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Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients with Biopsy-proven Nonalcoholic Fatty Liver Disease

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Abstract

Background & Aims—Magnetic-resonance-imaging (MRI) techniques and ultrasound-based transient elastography (TE) can be used in noninvasive diagnosis of fibrosis and steatosis in patients with nonalcoholic fatty liver disease (NAFLD). We performed a prospective study to compare the performance of magnetic resonance elastography (MRE) vs TE for in diagnosis of fibrosis, and MRI-based proton density fat fraction (MRI-PDFF) analysis vs TE-based controlled attenuation parameter (CAP) for diagnosis of steatosis in patients undergoing biopsy to assess NAFLD.

Methods—We performed a cross-sectional study of 104 consecutive adults (56.7% female) who underwent MRE, TE, and liver biopsy analysis (using the histological scoring system for NAFLD from the nonalcoholic steatohepatitis clinical research network scoring system) from October 2011 through May 2016 at a tertiary medical center. All patients received a standard clinical evaluation, including collection of history, anthropometric examination, and biochemical tests. The primary outcomes were fibrosis and steatosis. Secondary outcomes included dichotomized stages of fibrosis and NASH vs no NASH. Receiver operating characteristic (ROC) curve analyses were used to compare performances of MRE vs TE in diagnosis of fibrosis (stages 1–4 vs 0) and MRI-PDFF vs CAP for diagnosis of steatosis (grades 1–3 vs 0) with respect to findings from biopsy analysis.

Results—MRE detected any fibrosis (stage 1 or more) with an area under the ROC (AUROC) of 0.82 (95% CI, 0.74–0.91), which was significantly higher than that of TE (AUROC, 0.67; 95% CI, 0.56–0.78). MRI-PDFF detected any steatosis with an AUROC of 0.99 (95% CI, 0.98–1.00), which was significantly higher than that of CAP (AUROC, 0.85; 95% CI, 0.75–0.96). MRE detected fibrosis of stages 2, 3, or 4 with AUROC values of 0.89 (95% CI, 0.83–0.96), 0.87 (95% CI, 0.78–0.96), and 0.87 (95% CI, 0.71–1.00); TE detected fibrosis of stages 2, 3, or 4 with AUROC values of 0.86 (95% CI, 0.77–0.95), 0.80 (95% CI, 0.67–0.93), and 0.69 (95% CI, 0.45–0.94). MRI-PDFF identified steatosis of grades 2 or 3 with AUROC values of 0.90 (95% CI, 0.82–0.97) and 0.92 (95% CI, 0.84–0.99); CAP identified steatosis of grades 2 or 3 with AUROC values of 0.70 (95% CI, 0.58–0.82) and 0.73 (95% CI, 0.58–0.89).

Conclusions—In a prospective, cross-sectional study of more than 100 patients, we found MRE to be more accurate than TE in identification of liver fibrosis (stage 1 or more), using biopsy analysis as the standard. MRI-PDFF is more accurate than CAP in detecting all grades of steatosis in patients with NAFLD.

Keywords

noninvasive; assessment; comparative; biomarker

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is increasingly emerging as the predominant cause of chronic liver disease around the world.¹ In the United States, NAFLD is estimated

to affect nearly 100 million adults, or one-third of the population, and its prevalence is predicted to rise along with increasing rates of obesity, diabetes, and metabolic syndrome.^{2,3} NAFLD ranges from simple benign hepatic steatosis or nonalcoholic fatty liver (NAFL) to severe hepatocellular inflammation known as nonalcoholic steatohepatitis.^{4,5} This latter condition is estimated to affect 5% of the US population and carries higher risk of progressing to cirrhosis and hepatocellular carcinoma.⁶⁻⁸ Although liver biopsy is the current gold standard for assessing NAFLD, its accuracy has been questioned because of sampling errors and variable intra- and inter-observer agreement.⁹⁻¹¹ Moreover, biopsy is invasive, which limits use as a population screening tool. Thus, there is a need for accurate, noninvasive methods that can clinically assess NAFLD.

Liver fibrosis and steatosis are two features of NAFLD that have been investigated by noninvasive imaging tests to assess NAFLD. Transient elastography (TE; FibroScan®) is an ultrasound-based imaging technique that allows rapid, bed-side measurements of tissue stiffness.¹² TE-based liver stiffness measurements using the M Probe have shown to correlate with stages of fibrosis, particularly in severe fibrosis and cirrhosis.¹³⁻¹⁵ Additionally, the controlled attenuation parameter (CAP) allows TE to simultaneously assess steatosis.¹⁶⁻¹⁸ An important limitation of TE is the high failure rates in obese patients with BMI of > 28 kg/m²,^{19,20} which limits reliable measurement of liver stiffness and steatosis in a significant portion of obese NAFLD patients. However, the new XL probe equipped with CAP has shown to reduce the failure rate for measuring fibrosis and steatosis in obese patients.^{21,22}

Magnetic resonance imaging (MRI)-based techniques such as magnetic resonance elastography (MRE) and proton density fat fraction (MRI-PDFF) have shown to accurately diagnose fibrosis and steatosis, respectively, in NAFLD patients.²³⁻²⁹ Although MRI-based techniques have shown to be accurate and effective in patients with obesity,³⁰ they are more expensive and not widely available compared to TE.³¹ A recent Japanese study by Imajo et al.³² directly compared and demonstrated that MRE and MRI-PDFF have higher accuracy than TE and CAP, respectively, for diagnosing fibrosis and steatosis in NAFLD patients. However, this study assessed TE using only the M probe. Therefore, TE using M or XL probe, when indicated, has not been compared to MRE. Furthermore, MRI-based techniques and TE have not yet been compared in a western cohort of NAFLD patients, who are likely to have higher BMI and may have other characteristics that may affect the diagnostic performance of TE and MRE.

Using a well-characterized, prospective cohort of American adults with biopsy-proven NAFLD, we compared the accuracy of TE versus MRE for diagnosing fibrosis, and CAP versus MRI-PDFF for diagnosing steatosis in NAFLD patients. We hypothesize that MRE is superior to TE for diagnosing early fibrosis, and that MRI-PDFF is superior to CAP for diagnosing steatosis in NAFLD patients.

MATERIALS AND METHODS

Study Design

This was a prospective, cross-sectional study of patients with suspected NAFLD who underwent contemporaneous MRI and TE with a liver biopsy assessment. Between October 2011 and May 2016, 104 adult patients with clinical indication for liver biopsies for suspected NAFLD were consecutively enrolled with written informed consent. After undergoing evaluation for other causes of hepatic steatosis and liver disease, patients were invited to undergo standardized history, physical and anthropometric exam, laboratory testing, MRI at the UCSD MR3T Research Laboratory, and TE at the UCSD NAFLD Research Center.^{4, 33-37} This study was HIPAA compliant and approved by the UCSD Institutional Review Board and the Clinical and Translational Research Institute.

Inclusion/Exclusion criteria

We included patients 18 years old with suspected NAFLD patients who are willing and able to provide informed consent. Exclusion criteria were: history of significant alcohol intake within 2 years of recruitment (14 drinks/week for men or 7 drinks/week for women); any evidence of secondary causes of hepatic steatosis including nutritional, iatrogenic, or infectious etiology or HIV infection; evidence of liver diseases other than NAFLD, which include viral hepatitis (screened by positive serum hepatitis B surface antigen and hepatitis C RNA assays), autoimmune hepatitis, genetic or acquired disorders such as hemochromatosis, Wilson's disease, glycogen storage disease, alpha-1 antitrypsin deficiency, and cholestatic or vascular liver disease; evidence of decompensated liver disease (defined as Child-Pugh score > 7 points); active substance use; major systemic illnesses; contraindication(s) to MRI; pregnant or trying to be pregnant; or any other conditions believed by the principal investigator to affect patient's competence, compliance, or completion of the study.

Clinical Research Evaluation

All patients underwent a standardized clinical evaluation which included history, anthropometric exam, and biochemical tests at the UCSD NAFLD Research Center. Documented information from history and anthropometric exam included age, sex, height, weight, BMI, ethnic background, vital signs. Alcohol intake history was assessed in prior clinical visits and re-assessed at the research unit with the Alcohol Use Disorders Identification Test and the Skinner questionnaire. Other causes of liver diseases and secondary causes of hepatic steatosis such as steatogenic medications were ruled out systematically using history and biochemical tests. Biochemical tests included aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, albumin, fasting glucose, hemoglobin A1c, insulin, triglycerides, total cholesterol, HDL, LDL, platelet, prothrombin time and international normalized ratio.

Histologic Evaluation

All patients underwent liver biopsy for assessment by an experienced liver pathologist who was blinded to the patient's clinical and radiological data. Histologic scoring was done using the Nonalcoholic Steatohepatitis Clinical Research Network Histologic Scoring System.³⁸ This scoring system is further described in the **Supplementary Material**.

Outcome measures

The primary outcomes were fibrosis (stage 1-4 versus 0) and steatosis (grade 1-3 versus 0). Secondary outcomes included dichotomized stages of fibrosis (stage 2-4 (significant fibrosis) versus 0-1, stage 3-4 (advanced fibrosis) versus 0-2, and stage 4 (cirrhosis) versus stage 0-3), grades of steatosis (grade 2-3 versus 0-1, and grade 3 versus 0-2), and NASH versus no NASH.

Magnetic Resonance Imaging

MRI of the abdomen was performed at the UCSD MR3T Research Laboratory on a single 3T MR scanner (GE Signa EXCITE HDxt, GE Healthcare, Waukesha, WI). MRI-PDFF sequences were acquired according to previously-published methods.^{28, 29, 39} The median time interval between MRI and biopsy was 42 days.

Magnetic Resonance Elastography

MRE was performed according to previously described methods^{25, 30, 40} on commercially available software and hardware (Resoundant, Inc., Rochester, MN) and is further described in the **Supplementary Material**.

Transient Elastography

Transient elastography was performed using the FibroScan® 502 Touch model (M Probe; XL Probe; Echosens, Paris, France) by a trained technician, blinded to clinical and histologic data, according to previously-described methods.^{12, 22} Briefly, patients were asked to fast at least 3 hours prior to the exam. The procedure was performed in the supine position with the right arm fully adducted during a 10 second breath hold. Based on the manufacturer's recommendation, all patients were first scanned by applying the M probe (3.5 MHz) over the area of abdomen at the location of the right liver lobe. When indicated by the equipment upon initial assessment, patients were re-scanned using the XL probe (2.5 MHz). A minimum of 10 measurements was made to obtain the median valid liver stiffness measurements in kilopascals (kPa) and the interquartile range (IQR). Technical failure was defined as no stiffness measurement obtained or unreliable measurements (defined as success rate < 60% and/or IQR/med >30%).⁴¹ Simultaneous liver steatosis measurements were obtained using the CAP values in dB/m, co-localized to the valid liver stiffness measurements. All CAP data were collected prospectively. The median time interval between TE and biopsy was 107 days.

Statistical Analyses

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Patients' demographic, biochemical, and histological, and imaging characteristics were summarized

as mean and standard deviation for continuous variables and numbers and percentages for categorical variables. A two-tailed P value < 0.05 was considered statistically significant. **Main analyses:** Receiver operating characteristic (ROC) curve analyses were used to compare the performances of MRE versus TE for diagnosing fibrosis (stage 1-4 versus 0), and MRI-PDFF versus CAP for diagnosing steatosis (grade 1-3 versus 0) with respect to biopsy. For each ROC analysis, the area under the ROC curve (AUROC), the optimal thresholds, and the following performance parameters were calculated: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The optimal threshold of each modality was determined using the Youden index.⁴² The Delong test was used to compare the AUROCs of MRE versus TE for diagnosing fibrosis, and CAP versus MRI-PDFF for diagnosing steatosis.⁴³ Multivariable ROC analyses were performed to assess the effect of biopsy-to-imaging time interval and probe type on the AUROCs.

Secondary analyses

The following additional ROC curve analyses were performed: MRE versus TE for diagnosing other dichotomized stages of fibrosis (stage 2-4 0-1, stage 3-4 versus 0-2, and stage 4 versus 0-3) and NASH versus no NASH; and MRI-PDFF versus CAP for diagnosing other dichotomized grades of steatosis (grade 2-3 versus 0-1, and grade 3 versus 0-2). The Kruskal-Wallis test was used to compare liver stiffness and steatosis measurements between groups at different stages of fibrosis and grades of steatosis, respectively.

RESULTS

Baseline Characteristics

In this prospective study, 104 patients with liver biopsy, MRI, and TE were consecutively enrolled. The mean (\pm SD) age and body mass index were 50.8 (\pm 14.6) and 30.4 (\pm 5.2), respectively. Baseline cohort characteristics are summarized in **Table 1**. A total of 110 patients with biopsy-proven NAFLD were initially seen at the NAFLD Research Center, although 6 patients were excluded because TE was not performed. Of the 104 TE examinations, 7 exams (6.7%) resulted in technical failure.

Distribution of fibrosis stages and steatosis grades

Respectively, 47, 24, 11, 13, and 8 patients had stage 0, 1, 2, 3, and 4 fibrosis; and 9, 49, 29, and 16 patients had grade 0, 1, 2, and 3 steatosis.

Comparison of MRE and TE for diagnosing fibrosis

MRE had an AUROC of 0.82 (95% CI 0.74-0.91) for diagnosing fibrosis stage 1-4 versus 0. Using a threshold of 2.65 kPa, MRE had a sensitivity of 76.5%, specificity of 79.1%, PPV of 81.3%, and NPV of 73.9% (**Figure 1**). TE had an AUROC of 0.67 (95% CI 0.56-0.78) for diagnosing fibrosis. Using a threshold of 6.10 kPa, TE had a sensitivity of 66.7%, specificity of 65.1%, PPV of 69.4%, and NPV of 62.2%. Direct comparison using the Delong Test showed that MRE is significantly more accurate than TE ($P = 0.0116$) for diagnosing any fibrosis (**Table 2**).

Comparison of MRE and TE for diagnosing other dichotomized stages of fibrosis

The AUROCs of MRE and TE for diagnosing other dichotomized stages of fibrosis are summarized in **Table 2**. For diagnosing stages 2-4 versus 0-1, stage 3-4 versus 0-2, and stage 4 versus 0-3 fibrosis, respectively, MRE had AUROCs of 0.89 (95% CI 0.83-0.96), 0.87 (95% CI 0.78-0.96), and 0.87 (95% CI 0.71-1.00), and TE had AUROCs of 0.86 (95% CI 0.77-0.95), 0.80 (95% CI 0.67-0.93), and 0.69 (95% CI 0.45-0.94). Direct comparisons showed that MRE is more accurate than TE for diagnosing any fibrosis (stage 1-4 versus 0), but no significant difference existed between MRE and TE for diagnosing other dichotomized stages of fibrosis. Distributions of liver stiffness measurements by MRE and TE are illustrated in **Figure 3a**.

The mean (\pm SD) liver stiffness for stage 0, 1, 2, 3, and 4 fibrosis measured by MRE was 2.37 (\pm 0.38), 2.82 (\pm 0.65), 3.49 (\pm 0.71), 4.51 (\pm 1.74), and 5.16 (\pm 1.62) kPa, respectively. Similarly, the mean (\pm SD) liver stiffness for stage 0, stage 1, 2, 3, and 4 fibrosis by TE was 6.89 (\pm 10.37), 8.07 (\pm 13.48), 9.89 (\pm 2.67), 11.3 (\pm 4.93) and 10.39 (\pm 4.95), respectively.

Comparison of MRE and TE for diagnosing histologic NASH

For diagnosing NASH, MRE had AUROC of 1.70 (95% CI 0.57-0.82), which was significantly higher than TE AUROC ($p=0.0011$) of 0.35 (95% CI 0.22-0.49).

Comparison of MRI-PDFF and CAP for diagnosing steatosis

MRI-PDFF had an AUROC of 0.99 (95% CI 0.98-1.00) for diagnosing any steatosis (grades 1-3 versus 0). Using a threshold of 3.71 %, MRI-PDFF had a sensitivity of 95.8%, specificity of 100%, PPV of 100%, and NPV of 70.0% for diagnosing steatosis (**Figure 2**). CAP had an AUROC of 0.85 (95% CI 0.75-0.96). Using a threshold of 261 dB/m, CAP had a sensitivity of 71.8%, specificity of 85.7%, PPV of 98.1%, and NPV of 23.1%. Direct comparison showed that MRI-PDFF is more accurate than CAP for diagnosing ($P=0.0091$) any steatosis (**Table 3**).

Comparison of MRI-PDFF and CAP for diagnosing other dichotomized grades of steatosis

The AUROCs of MRI-PDFF and CAP for diagnosing other dichotomized grades of steatosis are summarized in **Table 3**. For diagnosing grade 2-3 versus 0-1 and grade 3-4 versus 0-2 steatosis, respectively, MRI-PDFF had AUROCs of 0.90 (95% CI 0.82-0.97) and 0.92 (95% CI 0.84-0.99), and CAP had AUROCs of 0.70 (95% CI 0.58-0.82) and 0.73 (95% CI 0.58-0.89). Direct comparison showed that MRI-PDFF was more accurate than CAP at all dichotomization cutoff points for diagnosing steatosis. Distributions of liver steatosis measurements by MRI-PDFF and CAP are illustrated in **Figure 3b**.

Multivariable-adjusted ROC analyses adjusted for biopsy-to-imaging time interval and probe type

The adjusted ROC analyses are summarized in **Supplementary Tables 1 and 2**. There was no significant difference in the performances of MRE, TE, MRI-PDFF, or CAP between unadjusted and adjusted models, when either biopsy-to-imaging time interval or type of probe were included as covariates.

DISCUSSION

Summary of main findings

Using a prospective, well-characterized, United States based cohort of patients, this study demonstrates that MRE is more accurate than TE for diagnosing liver fibrosis in patients with NAFLD. The key novelty of this study is that this is first study using XL-probe to perform head to head comparison between MRE versus TE, and MRI-PDFF versus CAP, and provided estimates of differences in diagnostic accuracy of these modalities in a Western NAFLD population that has a higher BMI than Asian NAFLD population so these results are more generalizable to Western cohorts.

Furthermore, this study showed that MRI-PDFF is significantly more accurate than CAP for diagnosing all dichotomized grades of hepatic steatosis. These results may have important implications in developing an optimal clinical approach for noninvasive assessment of NAFLD. Although cost-effectiveness studies are needed to determine the optimal approach, we propose that an MRI-based approach may be preferable to TE when accurate steatosis and fibrosis quantification is needed such as in the setting of a clinical trial because MR based methods have higher precision and accuracy than TE based assessment. TE may be preferable in routine clinical assessment at the level of population for screening out advanced fibrosis among low risk patient populations. However, further studies are needed to draw more definite conclusions.

In the context of published literature

This is the first prospective study to directly compare the accuracy of MRE and TE for diagnosing fibrosis, and MRI-PDFF versus CAP for diagnosing steatosis in a well-characterized cohort of American adults with biopsy-proven NAFLD. Both MRE and TE were not adequate for diagnosing NASH. Our study is consistent with prior studies showing MRI to have high diagnostic accuracy for fibrosis and steatosis in NAFLD patients.^{23-25, 28, 29} Our study is also consistent with prior studies showing TE to have high negative predictive value for diagnosing significant fibrosis (stages 2-4), severe fibrosis (stages 3-4), and cirrhosis,^{14, 15} and CAP to be accurate for diagnosing any steatosis, but not at higher dichotomized grades of steatosis.^{17, 18}

A recent seminal study by Imajo et al.³² has shown that MRE is more accurate than TE for diagnosing significant fibrosis (stage 2-4 versus 0-1) and cirrhosis in Japanese NAFLD patients. In comparison, our study showed that MRE is more accurate than TE for diagnosing any fibrosis (stage 1-4 versus 0) but not cirrhosis ($p = 0.0546$) Although Imajo et al. assessed TE with using the M probe only, we also used the XL probe when indicated during our examination ($n = 53$). Our cohort demographical characteristics such as race and higher BMI ($30.5 \pm 5.2 \text{ kg/m}^2$) may have reflected a more accurate assessment of the diagnostic performances and cutoffs of MRI and TE in a Western population. Future studies with larger cohort of patients may be needed to determine the optimal cutoff points for MRI-PDFF versus CAP for the grade of steatosis in NAFLD as well as MRE versus TE for the stage of fibrosis in NAFLD, which may be different for Western NAFLD population versus Asian NAFLD population.

Liver fibrosis and steatosis are clinically important features NAFLD that have been investigated by non-invasive tests such as MRI and TE. Steatosis alone is known to progress to NASH and fibrosis.⁸ Moreover, any fibrosis, even in the absence of severe fibrosis (stages 3-4), compared to no fibrosis was shown to be associated with increased mortality or liver transplantation rate in NAFLD patients.⁴⁴ Therefore, early diagnosis and screening of fibrosis and steatosis before progression to severe fibrosis and/or NASH may benefit NAFLD patients. We acknowledge that liver histology, liver stiffness by TE, liver stiffness by MRE, ultrasound attenuation for CAP assessment, and steatosis quantification by MRI-PDFP all assess different properties using different physical properties. Therefore, although some of these would be co-linear with each other, they are not likely to be identical as each assesses different properties of liver tissue. Furthermore, the prognostic significance of changes in liver fat have not yet been assessed in long-term clinical trials, reduction in liver fat content by MRI-PDFP may have utility in short term trials, as previously shown.^{34, 45, 46} Our study shows that MRI-based techniques are superior to TE for detecting any fibrosis and steatosis in NAFLD patients who may be at increased risk for mortality and other poor prognostic outcomes. Other advantages of MRI-based techniques over TE include larger area of the liver measured, which may reduce sampling variability secondary to heterogeneity of fibrosis,^{9, 11} and the utility of MRI-PDFP for assessing longitudinal changes in steatosis.⁴⁷ Although TE has excellent inter- and intra-operator reproducibility⁴⁸ and is accurate for diagnosing cirrhosis,¹² its applicability is limited by high failure rates in patients with narrow intercostal space and ascites,¹² interference of liver stiffness measurements by extrahepatic cholestasis and acute liver injury,^{49, 50} and reduced reproducibility in early stages of fibrosis and in the presence of steatosis.^{48, 51}

Strengths and limitations

The strength of this study included use of well-characterized, prospective cohort of NAFLD patients undergoing liver biopsy for clinical indication. Liver biopsy, used as the reference standard for imaging, was scored using the NASH Clinical Research Network Histologic Scoring System, which is well-validated for assessing NAFLD patients. This study was performed by experienced investigators at a dedicated research center that is specialized for both clinical and radiologic research in NAFLD, and patients were carefully evaluated to exclude for other causes of liver disease before inclusion in the study.

However, this study also had the following limitations. The cross-sectional design of the study did not allow the assessment of MRE and TE for monitoring longitudinal changes in fibrosis. Since this was a single center study in a highly specialized setting, the generalizability of its findings in other clinical settings is unknown. The median time interval between TE and biopsy was 107 days. A recent meta-analysis of paired liver biopsy studies has shown that the rate of fibrosis progression is slow, with an average progression of one stage to take 14.3 years in patients with NAFL and 7.1 years in patients with NASH⁶. Therefore, our time interval is reasonable as fibrosis stage is unlikely to change within a year. Furthermore, our analyses showed that the biopsy to imaging time interval did not affect the diagnostic accuracy of MRI and TE. Nevertheless, rapid changes in steatosis are possible, and ideally biopsy and imaging should be performed contemporaneously within 1 week, if feasible. MRI-based techniques, including MRE and MRI-PDFP, are often

expensive, although at our center the cost of MRE is lower than that of biopsy without the associated morbidity. Although TE is more widely available in some parts of the world, MRI techniques are more widely deployed in the United States (US), therefore MRE can also be made available on commercially available MRI platforms throughout the US. While TE may be more useful for wide-spread screening, MRE may play a role in clinical trial assessments that require higher accuracy and precision. Further studies are needed to evaluate the cost-effectiveness of MRI over TE for diagnosing NAFLD-related fibrosis and steatosis in before implementing these competing noninvasive approaches in routine clinical practice.

Implication for future research

Using prospective, head-to-head comparisons, we showed that MRI-based MRE and MRI-PDFF are significantly more accurate than ultrasound-based TE and CAP, respectively, for diagnosing fibrosis and steatosis in an American cohort of patients with biopsy-proven NAFLD. MRI-based techniques may be preferable to TE for accurate noninvasive assessment of NAFLD. Future studies are necessary to assess the clinical utility of MRI and TE for diagnosing fibrosis and steatosis in a multicenter, longitudinal design, both in observational and intervention studies. The cost-effectiveness of utilizing MRE versus TE and/or biopsy must also be evaluated to develop optimal diagnostic strategies for diagnosing NAFLD-associated fibrosis and steatosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AUROC	area under the receiver operator characteristic curve
BMI	body mass index
CAP	controlled attenuation parameter
CI	confidence interval
MRE	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
NAFLD	nonalcoholic fatty liver disease

NASH	nonalcoholic steatohepatitis
TE	transient elastography
UCSD	University of California at San Diego

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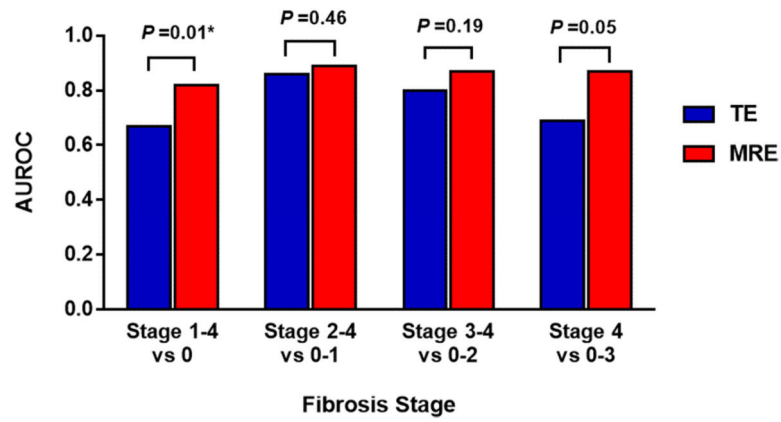


Figure 1. Diagnostic accuracy of MRE and TE for diagnosing dichotomized stages of fibrosis. MRE was significantly better than TE for diagnosis of any fibrosis with an AUROC of 0.82 (red bar) versus 0.67 ($P=0.01$).

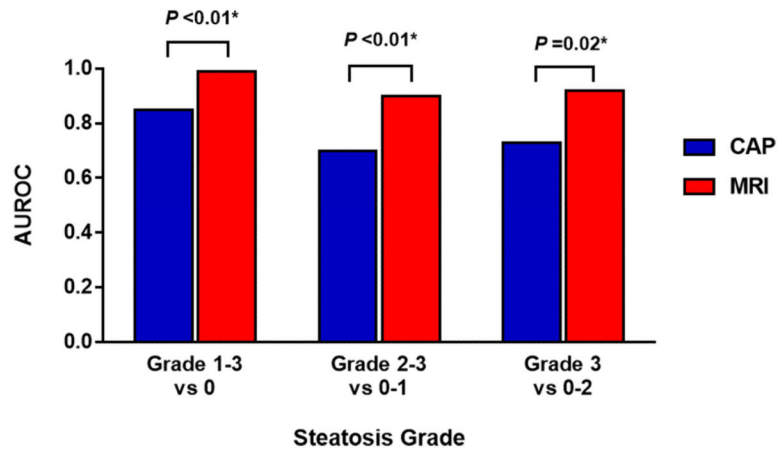


Figure 2. Diagnostic accuracy of MRI-PDFF and CAP for diagnosing dichotomized grades of steatosis. MRI-PDFF was significantly better than CAP for all comparison including grade 0 versus grade 1-3, grade 0-1 versus grade 2-3, grade 0-2 versus grade 3.

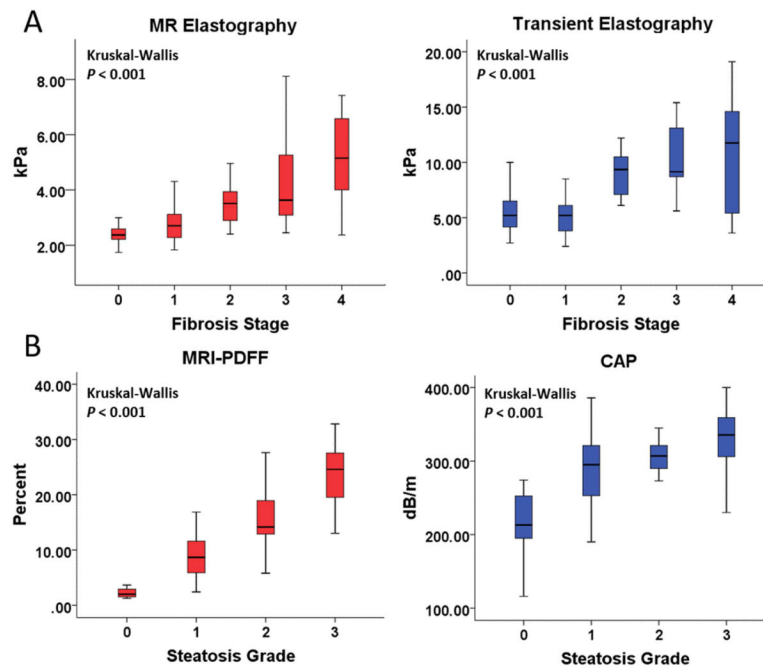


Figure 3.

Figure 3a: Distribution of liver stiffness measurements by MRE and TE stratified by fibrosis stage. Stiffness measurements by both MRE and TE increased with increasing fibrosis stage (Kruskal-Wallis test $P < 0.001$)

Figure 3b: Distribution of steatosis measurements by MRI-PDFF and CAP stratified by steatosis grade. Steatosis measurements by both MRI-PDFF and CAP (Kruskal-Wallis $P < 0.001$) increased with increasing steatosis grade.

Table 1

Demographical, biochemical, histological, and imaging characteristics of study cohort

Patients (n=104)	
Demographic	
Age at biopsy, mean (s.d.)	50.8 (14.6)
Male, n (%)	45 (43.3)
Female, n (%)	59 (56.7)
Height (m), mean (s.d.)	1.7 (0.1)
Weight (kg), mean (s.d.)	86.1 (17.9)
BMI (kg/m ²), mean (s.d.)	30.4 (5.2)
Race	
White, n (%)	48 (47.1)
African American, n (%)	0 (0)
Asian, n (%)	21 (20.5)
Hispanic, n (%)	32 (31.4)
Other, n (%)	1 (1.0)
Diabetes, n (%)	29 (27.9)
Biochemical profile	
AST (U/l), median (iqr)	31.0 (15.0)
ALT (U/l), median (iqr)	42.0 (34.0)
AST/ALT ratio, median (iqr)	0.8 (0.4)
Alkaline Phosphatase (U/l), median (iqr)	71.0 (30.5)
GGT (U/l), median (iqr)	35.0 (37.0)
Total bilirubin (mg/dl), median (iqr)	0.4 (0.3)
Direct bilirubin (mg/dl), median (iqr)	0.2 (0.1)
Albumin (g/dl), median (iqr)	4.5 (0.5)
Glucose (mg/dl), median (iqr)	98.0 (31.5)
Hgb A1C (%), median (iqr)	5.8 (0.8)
Insulin (u), median (iqr)	21.5 (20.0)
Triglycerides (mg/dl), median (iqr)	133.0 (92.0)
Total cholesterol (mg/dl), median (iqr)	180.0 (56.0)
HDL (mg/dl), median (iqr)	47.0 (19.0)
LDL (mg/dl), median (iqr)	100.0 (52.0)
Platelet count (10 ⁹ /L), median (iqr)	223000 (77000)
Prothombin time, median (iqr)	10.8 (1.0)
INR, median (iqr)	1.0 (0.1)
Histology	
Fibrosis	
0	47 (45.6)
1	24 (23.3)
2	11 (10.7)
3	13 (12.6)

Patients (n=104)	
4	8 (7.8)
Steatosis	
0	9 (8.7)
1	49 (47.6)
2	29 (28.2)
3	16 (15.5)
Lobular inflammation	
0	4 (3.9)
1	53 (52.0)
2	41 (40.2)
3	4 (3.9)
Ballooning	
0	43 (43.4)
1	44 (44.4)
2	12 (12.2)
NASH	
No NAFLD, n (%)	4 (4.0)
NAFLD, not NASH, n (%)	20 (20.0)
Borderline NASH, n (%)	13 (13.0)
Definite NASH, n (%)	63 (63.0)
NAS mean (SD)	3.8 (1.4)
Imaging	
TE (kPa), median (IQR)	6.1 (4.6)
CAP, median (IQR)	299 (80.0)
MRE(kPa), median (IQR)	2.7 (1.0)
MRI-PDFF (%), median (IQR)	11.5 (10.4)
Use of M probe, n (%)	51 (49.0)
Use of XL probe, n (%)	53 (51.0)
Technical Failures of Fibroscan, n (%)	7 (6.7)

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; GGT, Gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; Hgb, Hemoglobin; INR, international normalized ratio; kPa, kilopascal; NAFLD, LDL, low-density lipoprotein; Nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, Nonalcoholic steatohepatitis; SD, Standard deviation

Table 2

Diagnostic test characteristics of TE and MRE for the Diagnosis of Fibrosis

Overall N=94	AUROC (95% CI)	Threshold (kPa)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	TE vs MRE (p)*
<i>Primary analysis</i>							
Stage 1-4 (n=51)							
MRE	0.82 (0.74-0.91)	2.65	76.5	79.1	81.3	73.9	
Stage 0 (n=43)							
TE	0.67 (0.56-0.78)	6.10	66.7	65.1	69.4	62.2	0.0116
<i>Secondary analyses</i>							
Stage 2-4 (n=29)							
MRE	0.89 (0.83-0.96)	2.86	79.3	81.8	65.7	89.8	
Stage 0-1 (n=65)							
TE	0.86 (0.77-0.95)	6.90	79.3	84.6	69.7	90.2	0.4596
Stage 3-4 (n=18)							
MRE	0.87 (0.78-0.96)	2.99	77.8	80.3	48.3	93.8	
Stage 0-2 (n=76)							
TE	0.80 (0.67-0.93)	7.30	77.8	77.6	45.2	93.7	0.1942
Stage 4 (n=8)							
MRE	0.87 (0.71-1.00)	3.35	75.0	81.4	27.3	97.2	
Stage 0-3 (n=86)							
TE	0.69 (0.45-0.94)	6.90	62.5	66.3	14.7	95.0	0.0546
NAASH (n=72)							
MRE	0.70 (0.57-0.82)	2.53	63.9	68.2	86.8	36.6	
no NAASH (n=22)							
TE	0.35 (0.22-0.49)	5.60	61.1	59.1	83.0	31.7	0.0011

AUROC: Area under receiver operating characteristic curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

* p value: AUROC of TE versus MRE via Delong Test

Table 3
Diagnostic test characteristics of CAP and MRI-PDFF for the Diagnosis of Steatosis

Overall N=78	AUROC (95% CI)	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PDFF vs CAP (p) [*]
<i>Primary analysis</i>							
Grade 1-3 (n=71)	0.99 (0.98-1.00)	3.71	95.8	100	100	70.0	
Grade 0 (n=7)	0.85 (0.75-0.96)	261	71.8	85.7	98.1	23.1	0.0091
<i>Secondary analyses</i>							
Grade 2-3 (n=30)	0.90 (0.82-0.97)	13.03	80.0	83.3	75.0	87.0	
Grade 0-1 (n=48)	0.70 (0.58-0.82)	305	63.3	68.8	55.9	75.0	0.0017
Grade 3 (n=11)	0.92 (0.84-0.99)	16.37	81.8	83.6	45.0	96.6	
Grade 0-2 (n=67)	0.73 (0.58-0.89)	312	63.6	70.1	25.9	92.2	0.0238

AUROC: Area under receiver operating characteristic curve; CAP: Controlled attenuation parameter; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value
* p value: AUROC of CAP versus PDFF via Delong Test