Current Hepatology Reports (2025) 24:37
https://doi.org/10.1007/s11901-025-00711-9

REVIEW

Imaging Biomarkers in Metabolic Dysfunction Associated Steatotic Liver Disease

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Accepted: 24 October 2025

Abstract

Purpose of Review Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) is the most common chronic liver disease in developed countries, affecting up to one third of adults. While the majority of individuals experience a benign course, a significant subset develop progressive liver disease and complications. This review aims to evaluate the role of non-invasive magnetic resonance (MR) biomarkers in assessing the key features of MASLD, namely steatosis, steatohepatitis, and fibrosis.

Recent Findings Emerging evidence demonstrates that MR techniques, including magnetic resonance elastography (MRE), LiverMultiScan (LMS), and proton density fat fraction (PDFF), provide accurate and reproducible measures of fibrosis, steatosis, and disease activity. MRE shows the highest diagnostic accuracy for fibrosis staging, LMS has been validated in population studies, and PDFF is increasingly recognized as a predictor of treatment response.

Summary MR-based biomarkers are promising non-invasive tools for diagnosis, risk stratification, and monitoring of MASLD. They may reduce reliance on liver biopsy in clinical practice and trials, though further validation of standardized thresholds and cost-effectiveness analyses are still needed.

Keywords Magnetic resonance elastography · Proton density fat fraction · Liver Multiscan · Iron Corrected T1 · Diffusion weighted imaging · Dynamic contrast enhanced MRI

Introduction

Metabolic Dysfunction Associated Steatotic Liver disease (MASLD), previously known as Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease in Western countries, affecting up to a third of adults in the population [1]. The disease varies in severity from accumulation of liver fat only (simple steatosis) to fat associated with inflammation (Metabolic Dysfunction Associated Steatohepatitis; MASH) and fibrosis and cirrhosis. It is now well established that those with fibrosis are at increased risk of adverse clinical outcomes, while those with simple steatosis have better prognosis [2, 3]. The prognostic importance of MASH remains a matter of debate [4].

The terminology of non-alcoholic fatty liver disease (NAFLD) has been revised to metabolic dysfunction–associated steatotic liver disease (MASLD) to better reflect underlying pathophysiology. NAFLD/NASH definitions were limited by exclusionary criteria and stigmatizing language. A global Delphi consensus recommended the MASLD/MASH definitions, which require at least one cardiometabolic risk factor. This change aims to reduce stigma, improve diagnostic clarity, and enhance patient identification and research [5]. This change is also relevant to our review because the vast majority of studies we review here, were conducted before the nomenclature change and included participants based on the old definition of NAFLD/NASH. As there is substantial overlap between the old and new definitions, for the purposes of this review we consider

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Published online: 13 November 2025

the terms interchangeable and we use the new terms of MASLD/MASH throughout.

Liver biopsy is needed for the diagnostic classification of MASLD into simple steatosis or MASH and the staging of fibrosis. This presents a challenge in clinical practice and in the conduct of clinical trials. In clinical practice, it is important to identify people at high risk of MASLD related adverse clinical outcomes, so that they are prioritised for follow up in secondary care and for appropriate surveillance in those with liver cirrhosis. As MASLD is highly prevalent, liver biopsy is not practical as a diagnostic tool to be applied at a population level, because of its costs and invasiveness.

Up to now, liver biopsy has also been critically important in clinical trials where it is needed during screening procedures to identify potential participants with MASH and the appropriate level of fibrosis. Furthermore, changes in MASH and fibrosis are the only approved surrogate end-points in such trials. Participants in MASH clinical trials therefore need to have repeated liver biopsies. Sampling errors and observer dependent variability in liver biopsy reporting means that more study participants have to be recruited to achieve sufficient statistical power, while studies also suffer from high screening failure rates and dropouts. These challenges have now been accepted by regulators who recently published guidance on how non-invasive tests could be adopted as reasonably likely surrogate endpoints that can be used in place of liver biopsy [6].

Steatosis has traditionally been regarded as a "benign" feature of MASLD that has no bearing on the progression of liver disease. This may be in part because steatosis is routinely quantified histologically as the "number of hepatocytes containing lipid droplets", while MRI can quantify liver fat as a proportion (fat fraction, %) of liver tissue. The differences in histological and MRI assessment of steatosis are well described [7] and data suggest that MRI rather than histology is the gold standard for liver steatosis evaluation [8]. The benign nature of steatosis was challenged in a natural history study using MRI proton density fat fraction (PDFF) to quantify liver fat at baseline, where those with liver fat fraction $\geq$ 15.7% were more likely to have progressively worsening fibrosis (multivariable adjusted odds ratio 6.7; 95% CI 1.01–44.1; p = 0.049) [9].

Furthermore, evidence is emerging from clinical trials where liver fat is being assessed with MRI PDFF that suggests that reduction in liver fat is associated with histologic improvements. Data suggest that a relative decrease of 30% in MRI PDFF quantified liver fat is associated with improvements in MASH [10–12], and steatosis on biopsy and reductions of serum markers of fibrosis and MASH activity [13–16]. Furthermore, relative liver MRI PDFF reductions of 58% and 67% were observed in the study of the fibroblast growth factor −19 analogue NGM282 and these were associated with improvement in fibrosis [17, 18]

In summary, there is an unmet need for non-invasive biomarkers of fibrosis as this is an important prognostic factor, for the diagnosis of MASH for inclusion in clinical trials and assessment of effectiveness and for steatosis that can be an early predictor of response to treatment. To address these areas of unmet clinical need and to reduce reliance on liver biopsy for the assessment of MASLD in different contexts, several non-invasive techniques have been developed. These are generally divided into serum-based biomarkers, ultrasound elastography based biomarkers and magnetic resonance based biomarkers, which will be the focus of this chapter. In general, simple serum based markers are recommended for population screening in the community with direct serum markers [19] and transient elastography reserved as a second tier of assessment. MR based biomarkers are generally reserved for cases where transient elastography fails or in indeterminate cases [20].

Several MR biomarkers have been developed and evaluated in different contexts of MASLD. Our aim is therefore to provide a narrative review of the various MR techniques that have been applied for the evaluation of several aspects of MASLD. The main contexts of use we include are the distinction of MASH vs non-MASH, the staging of fibrosis, the prediction of adverse clinical outcomes and the monitoring of treatment response.

Magnetic Resonance Elastography

Overiew

Magnetic Resonance Elastography (MRE; Resoundant, Rochester, US) is an MR technique that measures liver stiffness. It requires additional hardware, software, and MR suite adaptations. During MRE, a plastic device is placed over the liver to transmit mechanical shear waves, which are visualized using 2D gradient-echo sequences to estimate stiffness. These data are then used to provide an estimate of the liver stiffness, which is mostly considered a biomarker of fibrosis. 2D-MRE is clinically available and is the most validated of the MR based biomarkers in MASLD. 3D-MRE, still in development, provides additional information beyond stiffness which may improve diagnostic performance.

MRE has a low failure rate (4.3%) [21] and excellent inter-observer agreement (ICC 0.95) [22]. In a recent study by the NIMBLE Consortium 2D MRE had a repeatability coefficient of 0.75 kPa (95% CI: 0.60–0.99), indicating a high level of measurement consistency. 3D MRE repeatability coefficient percentage was 19.7% (95% CI: 15.8–26.2), suggesting greater variability. These findings highlight that while both modalities provide valuable insights into liver

stiffness, 2D MRE offers more robust repeatability, which could be advantageous for longitudinal disease monitoring and clinical trial applications [23].

MASH vs Non-MASH

Reports on diagnostic performance of MRE for MASH vary. An early retrospective study reported an area under the receiver operating curve (AUROC) of 0.93 (24) (threshold 2.74 kPa, Se 0.94, Sp 0.73, PPV 0.85, NPV 0.89; threshold 2.90 kPa Se 0.83, Sp 0.82, PPV 0.88, NPV 0.75) for the diagnosis of MASH using 2D MRE. A more recent prospective study also reported similar results (AUROC of 0.89; threshold 3.3 kPa Se 0.79 and Sp 0.82) [24]. In this study, MRE performed better than PDFF derived from a 6-point Dixon method, and native T1 mapping using SMART1Map [24].

However, this level of performance has not been replicated in all studies. Five other prospective studies reported area under the curve (AUC) ranging from 0.70 to 0.81 [25–29], and showed that MRE does not offer any improvement in the diagnosis of MASH compared to transient elastography [26, 29–32]. Data from the prospective multicentre LITMUS Imaging Study [33] found MRE liver stiffness to be the best performing MR biomarker for MASH and at-risk-MASH but with AUROC < 0.80 in both cases [34].

Studies that have examined 3D MRE for the diagnosis of MASH have also only reported moderate diagnostic accuracy. In a study of 100 participants, 3D MRE (60 Hz) and 3D MRE (40 Hz) had AUROC of 0.76 and 0.74 respectively, compared to 2D MRE (60 Hz) of 0.75 [27]. In participants who were undergoing bariatric surgery, the AUROC for the diagnosis of MASH was 0.73 [35]. Approaches where MRE data is combined with clinical and laboratory parameters to create multivariable models have produced some encouragning results for the diagnosis of MASH (AUROC 0.84) [36]. Combination approaches for the diagnosis of what is termed as "at-risk MASH" (presence of MASH and at least F2 fibrosis) have also been fairly extensively validated. Of these, the MAST score that includes the parameters of MRE liver stiffness, MRI PDFF and AST has been the most promising [37, 38].

Staging of Fibrosis in MASLD

There is increasing evidence that MRE measured liver stiffness is the best performing biomarker for the assessment of liver fibrosis. Several studies have now examined this and liver fibrosis evaluation has been the subject of several meta-analysis with consistent results throughout. In a meta-analysis of 5 studies including 628 participants, the mean AUC of the pooled data for the diagnosis of significant fibrosis (F ≥ 2), advanced fibrosis (F ≥ 3) and cirrhosis were 0.88 (95% CI 0.83–0.92), 0.93 (0.90–0.97) and 0.92 (0.80–1.00) respectively. In a meta-analysis of 11 studies MRE liver stiffness had summary ROC of 0.92 and 0.90 for advanced fibrosis and cirrhosis respectively. In an individual participant data meta-analysis of 115 participants from eight studies, the AUC for the diagnosis of fibrosis stage ≥ 1, ≥ 2, ≥ 3, and 4 were 0.89 (0.81–0.97), 0.90 (0.79–0.93), 0.94 (0.91–0.98) and 0.90 (0.64–0.94) respectively. In a more recent individual participant data meta-analysis that included 798 participants MRE showed excellent diagnostic accuracy for significant fibrosis (F ≥ 2) with an AUROC of 0.92 (threshold of 3.14 kPa, the sensitivity was 79% and the specificity was 89%.) For advanced fibrosis (F ≥ 3), the AUROC was also 0.92, with a threshold of 3.53 kPa yielding a sensitivity of 87% and a specificity of 88% [39]. Most recently, the headline results from the LITMUS Imaging study have also reported similar performance, with an AUC of 0.91 for both advanced fibrosis and cirrhosis [34]. MRE appears to perform equally well in paediatric MASLD [40], and better than TE and serum-based indirect biomarkers [41, 42]. The results of some of the main individual studies that have examined MRE measured liver stiffness for fibrosis evaluation in MASLD are summarised in Table 1.

MRE liver stiffness is usually evaluated by manually selecting regions of interest in the MRE elastogram images. More recently, convolutional neural networks have been examined in the reporting of MRE with strong agreement between manual and CNN read values (Intraclass correlation coefficient: 0.98–0.99), minimal bias (0.10 kPa), and low variability (CV: 4.2–4.8%). Both methods demonstrated comparable diagnostic performance, with AUC values ranging from 0.87 to 0.93 across fibrosis stage comparisons, with no significant differences [52]. Application of machine learning techniques to read MRE scans has the potential to scale up the technology and lead to more widespread adoption.

Monitoring Treatment Response

MRE has been validated as an exploratory end point in several clinical trials. In an analysis of the data from the phase II trial of selonsertib [53], MRE had an AUC of 0.62 (95% CI: 0.46–0.78) for the prediction of fibrosis improvement [54]. In another secondary analysis of the placebo arms of two clinical trials [10, 55], a decrease of ≥ 5% in body mass index, was associated with a decrease in MRE liver stiffness, while patients who did not lose weight did not show any MRE changes [55, 56]. Treatment with pemafibrate was associated with a decrease in MRE liver stiffness in a phase 2 trial [57], however, MRE liver stiffness did not change after treatment with semaglutide, despite reduction in liver

Table 1 Diagnostic performance of magnetic resonance elastography for the assessment of fibrosis in metabolic dysfunction associated steatotic liver disease

Study	Study design	number of participants	Diagnostic performance
Kim 2013 [43]	Retrospective 2D MRE	142	AUC = 0.95 for F ≥ 3
Loomba 2014 [28]	Prospective 2D MRE	117	AUC = 0.84 for F ≥ 1 AUC = 0.86 for F ≥ 2 AUC = 0.92 for F ≥ 3 AUC = 0.89 for F4
Cui 2016 [44]	Prospective 2D MRE	125	AUC = 0.80 for F ≥ 1 AUC = 0.89 for F ≥ 2 AUC = 0.93 for F ≥ 3 AUC = 0.88 for F4
Imajo 2016 [45]	Prospective 2D MRE	142	AUC = 0.80 for F ≥ 1 AUC = 0.89 for F ≥ 2 AUC = 0.89 for F ≥ 3 AUC = 0.97 for F4
Loomba 2016 [27]	Prospective 2D MRE (60 Hz) 3D MRE (60 Hz) 3D MRE (40 Hz)	100	AUC = 0.85 for F ≥ 1 AUC = 0.88 for F ≥ 2 AUC = 0.92 for F ≥ 3 AUC = 0.98 for F4 AUC = 0.86 for F ≥ 1 AUC = 0.84 for F ≥ 2 AUC = 0.93 for F ≥ 3 AUC = 0.98 for F4 AUC = 0.85 for F ≥ 1 AUC = 0.86 for F ≥ 2 AUC = 0.98 for F ≥ 3 AUC = 0.99 for F4
Park 2017 [46]	Prospective 2D MRE	104	AUC = 0.82 for F ≥ 1 AUC = 0.89 for F ≥ 2 AUC = 0.87 for F ≥ 3 AUC = 0.87 for F4
Costa-Silva 2018 [25]	Prospective 2D MRE	49	AUC = 0.88 for F ≥ 1 AUC = 0.93 for F ≥ 2 AUC = 0.93 for F ≥ 3 AUC = 0.96 for F4
Jung 2020 [47]	Prospective 2D MRE	238	AUC for F ≥ 2 = 0.93
Imajo 2022 [48]	Prospective 2D MRE	201	AUC 0.95 for F ≥ 1 AUC 0.93 for F ≥ 2 AUC 0.93 F ≥ 3 AUC 0.92 F4
Tamaki 2023 [49]	Multicenter 2D MRE	806	For F ≥ 3 AUC 0.84 (training cohort) AUC 0.87 (validation cohort)
Duman 2024 [50]	Retrospective 2D MRE	119	AUC = 0.85 for F ≥ 2
Zhang 2021 [51]	Prospective 2D MRE	100	AUC for ≥ F1 = 0.81 AUC for ≥ F2 = 0.94 AUC for ≥ F3 = 0.95 AUC for ≥ F4 = 0.92
Pavlides 2025 [34]	Prospective 2D MRE	262	AUC 0.91 for F ≥ 3 AUC 0.91 for F4

fat as measured by MRI PDFF [58]. In two studies evaluating total diet replacement with very low calorie supplements MRE liver stiffness improved in non-cirrhotic MASH [59] but not in MASH with cirrhosis [60].

Predicting Adverse Clinical Outcomes

In an early retrospective study of patients with advanced fibrosis (25% had MASLD),MRE liver stiffness predicted decompensation independently of age, MELD score, serum albumin and hepatitis C diagnosis [61]. Increasing data is emerging that supports the use of MRE liver stiffness as a robust prognostic tool in MASLD.

In a study of 829 participants with MASLD, MRE liver stiffness predicted progression to cirrhosis in those without cirrhosis at baseline (HR = 2.93, C-statistic = 0.86), and adverse clinical outcomes in those with compensated cirrhosis at baseline (HR = 1.32) [62].

In another study, those with baseline MRE liver stiffness between 5–8 kPa had a hazard ratio (HR) of 11.0 for adverse outcomes, and those with stiffness ≥ 8 kPa had an even higher HR of 15.9, compared with patients < 5 kPa ($p < 0.001$). Baseline MRE liver stiffness was also predictive of hepatocellular carcinoma (HCC): the 3-year risk was 0.35% for patients < 5 kPa, 5.25% for those with 5–8 kPa, and 5.66% for those ≥ 8 kPa [63].

Combinations of MRE-LS with simple serum based markers have also been evaluated with encouraging results. The combined MEFIB score (MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6) was an especially strong predictor, with an HR of 20.6 and a 5-year negative predictive value (NPV) of 99.1% [63]. In another study of 1254 participants, an MRE-based multivariate model incorporating age, MRE-LS, albumin, AST, and platelet count demonstrated excellent prognostic accuracy. The c-statistics for predicting hepatic decompensation were 0.912 and 0.871 at 3 years in the training and validation cohorts, respectively, and 0.891 and 0.876 at 5 years. Similarly, the model predicted hepatocellular carcinoma development with c-statistics of 0.876 and 0.911 at 3 and 5 years, respectively, and all-cause mortality with c-statistics of 0.806 and 0.760. Notably, these values were significantly superior to those obtained with FIB-4 [64].

LiverMultiscan™

Overview

LiverMultiScan™ (LMS; Perspectum, Oxford, UK) combines shMOLLI T1 mapping, T2*, and PDFF. A key feature is correction of T1 for iron (measured by T2*), producing the iron-corrected T1 (cT1), which improves diagnostic

accuracy (67, 68). While not as extensively validated as MRE in cross sectional studies of MASLD, LMS is widely applied, including in the UK Biobank [65–68].

LMS has a low failure rate (2–5%), mainly due to patient factors such as claustrophobia, and shows excellent reproducibility across scanners and field strengths (CV 3.3%, bias 6.5 ms) with high scan–rescan repeatability (CV 1.7%) [69]. In a head-to-head comparison, LMS demonstrated superior test–retest repeatability versus MR elastography and transient elastography [70].

MASH vs Non-MASH and Staging of MASLD Fibrosis

In a study of 71 patients from one centre [71], LMS cT1 had an AUROC of 0.89 for the identification of significant MASLD as defined by the FLIP consortium algorithm [72]. In the same study there was good performance for the differentiation of MASH vs simple steatosis (AUROC 0.80). Furthermore, cT1 could identify patients with significant activity (ballooning + lobular inflammation; AUROC 0.83) and cirrhosis (AUROC 0.85). In a two centre study of 50 patients [73], LMS cT1 had moderate diagnostic performance for the distinction of MASH vs simple steatosis (AUROC 0.69) [74]. A 2022 multicenter analysis compared the diagnostic value of several MRI-derived biomarkers in differentiating MASH from non-MASH. The study found that cT1 achieved an AUROC of 0.78, comparable to MRI-derived liver fat (AUROC 0.78), while conventional MRI liver fat alone performed less well (AUROC 0.69). When cT1 and MRI liver fat were combined, the diagnostic accuracy increased to an AUROC of 0.82 [75].

In a study evaluating MRI-based biomarkers, both cT1 and PDFF were found to correlate with all components of the MASLD Activity Score (MAS) [76]. In a study from Japan LMS PDFF had an AUROC of 0.80 for the detection of MASH, while cT1 achieved an AUROC of 0.75 [77]. In the recent data from the prospective LITMUS imaging study LMS cT1 and LMS PDFF both had an AUC of 0.66 for the diagnosis of at-risk-MASH (MASH + ≥F2) [34].

Monitoring Treatment Response

LMS cT1 and PDFF have been included as exploratory endpoints in a number of clinical trials. Data from 150 participants of 3 studies are included in a recent analysis where there was a significant decrease in liver cT1 (−119 ms vs. −49 ms) and PDFF (−65% vs. −29%) in responders compared to non-responders ($p < 0.001$), respectively. The diagnostic accuracy to identify responders was 0.72 (AUC) for both cT1 and LMS-PDFF [78]. There were also significant improvements in cT1 and LMS-PDFF in people with non-cirrhotic and cirrhotic MASH treated with very low calorie diets [59, 60]. Liver cT1 also improved in those with BMI > 35 kg/m^2 treated with mastiha (a natural nutritional supplement from the resin of the tree Pistacia lentiscus) [79].

Predicting Adverse Clinical Outcomes

LMS has not been specifically tested for the prediction of clinical outcomes in MASLD cohorts. In a study including participants with mixed liver disease aetiologies (35% MASLD) and varying degrees of fibrosis, LMS cT1 had a hazard ratio of 9.7 for the prediction of liver related events [80]. In the same study, a model including all three LMS variables (cT1, T2* and PDFF) had a hazard ratio of 75.7 demonstrating how the multi-parameter approach in this test can provide improved performance.

Population studies have also shown association between liver cT1 and cardiovascuilar outcomes. In the Multi-Ethnic Study of Atherosclerosis liver T1 was found to correlate with heart failure, atrial fibrillation, and coronary heart disease [81]. More recently, data from the UK biobank have also corroborated these results showing that cT1 is associated with adverse cardiac outcomes [82]. Due to the lack of histological validation in these studies, it is difficult to know whether the cT1 elevation is related to fibroinflammatory processes in the liver which may then indirectly drive cardiovascular disease, or whether the elevated cT1 is due to other pathological processes like liver congestion from possible coextisting subclinical right heart dysfunction.

Detection of Metabolic Liver Injury (deMILI) MRI

Overview

Detection of metabolic liver injury (deMILI) MRI uses optical analysis of magnetic resonance images to define NASHMRI (0–1) and FibroMRI (0–1), measures of MASH and liver fibrosis respectively. Image acquisition does not require injection of intravenous contrast [83]. Available data suggest that the between scanner reproducibility is good when tested using independent cohorts in Phillips and GE scanners[83]. In small number of patients (n = 9) assessed by both Philips and GE scanners, FibroMRI correctly detected in fibrosis in 3/3 cases and correctly excluded in 5/6 cases using both Philips and GE devices. Furthermore,

MASH was correctly diagnosed in 3/4 cases and correctly excluded in 4/5 cases using NASHMRI on data from both scanners[83].

MASH vs Non-MASH and Staging of MASLD Fibrosis

In a prospective study, for histologically defined MASH, NASHMRI achieved AUROC values of 0.88 (Se 0.87, Sp 0.74) in the estimation cohort and 0.83 (Se 0.87, Sp 0.60) in the validation cohort, outperforming CK-18. For significant fibrosis (F0–F1 vs F2–F4), FibroMRI showed AUROCs of 0.94 (Se 0.81, Sp 0.85) and 0.85 (Se 0.77, Sp 0.80), with superior accuracy to serum-based scores and comparable performance to transient elastography [83]. The performance of the deMILI scores did not live up to their initial promise in the recent prospective LITMUS study [34].

Dynamic Contrast Enhanced MRI

Overview

Dynamic contrast-enhanced MRI (DCE-MRI) assesses liver function by measuring MR signal changes after intravenous gadoxetic acid. Signal intensity changes reflect hepatocyte number and function, allowing distinction between normal and diseased liver. DCE-MRI requires intravenous contrast which is contraindicated in significant renal dysfunction, but it can be applied across scanners and field strengths without standardization, as it relies on relative change. Most validation to date is retrospective.

MASH vs Non-MASH and Staging of MASLD Fibrosis

Some studies have shown utility of DCE-MRI in animal models [84–86]. A retrospective human study also showed that relative signal enhancement was associated with lobular inflammation ($p=0.002$), ballooning ($p=0.04$) and fibrosis ($p<0.0001$) [87].

In cohorts with mixed liver disease aetiologies DCE-MRI has shown some utility in the assessment of liver fibrosis [88], cirrhosis severity [89–91], and liver function [91, 92]. In some studies DCE MRI performed better for the assessment of fibrosis compared to unenhanced T1 and diffusion weighted imaging [93, 94]. However, generalisation of these results to MASLD must not be assumed.

A related approach to using gadolinium based contrast agents is to use iron containing contrast agents. Superparamagnetic iron oxide particles have been tested, but these have since been taken off the market [95]. More recently, there has been some interest in ultrasmall superparamagnetic iron oxide particles. The iron containing contrast leads to changes in tissue R2* which can be measured. In a small, prospective, proof-of-concept study, the AUC for the diagnosis of MASH vs simple steatosis was 0.87 (95% CI 0.72–1.0) [96]. However, the post contrast scans are acquired 72 h after injection which is impractical in clinical practice.

Diffusion Weighted Imaging

Overview

Diffusion-weighted imaging (DWI) tracks water diffusion in tissues, quantified by the apparent diffusion coefficient (ADC) and fractional anisotropy. Steatosis, inflammation, and fibrosis alter diffusion, and are measurable with DWI. The intravoxel incoherent motion (IVIM) method further accounts for diffusion signals from blood flow in vascular beds [97].

This method is limited by high failure rate [98] and the method of analysis can also have a significant impact on results [99].

MASH vs Non-MASH and Staging of MASLD Fibrosis

In a small study the IVIM parameters of "pure molecular diffusion; D", "perfusion-related diffusion, D* and "perfusion fraction; f" there was only moderate diagnostic accuracy for the diagnosis of MASH (AUC 0.74 for D, 0.68 for D*, 0.61 for f) and fibrosis (AUC 0.69 for D, 0.68 for D*, 0.62 for f) [100]. Steatosis and fibrosis appear to have significant and independent effects on D and f [101]. The effects of steatosis have also been observed in other studies [102–105].

Studies have explored how IVIM can be used to generate a "virtual elastogram" based on a calibrated relationship between ADC and liver elasticity [106] and examined its application for the evaluation of liver fibrosis [107] and tumours [108]. While this method lacks further prospective validation it could provide an added advantage over MRE by negating the need for additional hardware.

Conclusions

MR-based biomarkers are relatively new compared with serum and ultrasound elastography. Among available techniques, **MRE (with PDFF)** and **LiverMultiScan (LMS)** are the most validated. MRE best assesses advanced fibrosis, while both provide PDFF, an emerging predictor of histological response.

Their role in clinical pathways remains unclear. Current guidelines recommend MR techniques as third-tier tests after serum and elastography, though cost-effectiveness data are lacking and upfront use may prove more efficient. Further validation is needed for predefined thresholds, such as the 30% PDFF reduction associated with histological response, and for prognostic value in MASLD cohorts.

MR biomarkers offer advantages beyond diagnostic accuracy: they are reproducible, scalable (e.g., LMS in UK Biobank), and adaptable to technical advances such as diffusion-weighted "virtual elastography."

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  This reference demonstrates that MRI-based biomarkers exhibit high diagnostic accuracy in identifying MASH patients at elevated risk of disease progression.

Acknowledgements MP acknowledges support from the Oxford NIHR Biomedical Research Centre

Author Contribution DG did literature searches and prepared a draft of the manuscript. MP did literature searches and revised the manuscript for important intellectual content.

Funding No financial support was received for the preparation of this manuscript. MP is supported by the Oxford NIHR Biomerdical Research Centre.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest MP is a shareholder in Perspectum Ltd. Products of this company are discussed in the manuscript. DG has no interests to declare.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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