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Authors

Natarajan, Yamini
Loomba, Rohit

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Magnetic Resonance Elastography for the Clinical Risk Assessment of Fibrosis, Cirrhosis, and Portal Hypertension in Patients With NAFLD

Yamini Natarajan [*,†], Rohit Loomba [‡]

[*]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, USA, [†]Clinical Epidemiology and Comparative Effectiveness Program, Section of Health Services Research (IQuESt), Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, TX, USA and [‡]NAFLD Research Center, Division of Gastroenterology, Department of Medicine, University of California at San Diego, La Jolla, CA, USA

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming one of the most common causes of liver disease. The progressive subtype of NAFLD, nonalcoholic steatohepatitis (NASH), leads to cirrhosis, hepatocellular carcinoma, and mortality. Fibrosis is the strongest predictor for complications. Due to the invasive nature of liver biopsy, noninvasive testing methods have emerged to detect fibrosis and predict outcomes. Of these modalities, magnetic resonance elastography (MRE) has demonstrated the highest accuracy to detect fibrosis. In this review, we will focus on the emerging data regarding MRE and liver fibrosis, cirrhosis, and portal hypertension in NAFLD. (J Clin Exp Hepatol 2022;12:174–179)

Non-Alcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis on either imaging or histology in individuals who consume little or no alcohol and who do not have any secondary cause of hepatic steatosis such as medications, viral hepatitis, or human immunodeficiency virus infection.[1,2] NAFLD includes two subtypes: nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH). Steatosis, or increased fat content, is seen in both NAFL and NASH, but NASH also involves the presence of lobular inflammation and ballooning with or without perisinusoidal fibrosis.[3] Patients with NAFL are generally thought to have a benign course, but the NASH subtype is associated with increased risk of progression to cirrhosis, hepatocellular carcinoma (HCC), cardiovascular, and liver-related mortality.[1,4,5]

Paralleling the obesity epidemic, the clinical burden of NAFLD has increased steadily since the 1980s, currently affecting 25% of the global population. Even though a small percentage of patients with NAFLD have NASH, this population is burgeoning as well. It is estimated to affect 3–5% of the general population; this translates to over 30 million people worldwide.[6] The number of patients with NAFLD cirrhosis will likely double by the year 2030, leading to an estimated increase in 800,000 liver-related deaths.[7] NASH has become the number one indication in the United States for liver transplantation in women and patients older than 50.[8]

The presence of fibrosis strongly predicts mortality, rising dramatically with each stage greater than F2.[4] Liver biopsy is considered the gold standard to differentiate between NASH/NAFL, as well as identify fibrosis. However, this procedure is limited by its invasive nature, risk of bleeding, and other complications, and interobserver variability.[9,10] Noninvasive methods have been developed to detect fibrosis—these include serum calculators, genetic factors, and imaging modalities such as elastography.[11,12]

Of these modalities, MRE has emerged as the superior test to evaluate fibrosis. MRE differs from traditional MRI by utilizing an acoustic driver and a two-dimensional pulse sequence to generate shear waves within the liver. Unlike vibration-controlled transient elastography (VCTE), which evaluates shear waves at one location, MRE evaluates shear waves in four regional maps, called *elastograms*. These elastograms are interpreted in the context of the location of liver capsule, large blood vessels, and artifact. Liver stiffness is calculated in each region; an average of all four regions to determine mean 2D liver stiffness measurement (LSM).[13] Of note, these measurements are not on the same scale as VCTE, even though both are measured in kilopascals (kPa). Three-dimensional MRE, which obtains elastograms in multiple dimensions, has also shown promise in the evaluation of fibrosis.[14]

MRE has demonstrated superiority in diagnostic accuracy to other imaging modalities such as VCTE and 2-dimensional shear wave elastography (2D SWE) (Table 1).[15,16] Although VCTE and 2D SWE can assess LSM at particular points,

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Address for correspondence. Yamini Natarajan, MD, 2002 Holcombe Blvd (111-D), Houston, TX, 77030, USA.
E-mails: ynataraj@bcm.edu or roloomba@ucsd.edu; http://fattyliver.ucsd.edu
Abbreviations: HCC: hepatocellular carcinoma; LSM: liver stiffness measurement; MRE: magnetic resonance; NAFL: nonalcoholic fatty liver; NAFLD: Nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; VCTE: vibration-controlled transient elastography; 2D SWE: 2-dimensional shear wave elastography
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MRE can assess the stiffness of the entire liver. In addition, MRE performance is not affected by BMI, small ascites, and bowel gas. MRE is also less prone to operator error. Limitations of MRE include cost, access, and lack of portability. In this review, we will discuss MRE and its association with liver fibrosis, cirrhosis, and portal hypertension in patients with NAFLD. We refer the readers to other reviews that cover other aspects of noninvasive assessment.[12,15,17]

TECHNICAL CONSIDERATIONS

MRE can be performed on 1.5 T to 7 T MRI machines. Most patients are able to tolerate MRE, but they do need to be able to hold their breath for specific time periods. Liver stiffness is not affected by the presence of steatosis or increasing BMI.[18–20] Performance was similar in both male and female patients and does not vary with magnet strength.[19,21] Liver stiffness may be overestimated in patients with iron overload, large ascites, congestive hepatopathy, or acute inflammation; MRE should be interpreted keeping the clinical context of use in mind, especially in these patient populations.[22]

MRE FOR ASSESSMENT OF FIBROSIS

MRE has high diagnostic performance and a low failure rate for the assessment of fibrosis.[23] Interobserver variation is low and can be utilized on different types of MRI machines.[19] In a systematic review of 9 studies with 232 patients, MRE had a high AUROC for each stage of fibrosis: ≥F1—0.86 (cutoff: 2.88 kPa, sensitivity 0.75, specificity 0.77), ≥F2—0.87 (cutoff: 3.54 kPa, sensitivity 0.79, specificity 0.81), ≥F3—0.90 (cutoff: 3.77 kPa; sensitivity 0.83, specificity 0.86), ≥F4—0.91 (cutoff: 4.09 kPa; sensitivity 0.88, specificity 0.87).[19] These findings were confirmed in a 2019 systematic review and meta-analysis, which demonstrated higher diagnostic accuracy of MRE vs. VCTE at all stages of fibrosis.[21] There is a greater degree of discordance between VCTE and MRE measurements as BMI increases.[24] Three-dimensional MRE at 40 Hz has an even higher detection of advanced fibrosis in NAFLD compared to 2D MRE (AUROC 0.98 vs. 0.92).[14] This modality is not yet widely available clinically.

LONGITUDINAL ASSESSMENTS OF FIBROSIS

Changes in liver stiffness over time may also provide prognostic value in NAFLD. A prospective study of 100 patients

Table 1 Diagnostic Accuracy, Advantages, and Disadvantages of Noninvasive Measurements of Fibrosis.

Testing Modality	Cutoffs	AUROC	Advantages	Disadvantages
MRE	≥F1—2.88 kPa ≥F2—3.54 kPa ≥F3—3.77 kPa ≥F4—4.09 kPa	0.86 0.87 0.90 0.91	- Overall best performance - Performs well at high BMI - Can be easily performed with techniques to quantify liver fat - Largest area of the liver assessed	- Performed in radiology - Performed at a limited number of centers - Quality control not integrated - Lack of portability - Cost
VCTE	≥F2—4.8 to 8.2 (XL probe) ≥F3—5.7 to 9.3 (M Probe) ≥F3—7.6 to 8 (M Probe)	0.80 0.88 0.85	- Performed in liver clinic - Simultaneously quantify fat (CAP) - Integrated quality control - Larger area of liver assessed - No prior experience with ultrasound required	- Failure if narrow rib spaces - Failure if large ascites - Only measures CAP and LSM - Less cost-effective if also need an ultrasound
2-Dimensional Shear Wave Elastography	≥F2—2.67 to 9.4 ≥F3—3.02 to 10.6	0.88 0.95	- Low failure rate for experienced operators - Uses ultrasound probe	- Failure/lower accuracy as BMI increases - Learning curve: higher interobserver variability with less experienced operators
NAFLD Fibrosis Score	≥F3—0.67	0.84	- Easy to calculate - Clinical information for the score is often available	- Large number of individuals fall in the indeterminate range - Different cut-off values needed for younger or older participants - Limited usefulness in the general population
Fibrosis-4	≥F2—0.37 to 3.25 ≥F3—2.67	0.73 0.84	- Easy to calculate - Clinical information for the score is often available	- Large number of individuals fall in the indeterminate range - Various cutoffs used in studies - Limited usefulness in the general population
APRI	≥F2—1.0 ≥F3—1.5	0.76 0.77	- Easy to calculate - Clinical information for the score is often available	- Large number of individuals fall in the indeterminate range - Various cutoffs used in studies - Limited usefulness in the general population

MRE, magnetic resonance; VCTE, vibration-controlled transient elastography; NAFLD, nonalcoholic fatty liver disease.

determined that a 15% increase in LSM is associated with a threefold to fourfold increased risk of any progression of fibrosis stage and a fivefold increased risk of progression to advanced fibrosis.[25] Similarly, Gidener *et al.*, found that noncirrhotic patients that had a 1 kPa increase in LSM were threefold more likely to develop cirrhosis. In addition, cirrhotic patients that had a 1 kPa increase in LSM were prone to a fivefold increased risk of liver-related decompensation or mortality within 5 years.[26] Alternatively, weight loss is associated with a decrease in liver stiffness. Patients who had a 5% decrease in BMI experienced a ~16% decrease in liver stiffness.[13] A secondary analysis of phase II trial data for selonsertib showed that improvement in LSM measured by MRE was associated with improvement in fibrosis (48% positive predictive value, 79% negative predictive value). This study was limited by a small sample size.[27] Further studies are needed to confirm these outcomes and determine optimal intervals and cutoffs for changes in elastography.

In addition to elastography, changes in proton density fat fraction (PDFF) may be used to evaluate prognosis. PDFF is the MRI signal intensity ratio of fat to the sum of fat and water, reported as a percentage.[28] MRI-PDFF can assess regional variation of steatosis. Patients with high PDFF, defined as >15.7% had a sixfold to sevenfold increased risk of fibrosis progression on serial MRE (median time 1.4 years).[29] Conversely, improvements in PDFF are an independent predictor for fibrosis regression. Patients with a decrease of ≥30% PDFF are sevenfold more likely to have histologic improvement and 5.5 more likely to have a resolution of NASH.[30] This marker also predicts >1 stage improvement in fibrosis.[31] These data will need to be validated in future studies. Combining PDFF and MRE data may predict NASH (AUROC 0.87) and even estimate granular data previously only found on biopsy, such as NAFLD Activity Score (AUROC 0.85). The use of automated algorithms demonstrated high fidelity compared to expert radiologist interpretation.[32] These data are promising but need to be validated in larger multicenter studies.

MRE can be combined with serum markers to increase predictive capability and identify candidates for pharmacologic therapy. Using a FIB4 ≥1.6 and MRE liver stiffness ≥3.3 kPa identified NAFLD patients with ≥F2 fibrosis with a positive predictive value (PPV) of 97.1% ($P < 0.02$). This combination, known as MEFIB, was validated in a separate international cohort.[33] Studies are ongoing to determine how performance compares to the Fibroscan-AST score (FAST).

MRE FOR ASSESSMENT OF COMPENSATED CIRRHOSIS

MRE can be used to distinguish lower levels of fibrosis and cirrhosis. Studies evaluating the diagnostic performance of MRE for detection of cirrhosis have determined cutoffs of 3.35–6.7 kPa (AUROC 0.8–0.97).[21,27,34–38] Difference in findings can be accounted for by study population (single center vs. multicenter, Japan vs. western population). Based on a pooled analysis of individual participant data by Hsu, *et al.*, we consider liver stiffness ≥4.67 to be indicative of cirrhosis. To increase ease of use in clinical care, this can be rounded to 5 kPa.[21]

MRE FOR ASSESSMENT OF DECOMPENSATED CIRRHOSIS AND PORTAL HYPERTENSION

Increased levels of liver stiffness may be predictive of decompensated cirrhosis, portal hypertension, and liver-related outcomes. Baseline liver stiffness has been shown to be predictive of decompensated disease in a cohort of all etiologies.[39] Within a NAFLD cohort, the use of MRE to measure LSM with a cutoff of 6.48 kPa (AUROC 0.71) has been shown to differentiate between compensated and decompensated cirrhosis.[34] Evaluation of a NAFLD cohort at the Mayo demonstrated increasing LSM showed an increased risk of decompensation; a cutoff of 8 kPa is associated with a 20% risk of decompensation.[26] As noted above, a 1 kPa increase in liver stiffness confers a fivefold increased risk of mortality and liver-related events.[26] Baseline LSM by MRE has been shown to predict HCC and death in a cohort of patients with all types of chronic liver disease; these findings need to be specifically evaluated in NAFLD.[40]

Similarly, MRE may be used to rule out portal hypertension, minimizing the need for screening upper endoscopy for varices. One cross-sectional study of 627 patients using MRE cutoff 4.2 kPa and platelets >180,000 had a negative predictive value of 1.0.[41] This needs to be validated in prospective studies. MRE can be used to assess splenic stiffness in addition to liver stiffness. A 2021 meta-analysis found that splenic stiffness assessed by MRE had a sensitivity, specificity, and AUC values for spleen stiffness on MRE were 79% (95% CI 61–90%), 90% (95% CI 80–95%), and 92% (95% CI 89–94%), respectively (PMID: 32282542).[42] When evaluating specific manifestations of portal hypertension such as varices and ascites, liver stiffness has been used alone or in combination with spleen stiffness/spleen size in small series to predict the presence of esophageal varices.[43–47] These studies evaluated all types of liver disease and only included a small portion of NAFLD patients. In studies specifically evaluating NAFLD, the median LSM for patients with variceal bleeding was 10.15 kPa; however, this was limited by the small sample size.

There are limited data regarding the use of MRE to predict the development of ascites and hepatic encephalopathy. NAFLD patients with ascites or hepatic encephalopathy have higher median liver stiffness than those who do not. Further studies need to be done to evaluate cutoffs and the role of MRE in predicting these events.[34]

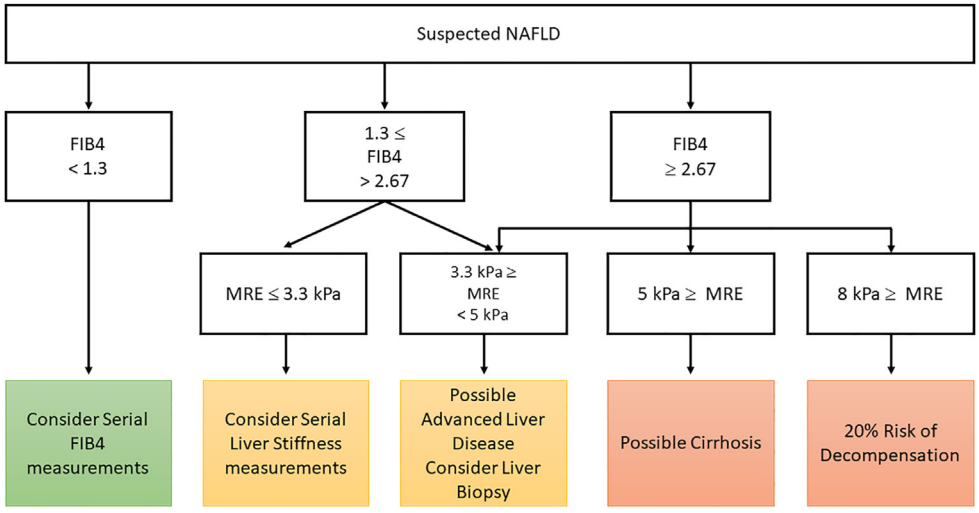

Figure 1 Risk Stratification of Patients with NAFLD using FIB4 and Magnetic Resonance Elastography. Abbreviations: NAFLD-Nonalcoholic Fatty liver disease; FIB4-Fibrosis-4 score; MRE- Magnetic Resonance Elastography; kPa-kilopascals.

THE BIG PICTURE

In patients with suspected NAFLD, we recommend a stepwise approach using FIB-4 score and MRE (Figure 1). For patients with FIB-4 < 1.3, no further assessment is needed; fibrosis can be assessed with a serial FIB-score. For patients with a FIB-4 score of >1.3, we recommend referral to a tertiary care center for MRE. Further management regarding biopsy, risk of cirrhosis, and decompensation is determined by LSM measurement.

The prevalence of NAFLD has grown considerably over the last two decades. Given the large burden of disease, the development of noninvasive testing is essential to risk stratification and monitoring. Magnetic resonance elastography has emerged as a comprehensive method to assess fibrosis throughout the liver. Longitudinal assessments may be predictive of disease progression or improvement. Additional studies are needed to determine the role of MRE in predicting liver-related outcomes and reducing the need for liver biopsy in patients with NAFLD.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Yamini Natarajan: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Rohit Loomba:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization.

CONFLICTS OF INTEREST

YN's institution has received grant support from Allergan and Gilead. RL serves as a consultant for Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Inipharm, Intercept, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sagimet, 89 bio, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Pfizer and Siemens. He is also co-founder of Liponexus, Inc.

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