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REVIEW

Magnetic resonance imaging proton density fat fraction as an imaging-based biomarker of treatment response in patients with nonalcoholic steatohepatitis

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide for which there remains no regulatory agency–approved drug therapy or cure. NAFLD encompasses a spectrum of histological features, including nonalcoholic fatty liver, nonalcoholic steatohepatitis (NASH), and cirrhosis. Invasive liver biopsy remains the gold standard for diagnosis and monitoring of treatment response in patients with NASH. At this time, liver histology is required not only as an end point for all late-phase NASH clinical trials but also for any drug-seeking conditional approval from US regulatory approval agencies.[1]

Liver biopsy has many limitations, many of which limit clinical trial participation and include sampling error, cost, and procedural complications. Moreover, liver biopsy has poor reliability, owing largely to significant liver pathologist reading variability for not only the individual components of the NAFLD activity score (NAS) of steatosis, lobular inflammation, and hepatocyte ballooning but also liver fibrosis stage, which greatly impacts the conduct of highly rigorous NASH clinical trials. Poor reliability may permit improper study entry, misclassification, or even diminishment of observed treatment effect because of the inadvertent reduction of statistical power and may lead to early abandonment of potentially beneficial drug therapies.[2]

There is a clear unmet need for accurate and reliable noninvasive modalities to replace invasive liver biopsy for the diagnosis and monitoring of treatment response in NASH in clinical trials.[3] This has been recognized as a top public health priority by both the US Food and Drug Administration and the National Institutes of Health, the latter of which recently funded the NIMBLE (Non-Invasive Biomarkers of Metabolic Liver Disease) consortium to develop and qualify potential serum-based and imaging biomarkers and to improve NASH drug development and regulatory decision making for drug approval.[4]

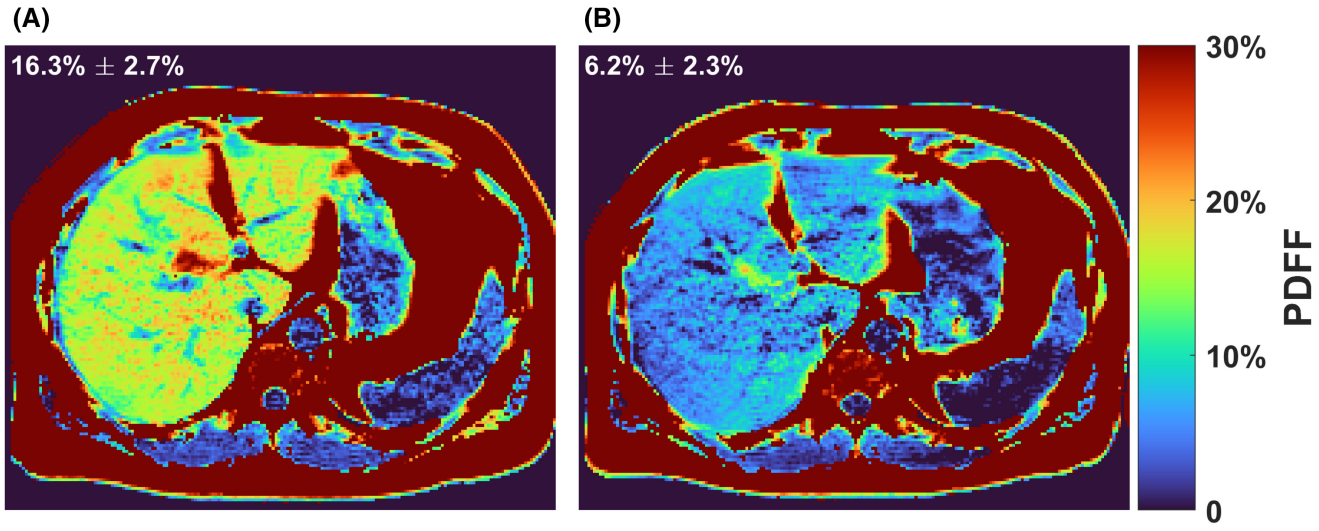

FIGURE 1 MRI-PDFF scans demonstrating ≥30% relative reduction in liver fat. (A) Baseline MRI-PDFF scan meeting diagnostic criteria for NAFLD. (B) Treatment response scan demonstrating ≥30% relative reduction in liver fat.

Over the past 10+ years, magnetic resonance imaging (MRI)-based technologies, including MRI-estimated proton density fat fraction (MRI-PDFF), have emerged as acceptable imaging biomarker alternatives to liver biopsy. MRI-PDFF is accurate, highly reproducible, and more sensitive than liver biopsy to small longitudinal changes in liver fat.[5] Although MRI-PDFF was originally intended as a biomarker of liver fat and not histological NASH activity or liver fibrosis, several reports within the last year suggest that MRI-PDFF may have an emerging role as a biomarker of liver histology.[6,7]

A recent systematic review with meta-analysis of seven NASH clinical trials across nearly 350 patients, including those investigating both antisteatogenic drugs and lifestyle modification, found that if a relative reduction in MRI-PDFF of at least 30% was achieved (Figure 1), the odds of NAS improvement without liver fibrosis stage worsening and NASH resolution were 7- and 5.5-fold, respectively (Figure 2).[6] This was followed by a single-center study amalgamating 100 patients from multiple NASH clinical trials studying largely antisteatogenic drugs, which found that if the ≥30% threshold of relative reduction was achieved, improvement in liver fibrosis by at least one stage was nearly 6.5-fold.[7] Taken together, these studies suggest that MRI-PDFF can be used in lieu of liver biopsy in early-phase NASH clinical trials as a surrogate marker of histological response; in fact, MRI-PDFF is now the preferred method to assess patients for inclusion in early-phase NASH clinical trials investigating antisteatogenic medications.

At this time, the role of MRI-PDFF in NASH clinical trials studying antifibrotic medications remains unclear. Given the emerging data that this technology can surrogate for liver fibrosis improvement, we remain optimistic for future larger-scale evidence to emerge in support of these early findings. Whether MRI-PDFF can also be routinely used to monitor treatment response to lifestyle modification is also unknown, although a recent lifestyle modification trial found subjects who completed 20 weeks of exercise training to achieve ≥30% relative reduction in MRI-PDFF at rates similar to those seen for early-phase NASH drug trials.[8]

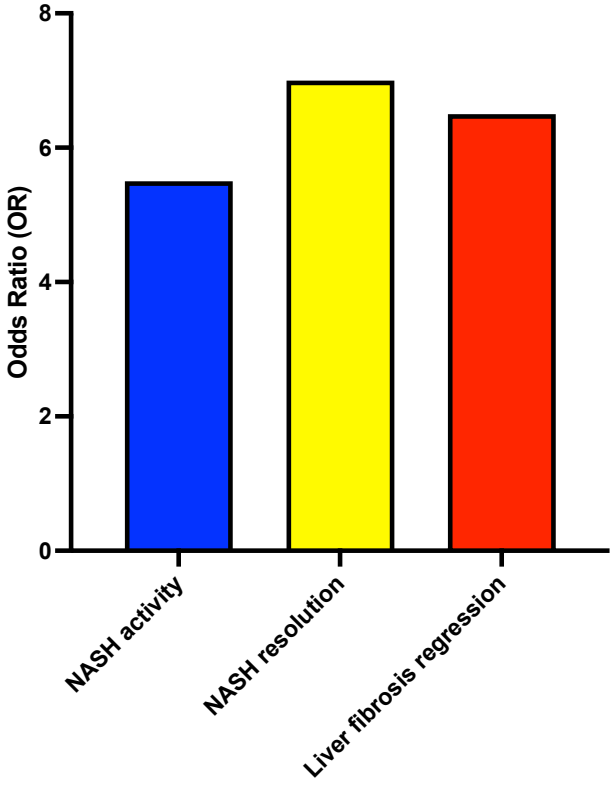

FIGURE 2 Odds of histological response if a ≥ 30% relative reduction in liver fat is achieved. NASH activity (reduction in NAS ≥ 2 without fibrosis worsening, OR 7.0, 95% CI: 2.4–20.4), NASH resolution (NAS < 4, OR 5.5, 95% CI: 1.5–19.5), and liver fibrosis regression (≥1 stage, OR 6.5, 95% CI: 1.1–37.0) can all be expected if the 30% or greater threshold of response is achieved.

The clinical implications of achieving a 30% or greater relative reduction in MRI-PDFF are also highly significant because liver fibrosis is an important factor associated with major adverse liver outcomes (MALOs) and overall survival in patients with NASH.[9] Targeting this minimal clinically important difference in MRI-PDFF may help guide clinicians in noninvasively determining treatment response from all types of intervention, including lifestyle modification and drug therapy. Prior to widespread adaptation of this therapeutic monitoring plan, additional prospective, longitudinal data are required, and we look to future clinical trials, including the NIMBLE consortium, to answer this important question.

The clinical role of MRI-PDFF may also be determined by its incorporation with the sister technology of magnetic resonance elastography (MRE), which has been shown to directly predict MALOs.[10] Both are widely available in commercial MRI systems. Importantly, PDFF maps can be automatically reconstructed without additional equipment, cost, or expertise. While we await validation of a threshold of treatment response for MRE, envisioning a complete treatment plan where MRI-PDFF and MRE are routinely combined seems on the horizon and can be viewed in similar fashion to the parameters reported by vibration-controlled transient elastography, where both liver fat (controlled attenuation parameter) and liver stiffness are measured. Moreover, MRI offers several advantages over vibration-controlled transient elastography, including greater accuracy, especially in patients with obesity, as well as in determining intermediate stages of liver fibrosis.

In summary, because liver biopsy has many well-known limitations, methods for routinely noninvasively monitoring treatment response in patients with NASH remains of great clinical importance. MRI-PDFF is a highly validated, quantitative, precise, reproducible, noninvasive imaging-based biomarker of treatment response that is now routinely incorporated into early-phase NASH clinical trials. Emerging evidence suggests that if a 30% or greater relative reduction in MRI-PDFF is achieved, histological improvement in NASH activity and liver fibrosis regression can be expected. At this time, future longitudinal prospective studies are needed to determine whether this threshold of MRI-PDFF reduction leads to a reduction in patient outcomes, including MALOs, as well as overall mortality.

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CONFLICT OF INTEREST

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