2016.05.046]

52. Oh TG, Kim SM, Caussy C, et al. A Universal Gut-Microbiome-Derived Signature Predicts Cirrhosis. *Cell Metab*. 2020;32(5):878-88.e6.[DOI:10.1016/j.cmet.2020.06.005]

53. Caussy C, Loomba R. Gut microbiome, microbial metabolites and the development of NAFLD. *Nat Rev Gastroenterol Hepatol*. 2018;15(12):719-20.[DOI:10.1038/s41575-018-0058-x]

54. Quesada-Vázquez S, Castells-Nobau A, Latorre J, et al. Potential therapeutic implications of histidine catabolism by the gut microbiota in NAFLD patients with morbid obesity. *Cell Rep Med*. 2023;4(12):101341.[DOI:10.1016/j.xcrm.2023.101341]

55. Furlan A, Tublin ME, Yu L, Chopra KB, Lippello A, Behari J. Comparison of 2D Shear Wave Elastography, Transient Elastography, and MR Elastography for the Diagnosis of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *AJR Am J Roentgenol*. 2020;214(1):W20-6.[DOI:10.2214/AJR.19.21267]

56. Siddiqui MS, Vuppalanchi R, Van Natta ML, et al. Vibration-controlled Transient Elastography to Assess Fibrosis and Steatosis in Patients With Nonalcoholic Fatty Liver

Disease. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2019;17(1):156-63.e2.[DOI:10.1016/j.cgh.2018.04.043]

57. Wong VWS, Vergniol J, Wong GLH, et al. Diagnosis of Fibrosis and Cirrhosis Using Liver Stiffness Measurement in Nonalcoholic Fatty Liver Disease. *Hepatology*. 2010;51(2):454.[DOI:10.1002/hep.23312]

58. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. *J Hepatol*. 2016;65(3):570-8.[DOI:10.1016/j.jhep.2016.04.023]

59. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J Hepatol*. 2017;66(5):1022-30.[DOI:10.1016/j.jhep.2016.12.022]

60. Braude M, Roberts S, Majeed A, et al. Liver stiffness (Fibroscan®) is a predictor of all-cause mortality in people with non-alcoholic fatty liver disease. *Liver Int*. 2023;43(1):90-9.[DOI:10.1111/liv.15415]

61. Shili-Masmoudi S, Wong GLH, Hiriart JB, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int*. 2020;40(3):581-9.[DOI:10.1111/liv.14301]

62. Wong VWS, Vergniol J, Wong GLH, et al. Liver Stiffness Measurement Using XL Probe in Patients With Nonalcoholic Fatty Liver Disease. *Am J Gastroenterol*. 2012;107(12):1862-71.[DOI:10.1038/ajg.2012.331]

63. Petta S, Sebastiani G, Viganò M, et al. Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver disease. *Clin Gastroenterol Hepatol.* Published online April 2021.[DOI:10.1016/j.cgh.2020.06.045]

64. Boursier J, Hagström H, Ekstedt M, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. *J Hepatol*. 2022;76(5):1013-20.[DOI:10.1016/j.jhep.2021.12.031]

65. Serra-Burriel M, Graupera I, Torán P, et al. Transient elastography for screening of

liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia. *J Hepatol*. 2019;71(6):1141-51.[DOI:10.1016/j.jhep.2019.08.019]

66. Jang JK, Lee ES, Seo JW, et al. Two-dimensional Shear-Wave Elastography and US Attenuation Imaging for Nonalcoholic Steatohepatitis Diagnosis: A Cross-sectional, Multicenter Study. *Radiology*. 2022;305(1):118-26.[DOI:10.1148/radiol.220220]

67. Lee DH, Cho EJ, Bae JS, et al. Accuracy of Two-Dimensional Shear Wave Elastography and Attenuation Imaging for Evaluation of Patients With Nonalcoholic Steatohepatitis. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2021;19(4):797-805.e7.[DOI:10.1016/j.cgh.2020.05.034]

68. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. *Hepatology*. 2018;67(1):260-72.[DOI:10.1002/hep.29179]

69. Zhou J, Yan F, Xu J, et al. Diagnosis of steatohepatitis and fibrosis in biopsy-proven nonalcoholic fatty liver diseases: including two-dimension real-time shear wave elastography and noninvasive fibrotic biomarker scores. *Quant Imaging Med Surg*. 2022;12(3):1800-14.[DOI:10.21037/qims-21-700]

70. Indre MG, Leucuta DC, Lupsor-Platon M, et al. Diagnostic accuracy of 2D-SWE ultrasound for liver fibrosis assessment in MASLD: A multilevel random effects model meta-analysis. *Hepatology*. 2025;82(2):454-69.[DOI:10.1097/HEP.0000000000001190]

71. Ozturk A, Mohammadi R, Pierce TT, et al. Diagnostic Accuracy of Shear Wave Elastography as a Non-invasive Biomarker of High-Risk Non-alcoholic Steatohepatitis in Patients with Non-alcoholic Fatty Liver Disease. *Ultrasound Med Biol*. 2020;46(4):972-80.[DOI:10.1016/j.ultrasmedbio.2019.12.020]

72. Chen G, Yang JC, Zhang GX, Cheng Z, Du X. Evaluation of Six Noninvasive Methods for the Detection of Fibrosis in Chinese Patients with Obesity and Nonalcoholic Fatty Liver Disease. *Obes Surg*. 2022;32(11):3619-26.[DOI:10.1007/s11695-022-06251-1]

73. Mendoza YP, Rodrigues SG, Delgado MG, et al. Inflammatory activity affects the accuracy of liver stiffness measurement by transient elastography but not by

two-dimensional shear wave elastography in non-alcoholic fatty liver disease. *Liver Int Off J Int Assoc Study Liver*. 2022;42(1):102-11.[DOI:10.1111/liv.15116]

74. Pierce TT, Ozturk A, Sherlock SP, et al. Reproducibility and Repeatability of US Shear-Wave and Transient Elastography in Nonalcoholic Fatty Liver Disease. *Radiology*. 2024;312(3):e233094.[DOI:10.1148/radiol.233094]

75. Zhang YN, Fowler KJ, Boehringer AS, et al. Comparative diagnostic performance of ultrasound shear wave elastography and magnetic resonance elastography for classifying fibrosis stage in adults with biopsy-proven nonalcoholic fatty liver disease. *Eur Radiol*. 2022;32(4):2457-69.[DOI:10.1007/s00330-021-08369-9]

76. Imajo K, Honda Y, Kobayashi T, et al. Direct Comparison of US and MR Elastography for Staging Liver Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2022;20(4):908-17.e11.[DOI:10.1016/j.cgh.2020.12.016]

77. Banerjee R, Pavlides M, Tunnicliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. *J Hepatol*. 2014;60(1):69-77.[DOI:10.1016/j.jhep.2013.09.002]

78. Pavlides M, Banerjee R, Tunnicliffe EM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. *Liver Int*. 2017;37(7):1065-73.[DOI:10.1111/liv.13284]

79. Pavlides M, Banerjee R, Sellwood J, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. *J Hepatol*. 2016;64(2):308-315.[DOI:10.1016/j.jhep.2015.10.009]

80. Wang YXJ, Yuan J, Chu ESH, et al. T1ρ MR Imaging Is Sensitive to Evaluate Liver Fibrosis: An Experimental Study in a Rat Biliary Duct Ligation Model. *Radiology*. 2011;259(3):712-9.[DOI:10.1148/radiol.11101638]

81. Allkemper T, Sagmeister F, Cicinnati V, et al. Evaluation of Fibrotic Liver Disease with Whole-Liver T1ρ MR Imaging: A Feasibility Study at 1.5 T. *Radiology*. 2014;271(2):408-15.[DOI:10.1148/radiol.13130342]

82. Rauscher I, Eiber M, Ganter C, et al. Evaluation of T1ρ as a potential MR biomarker

for liver cirrhosis: Comparison of healthy control subjects and patients with liver cirrhosis. *Eur J Radiol*. 2014;83(6):900-4.[DOI:10.1016/j.ejrad.2014.02.017]

83. Liu X, Wang Y, Xu C, Li Y, Lei J. Magnetic resonance T1ρ relaxation in patients with liver fibrosis: a systematic review and meta-analysis. *Diagn Interv Radiol*. 32(1):16-24.[DOI:10.4274/dir.2025.253325]

84. Mesropyan N, Chang J, Lutz P, et al. Clinical validation of T1ρ mapping for the assessment of hepatic fibrosis in patients with chronic liver disease. *Eur Radiol*. 2026;36(5):3983-93.[DOI:10.1007/s00330-025-12225-5]

85. Qian Y, Hou J, Jiang B, et al. Characterization and correction of the effects of hepatic iron on $T_{1\rho}$ relaxation in the liver at 3.0T. *Magn Reson Med*. 2022;88(4):1828-39.[DOI:10.1002/mrm.29310]

86. Wilczynski E, Sasson E, Eliav U, Navon G, Nevo U. Quantitative Magnetization EXchange MRI Measurement of Liver Fibrosis Model in Rodents. *J Magn Reson Imaging*. 2023;57(1):285-95.[DOI:10.1002/jmri.28228]

87. Yarnykh VL, Tartaglione EV, Ioannou GN. Fast macromolecular proton fraction mapping of the human liver in vivo for quantitative assessment of hepatic fibrosis. *NMR Biomed*. 2015;28(12):1716-25.[DOI:10.1002/nbm.3437]

88. Hou J, Wong VWS, Qian Y, et al. Detecting Early-Stage Liver Fibrosis Using Macromolecular Proton Fraction Mapping Based on Spin-Lock MRI: Preliminary Observations. *J Magn Reson Imaging*. 2023;57(2):485-92.[DOI:10.1002/jmri.28308]

89. Qian Y, Wong VWS, Hou J, Jiang B, Chu WCW, Chen W. Inhomogeneous liver fibrosis distribution revealed by macromolecular proton fraction quantification based on spin-lock MRI. *Quant Imaging Med Surg*. 2022;12(8):4341-5.[DOI:10.21037/qims-22-302]

90. Hou J, Wong VWS, Jiang B, et al. Macromolecular proton fraction mapping based on spin-lock magnetic resonance imaging. *Magn Reson Med*. 2020;84(6):3157-71.[DOI:10.1002/mrm.28362]

91. Shan Q, Yu Z, Jiang B, et al. Quantitative Macromolecular Proton Fraction Imaging using Pulsed Spin-Lock. *arXiv*. Preprint posted online May 28,

2025:arXiv:2505.21853.[DOI:10.48550/arXiv.2505.21853]

92. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. *Radiology*. 2016;278(2):563-77.[DOI:10.1148/radiol.2015151169]

93. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol*. 2017;14(12):749-62.[DOI:10.1038/nrclinonc.2017.141]

94. Morin O, Vallières M, Jochems A, et al. A Deep Look Into the Future of Quantitative Imaging in Oncology: A Statement of Working Principles and Proposal for Change. *Int J Radiat Oncol*. 2018;102(4):1074-82.[DOI:10.1016/j.ijrobp.2018.08.032]

95. Zwanenburg A, Vallières M, Abdalah MA, et al. The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping. *Radiology*. 2020;295(2):328-38.[DOI:10.1148/radiol.2020191145]

96. Meng F, Wu Q, Zhang W, Hou S. Application of Interpretable Machine Learning Models Based on Ultrasonic Radiomics for Predicting the Risk of Fibrosis Progression in Diabetic Patients with Nonalcoholic Fatty Liver Disease. *Diabetes Metab Syndr Obes*. 2023;Volume 16:3901-13.[DOI:10.2147/DMSO.S439127]

97. Zhang H, Liu J, Su D, et al. Diagnostic of fatty liver using radiomics and deep learning models on non-contrast abdominal CT. *PLOS ONE*. 2025;20(2):e0310938.[DOI:10.1371/journal.pone.0310938]

98. Xu X, Zhu H, Li R, et al. Whole-liver histogram and texture analysis on T1 maps improves the risk stratification of advanced fibrosis in NAFLD. *Eur Radiol*. 2021;31(3):1748-59.[DOI:10.1007/s00330-020-07235-4]

99. Chen ZW, Xiao HM, Ye X, et al. A novel radiomics signature based on T2-weighted imaging accurately predicts hepatic inflammation in individuals with biopsy-proven nonalcoholic fatty liver disease: a derivation and independent validation study. *Hepatobiliary Surg Nutr*. 2022;11(2):212-26.[DOI:10.21037/hbsn-21-23]

100. Tang S, Wu J, Xu S, Li Q, He J. Clinical-radiomic analysis for non-invasive prediction of liver steatosis on non-contrast CT: A pilot study. *Front Genet*.

2023;14:1071085.[DOI:10.3389/fgene.2023.1071085]

101. Boursier J, Guillaume M, Leroy V, et al. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. *J Hepatol*. 2019;71(2):389-96.[DOI:10.1016/j.jhep.2019.04.020]

102. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut*. 2006;55(3):403-8.[DOI:10.1136/gut.2005.069153]

103. Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: Clinical trials to clinical practice. *J Hepatol*. 2016;65(5):1006-16.[DOI:10.1016/j.jhep.2016.06.005]

104. Imajo K, Kessoku T, Honda Y, et al. Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography. *Gastroenterology*. 2016;150(3):626-37.e7.[DOI:10.1053/j.gastro.2015.11.048]

105. Park CC, Nguyen P, Hernandez C, et al. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients with Biopsy-proven Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2017;152(3):598-607.e2.[DOI:10.1053/j.gastro.2016.10.026]

106. Liang J xu, Ampuero J, Niu H, et al. An individual patient data meta-analysis to determine cut-offs for and confounders of NAFLD-fibrosis staging with magnetic resonance elastography. *J Hepatol*. 2023;79(3):592-604.[DOI:10.1016/j.jhep.2023.04.025]

107. Ajmera V, Kim BK, Yang K, et al. Liver Stiffness on Magnetic Resonance Elastography and the MEFIB Index and Liver-Related Outcomes in Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Individual Participants. *Gastroenterology*. 2022;163(4):1079-89.e5.[DOI:10.1053/j.gastro.2022.06.073]

108. Labenz C, Arslanow A, Nguyen-Tat M, et al. Structured Early detection of Asymptomatic Liver Cirrhosis: Results of the population-based liver screening program SEAL. *J Hepatol*. 2022;77(3):695-701.[DOI:10.1016/j.jhep.2022.04.009]

109. De Vincentis A, Tavaglione F, Jamialahmadi O, et al. A Polygenic Risk Score to Refine Risk Stratification and Prediction for Severe Liver Disease by Clinical Fibrosis Scores. *Clin Gastroenterol Hepatol*. 2022;20(3):658-73.[DOI:10.1016/j.cgh.2021.05.056]

110. Eslam M, Hashem AM, Romero-Gomez M, et al. FibroGENE: A gene-based model for staging liver fibrosis. *J Hepatol*. 2016;64(2):390-8.[DOI:10.1016/j.jhep.2015.11.008]

111. Verweij N, Haas ME, Nielsen JB, et al. Germline Mutations in CIDEB and Protection against Liver Disease. *N Engl J Med*. 2022;387(4):332-44.[DOI:10.1056/NEJMoa2117872]

112. Bianco C, Jamialahmadi O, Pelusi S, et al. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. *J Hepatol*. 2021;74(4):775-82.[DOI:10.1016/j.jhep.2020.11.024]

113. Chen VL, Oliveri A, Miller MJ, et al. PNPLA3 genotype and diabetes identify patients with non-alcoholic fatty liver disease at high risk of incident cirrhosis. *Gastroenterology*. 2023;164(6):966-77.e17.[DOI:10.1053/j.gastro.2023.01.040]

114. Sun J, Shi R, Wu Y, et al. Integration of transcriptomic analysis and multiple machine learning approaches identifies NAFLD progression-specific hub genes to reveal distinct genomic patterns and actionable targets. *J Big Data*. 2024;11(1):40.[DOI:10.1186/s40537-024-00899-5]

115. Abul-Husn NS, Cheng X, Li AH, et al. A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease. *N Engl J Med*. 2018;378(12):1096-106.[DOI:10.1056/NEJMoa1712191]

116. Baselli GA, Jamialahmadi O, Pelusi S, et al. Rare ATG7 genetic variants predispose patients to severe fatty liver disease. *J Hepatol*. 2022;77(3):596-606.[DOI:10.1016/j.jhep.2022.03.031

117. Govaere O, Cockell S, Tiniakos D, et al. Transcriptomic profiling across the nonalcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis. *Sci Transl Med*. 2020;12(572):eaba4448.[DOI:10.1126/scitranslmed.aba4448]

118. Conway J, Pouryahya M, Gindin Y, et al. Integration of deep learning-based histopathology and transcriptomics reveals key genes associated with fibrogenesis in patients with advanced NASH. *Cell Rep Med*. 2023;4(4):101016.[DOI:10.1016/j.xcrm.2023.101016]

119. Tobaruela-Resola AL, Milagro FI, Elorz M, et al. Circulating miR-122-5p, miR-151a-3p, miR-126-5p and miR-21-5p as potential predictive biomarkers for Metabolic Dysfunction-Associated Steatotic Liver Disease assessment. *J Physiol Biochem*. 2025;81(4):1275-88.[DOI:10.1007/s13105-024-01037-8]

120. Starmann J, Fälth M, Spindelböck W, et al. Gene Expression Profiling Unravels Cancer-Related Hepatic Molecular Signatures in Steatohepatitis but Not in Steatosis. Syn WK, ed. *PLoS ONE*. 2012;7(10):e46584.[DOI:10.1371/journal.pone.0046584]

121. Govaere O, Hasoon M, Alexander L, et al. A proteo-transcriptomic map of non-alcoholic fatty liver disease signatures. *Nat Metab*. 2023;5(4):572-8.[DOI:10.1038/s42255-023-00775-1]

122. Bell LN, Theodorakis JL, Vuppalanchi R, et al. Serum Proteomics and Biomarker Discovery Across the Spectrum of Nonalcoholic Fatty Liver Disease. *Hepatology*. 2010;51(1):111-20.[DOI:10.1002/hep.23271]

123. Feng G, Zhang X, Zhang L, et al. Novel urinary protein panels for the non-invasive diagnosis of non-alcoholic fatty liver disease and fibrosis stages. *Liver Int*. 2023;43(6):1234-46.[DOI:10.1111/liv.15565]

124. Yuan X, Sun Y, Cheng Q, et al. Proteomic analysis to identify differentially expressed proteins between subjects with metabolic healthy obesity and non-alcoholic fatty liver disease. *J Proteomics*. 2020;221:103683.[DOI:10.1016/j.jprot.2020.103683]

125. Luo Y, Wadhawan S, Greenfield A, et al. SOMAscan Proteomics Identifies Serum Biomarkers Associated With Liver Fibrosis in Patients With NASH. *Hepatol Commun*. 2021;5(5):760-73.[DOI:10.1002/hep4.1670]

126. Jiang Y, Zhuang X, Zhang J, et al. Clinical characterization and proteomic profiling of lean nonalcoholic fatty liver disease. *Front Endocrinol*. 2023;14:1171397.[DOI:10.3389/fendo.2023.1171397]

127. Rodríguez-Suárez E, Duce AM, Caballería J, et al. Non-alcoholic fatty liver disease proteomics. *PROTEOMICS - Clin Appl*. 2010;4(4):362-71.[DOI:10.1002/prca.200900119]

128. Kalhan SC, Guo L, Edmison J, et al. Plasma Metabolomic Profile in Non-Alcoholic Fatty Liver Disease. *Metabolism*. 2011;60(3):404-13.[DOI:10.1016/j.metabol.2010.03.006]

129. Younossi ZM, Baranova A, Ziegler K, et al. A Genomic and Proteomic Study of the Spectrum of Nonalcoholic Fatty Liver Disease *. *Hepatology*. 2005;42(3):665-74.[DOI:10.1002/hep.20838]

130. Atabaki-Pasdar N, Ohlsson M, Viñuela A, et al. Predicting and elucidating the etiology of fatty liver disease: A machine learning modeling and validation study in the IMI DIRECT cohorts. Heider D, ed. *PLOS Med*. 2020;17(6):e1003149.[DOI:10.1371/journal.pmed.1003149]

131. Wen W, Liu Z, Tan W, et al. Integrating multi-omics and machine learning systematically deciphers cellular heterogeneity and fibrotic regulatory networks in the progression from MASLD to MASH. *Npj Digit Med*. 2026;9(1):167.[DOI:10.1038/s41746-026-02352-8]

132. Leung H, Long X, Ni Y, et al. Risk assessment with gut microbiome and metabolite markers in NAFLD development. *Sci Transl Med*. 2022;14(648):eabk0855.[DOI:10.1126/scitranslmed.abk0855]

133. Sveinbjornsson G, Ulfarsson MO, Thorolfsdottir RB, et al. Multiomics study of nonalcoholic fatty liver disease. *Nat Genet*. 2022;54(11):1652-63.[DOI:10.1038/s41588-022-01199-5]

134. Li Z, Luo G, Gan C, et al. Spatially resolved multi-omics of human metabolic dysfunction-associated steatotic liver disease. *Nat Genet*. 2025;57(12):3112-25.[DOI:10.1038/s41588-025-02407-8]

135. Bae JS, Lee JM, Park SJ, Lee KB, Han JK. Magnetic resonance elastography of healthy livers at 3.0 T: Normal liver stiffness measured by SE-EPI and GRE. *Eur J Radiol*. 2018;107:46-53.[DOI:10.1016/j.ejrad.2018.08.015]

136. Lubner MG, Malecki K, Kloke J, Ganeshan B, Pickhardt PJ. Texture analysis of the liver at MDCT for assessing hepatic fibrosis. *Abdom Radiol*. 2017;42(8):2069-78.[DOI:10.1007/s00261-017-1096-5]

137. Wang J, Tang S, Mao Y, et al. Radiomics analysis of contrast-enhanced CT for staging liver fibrosis: an update for image biomarker. *Hepatol Int*. 2022;16(3):627-39.[DOI:10.1007/s12072-022-10326-7]

138. Dichtel LE, Tabari A, Mercaldo ND, et al. CT Texture Analysis in Nonalcoholic Fatty Liver Disease (NAFLD). *J Clin Exp Hepatol*. 2023;13(5):760-6.[DOI:10.1016/j.jceh.2023.04.001]

139. Cui E, Long W, Wu J, et al. Predicting the stages of liver fibrosis with multiphase CT radiomics based on volumetric features. *Abdom Radiol*. 2021;46(8):3866-76.[DOI:10.1007/s00261-021-03051-6]

140. Chen ZW, Tang K, Zhao YF, et al. Radiomics based on fluoro-deoxyglucose positron emission tomography predicts liver fibrosis in biopsy-proven MAFLD: a pilot study. *Int J Med Sci*. 2021;18(16):3624-30.[DOI:10.7150/ijms.64458]

141. Xia F, Wei W, Wang J, Duan Y, Wang K, Zhang C. Machine learning model for non-alcoholic steatohepatitis diagnosis based on ultrasound radiomics. *BMC Med Imaging*. 2024;24:221.[DOI:10.1186/s12880-024-01398-y]

142. Li N, Dong X, Zhu C, et al. Association study of NAFLD with pericoronary adipose tissue and pericardial adipose tissue: Diagnosis of stable CAD patients with NAFLD based on radiomic features. *Nutr Metab Cardiovasc Dis*. 2025;35(1):103678.[DOI:10.1016/j.numecd.2024.06.020]

143. Cannella R, Borhani AA, Tublin M, Behari J, Furlan A. Diagnostic value of MR-based texture analysis for the assessment of hepatic fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). *Abdom Radiol*. 2019;44(5):1816-24.[DOI:10.1007/s00261-019-01931-6]

144. Li F, Liang Y, Xia X, et al. MRI-Based Radiomic Biomarkers for Non-invasive Assessment of Liver Fibrosis in MASLD: Diagnostic Performance and Molecular Mechanisms in a Rat Model. *Acad Radiol*.

2025;32(10):5802-13.[DOI:10.1016/j.acra.2025.05.069]