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Application and Advances of Non-in vasive Magnetic Resonance Proton Density Fat Fraction in Hepatic Steatosis

Boli Ruan, Yao Zhang, Hongwei Lei *

Department of Radiology, The First Affiliated Hospital of Yangtze University, Jingzhou, Hubei, 434000, China
*** Corresponding author:** Hongwei Lei (Email: sslhw@sina.com)

Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD), affecting approximately 32% of the global adult population, represents a leading cause of chronic liver disease. Hepatic steatosis, characterized by abnormal lipid accumulation in hepatocytes, serves as a fundamental histological hallmark and a key driver of disease progression towards metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. Accurate, non-invasive quantification of liver fat content is therefore paramount for diagnosis, risk stratification, and therapeutic monitoring in MASLD. Magnetic Resonance Imaging-proton density fat fraction (MRI-PDFF), based on chemical shift-encoded water-fat separation, has emerged as a highly accurate, reproducible, and quantitative non-invasive biomarker for assessing hepatic steatosis. This review synthesizes current evidence demonstrating the superior diagnostic performance of MRI-PDFF in grading hepatic steatosis compared to traditional techniques like Controlled Attenuation Parameter (CAP) and transient elastography (TE), as evidenced by high area-under-the-receiver-operating-characteristic-curve (AUROC) values across multiple studies. Furthermore, MRI-PDFF plays a pivotal role in evaluating treatment efficacy in clinical trials, effectively detecting significant reductions in liver fat content in response to pharmacotherapy. While MRI-PDFF excels in fat quantification, its combination with other MRI-based techniques (e.g., Magnetic Resonance Elastography - MRE, corrected T1 - cT1) significantly enhances the non-invasive assessment of co-existing pathologies like MASH and fibrosis. Despite advantages such as whole-liver coverage and excellent reproducibility, limitations including high cost, technical standardization challenges, and restricted applicability in certain patient populations remain. In conclusion, MRI-PDFF stands as a cornerstone non-invasive tool for quantifying liver fat in MASLD, driving advancements in diagnosis, therapeutic monitoring, and clinical trial endpoints, with ongoing developments in multimodal approaches and standardization promising further optimization of MASLD management.

Keywords: Magnetic Resonance Imaging (MRI); Proton Density Fat Fraction (PDFF); Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD); Nonalcoholic Fatty Liver Disease (NAFLD); Hepatic Steatosis; Non-invasive Diagnosis; Quantitative Imaging.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is a leading cause of chronic liver disease globally, with an estimated adult prevalence of 32% [1]. The disease spectrum encompasses a multi-stage progression from simple hepatic steatosis (non-alcoholic fatty liver, NAFL), to inflammatory steatohepatitis (metabolic dysfunction-associated steatohepatitis, MASH, formerly non-alcoholic steatohepatitis, NASH), and onward to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [2]. The prevalence of MASLD is further influenced by diabetes, metabolic syndrome, and obesity, with its incidence rising in parallel with the increasing prevalence of these conditions [3]. A fundamental histological feature of MASLD is hepatic steatosis, pathologically characterized by the abnormal accumulation of lipids within hepatocytes. Studies indicate that the degree of this abnormal lipid accumulation correlates with the progression of fibrosis and cirrhosis in MASLD patients [4, 5], and MASLD is also closely linked to cardiovascular disease, metabolic syndrome, and type 2 diabetes [6, 7]. Crucially, hepatic steatosis in MASLD can be reversed with appropriate interventions, making the assessment of liver fat content particularly important. Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) has emerged in recent years as a widely used non-invasive method for quantifying liver fat content. It plays a vital role in assessing MASLD severity, monitoring disease progression, and evaluating new drug therapies and treatment efficacy in clinical trials [8].

2. Basic Principles of MRI-PDFF

The core technology of MRI-PDFF is chemical shift-encoded water-fat separation imaging. It quantifies the percentage of triglyceride proton signal intensity relative to the total proton signal intensity (water + fat) to achieve fat quantification [9]. This technique enables precise, non-invasive quantitative assessment of liver fat with excellent reproducibility [10, 11]. Research confirms that MRI-PDFF is currently recognized as one of the most accurate non-invasive methods for diagnosing liver fat content [12].

3. Quantitative Assessment Role of MRI-PDFF in Hepatic Steatosis of MASLD

In a study of 635 cases, MRI-PDFF demonstrated pooled AUROC values of 0.98, 0.91, and 0.90 for classifying steatosis grades 0 vs. 1-3, 0-1 vs. 2-3, and 0-2 vs. 3, respectively. The pooled sensitivity and specificity for distinguishing these grades were 0.93/0.94, 0.74/0.90, and

0.74/0.87, respectively, indicating excellent diagnostic value for assessing liver fat content and histological steatosis grading in MASLD patients [13].A meta-analysis of 7 studies involving 346 MASLD patients who underwent repeated paired liver biopsies and MRI-PDFF assessment showed that MRI-PDFF responders had a significantly higher likelihood of histological response (51% vs. 14%, $p < 0.001$; OR 6.98, 95% CI 2.38–20.43, $p < 0.001$) and MASH/NASH resolution (41% vs. 7%, $p < 0.001$; OR 5.45, 95% CI 1.53–19.46, $p = 0.009$). This analysis suggests that a relative decline in MRI-PDFF of ≥30% is associated with higher odds of histological response and MASH/NASH resolution, confirming a strong correlation between histological improvement and changes in MRI-PDFF [14].In a study of 169 children, PDFF demonstrated good diagnostic performance for liver steatosis grading: 1) For detecting grade ≥1 steatosis, a logistic regression model achieved an AUROC of 0.87 (95% CI: 0.80–0.94). 2) For distinguishing grades 1-2 vs. 3, the AUROC was 0.79 (95% CI: 0.70–0.87). 3) PDFF thresholds optimized for specificity were 17.5% (specificity 90%) for grade ≥2 steatosis and 23.3% (specificity 90%) for grade 3 steatosis. These results indicate that MRI-PDFF has good quantitative assessment utility for steatosis grading, particularly for distinguishing early (grade 1) and severe (grade 3) steatosis. In a prospective study of 104 patients with liver biopsy, MRI-PDFF achieved an AUROC of 0.99 (0.98–1.00) for detecting any steatosis, significantly outperforming CAP (0.85; 0.75–0.96). For distinguishing grade 2 and grade 3 steatosis, MRI-PDFF AUROCs were 0.90 (0.82–0.97) and 0.92 (0.84–0.99), respectively, compared to only 0.70 and 0.73 for CAP. These results demonstrate the superior performance of MRI-PDFF in steatosis staging compared to traditional non-invasive techniques (CAP and TE) [12].Similarly, in a study by Seung Joon Cho et al., MRI-PDFF showed high agreement with MR spectroscopy (MRS) for liver fat quantification ($r=0.978$ vs. $r=0.727$ for TE-CAP, both $P<0.001$), indicating its significantly better overall performance compared to traditional techniques (TE, CAP, ELF). Furthermore, in another study of 186 cases, the diagnostic performance of CAP progressively decreased with worsening steatosis severity (from S>33% to NASH), suggesting significantly reduced accuracy in severe steatosis and complex lesions like MASH/NASH, whereas MRI-PDFF maintained high diagnostic performance even in advanced steatosis [15].

The above studies demonstrate that MRI-PDFF is an ideal non-invasive technique and quantitative biomarker, showing excellent diagnostic performance in detecting hepatic steatosis. Consequently, MRI-PDFF is currently recommended in various guidelines for the quantitative diagnosis of hepatic steatosis in MASLD.

4. MRI-PDFF for Evaluating Clinical Treatment Efficacy in MASLD

Given the invasive nature of liver biopsy, which precludes its repeated use in patients, and leveraging the advantages of MRI-PDFF for non-invasive quantitative assessment of hepatic steatosis in MASLD, MRI-PDFF has been widely adopted for patient enrollment diagnosis and treatment efficacy evaluation in MASLD-related clinical trials. In a controlled study of ALS-L1023 for MASLD, after 24 weeks of treatment, MRI-PDFF detected a significant 15.0% reduction in liver fat content from baseline in the 1800mg group ($p=0.03$), indicating a direct fat-reducing effect. No significant changes in MRI-PDFF were observed in the 1200mg or placebo groups. These results suggest that ALS-L1023 exhibits dose-dependent efficacy over 24 weeks, with the high dose (1800mg) directly reducing hepatic fat deposition [16].In a randomized controlled trial evaluating ezetimibe combined with statin therapy for MASLD, pharmacodynamic assessment revealed: the high-dose group (1800mg) achieved a 15.0% relative reduction in liver fat via AMPK pathway activation ($P=0.03$). The combination therapy group showed an additional 3.2 percentage point reduction ($\Delta=3.2\%$, $P=0.02$) compared to monotherapy groups due to synergistic effects. This result provided the first confirmation of dose-dependent effects and drug synergy mechanisms [17].In a Phase II clinical trial of semaglutide combined with different doses of cilofexor and firsocostat for MASH/NASH, after 24 weeks, MRI-PDFF revealed similar weight reductions across all groups (7%-10%). However, the absolute reduction in liver fat was significantly greater in the combination therapy groups compared to monotherapy groups (least-squares mean: -9.8% to -11.0% vs. -8.0%), suggesting superior efficacy with combination therapy [18].n summary, owing to its non-invasive nature, high precision, and dynamic monitoring capability, MRI-PDFF has become a core tool for evaluating drug efficacy in MASLD.

5. Application of MRI-PDFF Combined with Other Metrics in MASLD

Although magnetic resonance proton density fat fraction (MRI-PDFF) demonstrates significant advantages in quantifying hepatic steatosis, it lacks specific diagnostic capability for other key pathological features such as hepatic inflammatory activity and fibrosis. To address this limitation, current research focuses on multi-modal diagnostic strategies to build comprehensive diagnostic models. In the study by Troelstra et al., multimodal MRI validation showed that combining PDFF (AUROC=0.86), magnetic resonance elastography (MRE) (AUROC=0.92), and intravoxel incoherent motion (IVIM) (AUROC=0.88) enabled precise stratification of MASLD steatosis, fibrosis, and MASH/NASH, providing a reliable combination of imaging biomarkers for non-invasive diagnosis [19].Recent studies indicate that combining MRI-PDFF with magnetic resonance elastography (MRE) significantly improves the diagnostic accuracy for metabolic dysfunction-associated steatohepatitis (MASH/NASH). In a prospective study of 68 biopsy-confirmed MASLD patients (53 MASH/NASH, 15 NAFL), MRE alone had an AUROC of 0.74 for diagnosing MASH/NASH. However, combining MRE with PDFF increased the AUROC to 0.84 ($P=0.008$), indicating that the combination more accurately distinguishes MASH/NASH from simple steatosis (NAFL)[20].The combination of three-dimensional multi-frequency magnetic resonance elastography (3D-MRE) and MRI-PDFF offers a new approach for diagnosing early MASH/NASH. A study of 175 obese patients (81 with confirmed MASH/NASH) demonstrated that a model incorporating 3D-MRE-derived shear stiffness (60Hz), damping ratio (40Hz), and MRI-PDFF significantly predicted MASH/NASH, with a cross-validated AUROC of 0.73 (sensitivity=67%, specificity=80%) [21].In a prospective study of a Japanese cohort, the AUCs for PDFF and corrected T1 (cT1) alone in diagnosing MASH/NASH

were 0.80 (95% CI: 0.73–0.87) and 0.75 (95% CI: 0.67–0.84), respectively. Combining PDFF and cT1 increased the AUC to 0.83 (95% CI: 0.76–0.90), significantly outperforming either single parameter [22].

6. Advantages and Disadvantages of MRI-PDFF in the Diagnosis and Management of MASLD

As a non-invasive quantitative technique, MRI-PDFF demonstrates significant advantages in assessing liver fat content and dynamically monitoring disease progression in MASLD patients. Magnetic resonance spectroscopy (MRS) is widely regarded as the reference standard for measuring PDFF, and MRI-PDFF results show high concordance with MRS [23]. Due to its whole-liver coverage, operational convenience, and result stability, MRI-PDFF has become the preferred non-invasive fat quantification tool in clinical practice [9].

6.1. Advantages

High reproducibility, significantly superior to controlled attenuation parameter (CAP), which is susceptible to interference from obesity, ascites, etc., and has high measurement failure rates (up to 30% in obese patients). Ultrasound techniques are operator-dependent and affected by obesity and comorbidities (e.g., limited acoustic windows in renal disease), making precise fat quantification difficult and unsuitable as a first-line diagnostic tool for MASLD.

6.2. Disadvantages

Despite its potential as a gold standard for fat quantification, the clinical application of MRI-PDFF faces several limitations: High equipment costs (single examination cost approximately 5-10 times that of ultrasound) and time-consuming manual analysis limit its widespread use in primary care and large-scale screening. Not suitable for patients unable to follow breathing instructions (e.g., children, patients with impaired consciousness) or those with metallic implants. Differences in magnetic field strength between MRI scanners from different manufacturers (1.5T vs. 3.0T) and incomplete standardization of post-processing algorithms may affect the comparability of results in multi-center studies.

7. Conclusion and Perspectives

Hepatic steatosis is not only the pathological basis of MASLD but also an independent risk factor driving disease progression to metabolic dysfunction-associated steatohepatitis (MASH) and both hepatic and extrahepatic complications (such as fibrosis, cirrhosis, and hepatocellular carcinoma). With the continuously rising global prevalence of MASLD and the inherent limitations of liver biopsy (invasive risks, sampling error, inter-observer variability), there is an urgent clinical need for accurate, non-invasive liver fat quantification techniques. Against this backdrop, magnetic resonance proton density fat fraction (MRI-PDFF), leveraging its whole-liver coverage and high accuracy, has gradually become a core imaging biomarker alternative to liver biopsy. Although its higher cost (approximately 2-3 times the cost of a single liver biopsy) and limited applicability in specific populations (e.g., those with metallic implants) remain challenges, ongoing developments in technical standardization, AI-assisted analysis (reducing manual processing time), and multi-modal combined models (e.g., PDFF + MRE) hold promise for further optimizing clinical pathways. MRI-PDFF is poised to advance early screening, precise stratification, and personalized intervention in MASLD, ultimately improving patient outcomes. It is believed that with the continued optimization of MRI-PDFF technology, more MASLD cases will be detected early, allowing patients to benefit from timely intervention.

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