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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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CLINICAL LIVER

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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 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 histologic 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 nonalcoholic steatohepatitis vs no nonalcoholic steatohepatitis. Receiver operating characteristic 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 receiver operating characteristic curve (AUROC) of 0.82 (95% confidence interval [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.

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 rates of obesity, diabetes, and metabolic syndrome.[2,3] NAFLD ranges from simple benign hepatic steatosis or nonalcoholic fatty liver to severe hepatocellular inflammation known as nonalcoholic steatohepatitis.[4,5] This latter condition is estimated to affect 5% of the US population and carries a 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] In addition, biopsy is invasive, which limits its use as a population

Abbreviations used in this paper: **AUROC, area under the receiver operator characteristic curve; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NPV, negative predictive value; PPV, positive predictive value; TE, transient elastography; UCSD, University of California at San Diego.**

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screening tool. There is a need for accurate, noninvasive methods that can clinically assess NAFLD.

Liver fibrosis and steatosis are 2 features of NAFLD that have been investigated by noninvasive imaging tests to assess NAFLD. Transient elastography (TE; FibroScan, Echosens, Paris, France) is an ultrasound-based imaging technique that allows rapid, bedside 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 body mass index (BMI) >28 kg/m^2, which limits reliable measurement of liver stiffness and steatosis in a significant portion of obese NAFLD patients.[19,20] However, the new XL probe equipped with CAP has been 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 (PDFF) have been shown to accurately diagnose fibrosis and steatosis, respectively, in NAFLD patients.[23–29] Although MRI-based techniques have been found to be accurate and effective in patients with obesity,[30] they are more expensive and not widely available compared with 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 the M probe only. Therefore, TE using M or XL probe, when indicated, has not been compared with 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 can 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 vs MRE for diagnosing fibrosis, and CAP vs 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, one hundred and four 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 examination, laboratory testing, MRI at the University of California at San Diego (UCSD) MR3T Research Laboratory, and TE at the UCSD NAFLD Research Center.[4,33–37] This study was Health Insurance Portability and Accountability Act of 1996–compliant and approved by the UCSD Institutional Review Board and the Clinical and Translational Research Institute.

Inclusion/Exclusion Criteria

We included patients $\geq$18 years old with suspected NAFLD patients who are willing and able to provide informed consent. Exclusion criteria were history of significant alcohol intake within 2 years of recruitment ($\geq$14 drinks/wk for men or $\geq$7 drinks/wk for women); any evidence of secondary causes of hepatic steatosis, including nutritional, iatrogenic, or infectious etiology or human immunodeficiency virus 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, α-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 become 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 that included history, anthropometric examination, and biochemical tests at the UCSD NAFLD Research Center. Documented information from history and anthropometric examination included age, sex, height, weight, BMI, ethnic background, and vital signs. Alcohol intake history was assessed in prior clinical visits and reassessed 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, γ–glutamyl transpeptidase, total bilirubin, direct bilirubin, albumin, fasting glucose, hemoglobin A1c, insulin, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, 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 radiologic data. Histologic scoring was done using the Nonalcoholic Steatohepatitis Clinical Research Network Histologic Scoring System.[38] This scoring system is described further in the Supplementary Material.

Outcome Measures

The primary outcomes were fibrosis (stages 1–4 vs 0) and steatosis (grades 1–3 vs 0). Secondary outcomes included dichotomized stages of fibrosis (stages 2–4 [significant fibrosis] vs 0–1, stages 3–4 [advanced fibrosis] vs 0–2, and stage 4 [cirrhosis] vs stages 0–3), grades of steatosis (grades 2–3 vs 0–1, and grades 3 vs 0–2), and nonalcoholic steatohepatitis (NASH) vs 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 methods published previously.[28,29,39] Median time interval between MRI and biopsy was 42 days.

Magnetic Resonance Elastography

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

Transient Elastography

TE 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 methods described previously.[12,22] Briefly, patients were asked to fast at least 3 hours before the examination. 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 rescanned using the XL probe (2.5 MHz). A minimum of 10 measurements were made to obtain the median valid liver stiffness measurements (in kPa) and interquartile range. Technical failure was defined as no stiffness measurement obtained or unreliable measurements (defined as success rate $<60\%$ or interquartile range/median $>30\%$).[41] Simultaneous liver steatosis measurements were obtained using the CAP values in dB/m, colocalized to the valid liver stiffness measurements. All CAP data were collected prospectively. Median time interval between TE and biopsy was 107 days.

Statistical Analyses

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Patients' demographic, biochemical, histologic, and imaging characteristics were summarized as mean and SD for continuous variables and numbers and percentages for categorical variables. A 2-tailed P value $\leq .05$ was considered statistically significant.

Main analyses. Receiver operating characteristic curve analyses were used to compare the performances of MRE vs TE for diagnosing fibrosis (stages 1–4 vs 0), and MRI-PDFF vs CAP for diagnosing steatosis (grades 1–3 vs 0) with respect to biopsy. For each receiver operating characteristic analysis, the area under the receiver operating characteristic 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 vs TE for diagnosing fibrosis, and CAP vs 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 vs TE for diagnosing other dichotomized stages of fibrosis (stages 2–4 vs 0–1; stages 3–4 vs 0–2, and stages 4 vs 0–3) and NASH vs no NASH; and MRI-PDFF vs CAP for diagnosing other dichotomized grades of steatosis (grades 2–3 vs 0–1, and grade 3 vs 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. Mean ± SD age and BMI were 50.8 ± 14.6 years and 30.4 ± 5.2 kg/m^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 (6.7%) resulted in technical failure.

Distribution of fibrosis stages and steatosis grades. There were 47, 24, 11, 13, and 8 patients with stages 0, 1, 2, 3, and 4 fibrosis, respectively; and 9, 49, 29, and 16 patients with grades 0, 1, 2, and 3 steatosis, respectively.

Comparison of magnetic resonance elastography and transient elastography for diagnosing fibrosis. MRE had an AUROC of 0.82 (95% confidence interval [CI], 0.74−0.91) for diagnosing fibrosis stages 1–4 vs 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 ($P = .0116$) 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 vs 0–1, stages 3–4 vs 0–2, and stages 4 vs 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 (stages 1–4 vs 0), but no significant difference existed between MRE and TE for diagnosing other dichotomized stages of fibrosis.

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

Comparison of magnetic resonance elastography and transient elastography for diagnosing histologic

Table 1. Demographic, Biochemical, Histologic, and Imaging Characteristics of Study Cohort

Characteristic	Patients (n = 104)
Demographic	
Age at biopsy, *y*, mean ± SD	50.8 ± 14.6
Male, n (%)	45 (43.3)
Female, n (%)	59 (56.7)
Height, *m*, mean ± SD	1.7 ± 0.1
Weight, *kg*, mean ± SD	86.1 ± 17.9
BMI, kg/m^2, mean ± SD	30.4 ± 5.2
Race, n (%)	
White	48 (47.1)
African American	0 (0)
Asian	21 (20.5)
Hispanic	32 (31.4)
Other	1 (1.0)
Diabetes, n (%)	29 (27.9)
Biochemical profile, median (IQR)	
AST, *U/L*	31.0 (15.0)
ALT, *U/L*	42.0 (34.0)
AST/ALT ratio	0.8 (0.4)
ALP, *U/L*	71.0 (30.5)
GGT, *U/L*	35.0 (37.0)
Total bilirubin, *mg/dL*	0.4 (0.3)
Direct bilirubin, *mg/dL*	0.2 (0.1)
Albumin, *g/dL*	4.5 (0.5)
Glucose, *mg/dL*	98.0 (31.5)
Hemoglobin A1C, %	5.8 (0.8)
Insulin, *U*	21.5 (20.0)
Triglycerides, *mg/dL*	133.0 (92.0)
Total cholesterol, *mg/dL*	180.0 (56.0)
HDL, *mg/dL*	47.0 (19.0)
LDL, *mg/dL*	100.0 (52.0)
Platelet count, $10^9/L$	223,000 (77,000)
Prothombin time	10.8 (1.0)
INR	1.0 (0.1)
Histology	
Fibrosis	
0	47 (45.6)
1	24 (23.3)
2	11 (10.7)
3	13 (12.6)
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, n (%)	
No NAFLD	4 (4.0)
NAFLD, not NASH	20 (20.0)
Borderline NASH	13 (13.0)
Definite NASH	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)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; INR, international normalized ratio; IQR, interquartile range; kPa, kilopascal; LDL, low-density lipoprotein; NAS, NAFLD Activity Score.

nonalcoholic steatohepatitis. For diagnosing NASH, MRE had AUROC of 0.70 (95% CI, 0.57−0.82), which was significantly higher than TE AUROC ($P = .0011$) of 0.35 (95% CI, 0.22−0.49).

Comparison of magnetic resonance imaging proton density fat fraction and controlled attenuation parameter for diagnosing steatosis. MRI-PDFF had an AUROC of 0.99 (95% CI, 0.98−1.00) for diagnosing any steatosis (grades 1–3 vs 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 ($P = .0091$) any steatosis (Table 3).

Comparison of magnetic resonance imaging proton density fat fraction and controlled attenuation parameter 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 grades 2–3 vs 0–1 and grades 3–4 vs 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 stiffness measurements by MRE and TE are illustrated in Figure 3*A*. Distributions of liver steatosis measurements by MRI-PDFF and CAP are illustrated in Figure 3*B*.

Multivariable-adjusted receiver operating characteristic 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 was included as covariates.

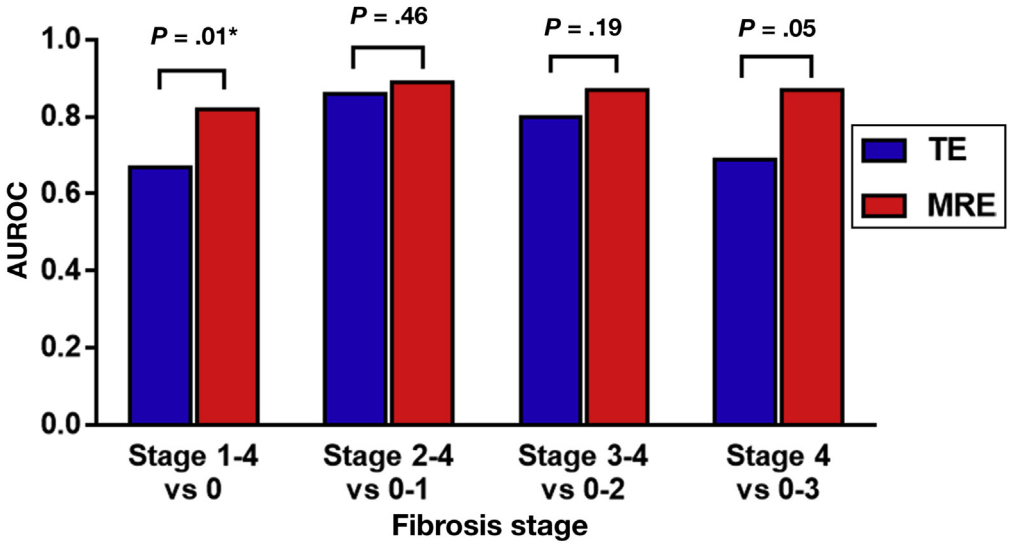

Figure 1. Diagnostic accuracy of MRE and TE for diagnosing dichotomized stages of fibrosis. MRE was significantly better than TE for diagnosis of any fibrosis with an AUROC of 0.82 (*red bar*) vs 0.67 ($P = .01$).

Discussion

Summary of Main Findings

Using a prospective, well-characterized, US-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 the XL probe to perform head-to-head comparison between MRE vs TE, and MRI-PDFF vs CAP, providing 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

Table 2. Diagnostic Test Characteristics of Transient Elastography and Magnetic Resonance Elastography for the Diagnosis of Fibrosis

Overall (n = 94)	AUROC (95% CI)	Threshold, *kPa*	Sensitivity, %	Specificity, %	PPV, %	NPV, %	TE vs MRE, *P* value[a]
Primary analysis							
Stages 1–4 (n = 51) vs stage 0 (n = 43)							
MRE	0.82 (0.74–0.91)	2.65	76.5	79.1	81.3	73.9	
TE	0.67 (0.56–0.78)	6.10	66.7	65.1	69.4	62.2	**.0116**
Secondary analyses							
Stages 2–4 (n = 29) vs stages 0–1 (n = 65)							
MRE	0.89 (0.83–0.96)	2.86	79.3	81.8	65.7	89.8	
TE	0.86 (0.77–0.95)	6.90	79.3	84.6	69.7	90.2	.4596
Stages 3–4 (n = 18) vs stages 0–2 (n = 76)							
MRE	0.87 (0.78–0.96)	2.99	77.8	80.3	48.3	93.8	
TE	0.80 (0.67–0.93)	7.30	77.8	77.6	45.2	93.7	.1942
Stage 4 (n = 8) vs stages 0–3 (n = 86)							
MRE	0.87 (0.71–1.00)	3.35	75.0	81.4	27.3	97.2	
TE	0.69 (0.45–0.94)	6.90	62.5	66.3	14.7	95.0	.0546
NASH (n = 72) vs no NASH (n = 22)							
MRE	0.70 (0.57–0.82)	2.53	63.9	68.2	86.8	36.6	
TE	0.35 (0.22–0.49)	5.60	61.1	59.1	83.0	31.7	**.0011**

NOTE. Boldface indicates significant *P* values.
[a]AUROC of TE vs MRE via Delong test.

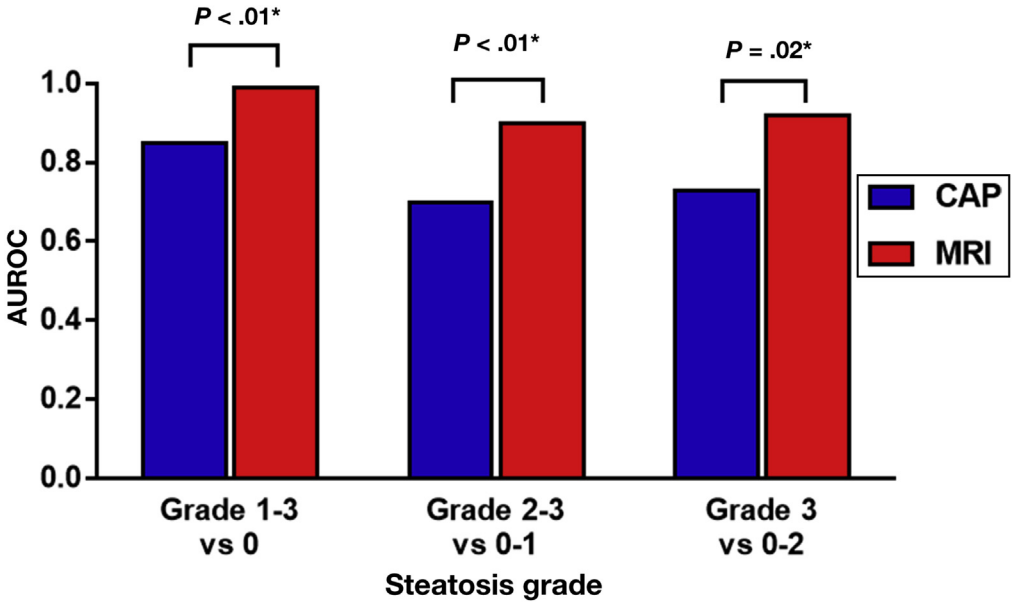

Figure 2. Diagnostic accuracy of MRI-PDFF and CAP for diagnosing dichotomized grades of steatosis. MRI-PDFF was significantly better than CAP for all comparison including grade 0 vs grades 1–3, grades 0–1 vs grades 2–3, grades 0–2 vs grade 3.

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, additional 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 vs 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 (stages 2–4 vs 0–1) and cirrhosis in Japanese NAFLD patients. In comparison, our study showed that MRE

Table 3. Diagnostic Test Characteristics of Controlled Attenuation Parameter and Magnetic Resonance–based Proton Density Fat Fraction for the Diagnosis of Steatosis

Overall (n = 78)	AUROC (95% CI)	Threshold	Sensitivity, %	Specificity, %	PPV, %	NPV, %	PDFF vs CAP, *P* value[a]
Primary analysis							
Grades 1–3 (n = 71) vs grade 0 (n = 7)							
MRI-PDFF	0.99 (0.98–1.00)	3.71	95.8	100	100	70.0	
CAP	0.85 (0.75–0.96)	261	71.8	85.7	98.1	23.1	**.0091**
Secondary analyses							
Grades 2–3 (n = 30) vs grades 0–1 (n = 48)							
MRI-PDFF	0.90 (0.82–0.97)	13.03	80.0	83.3	75.0	87.0	
CAP	0.70 (0.58–0.82)	305	63.3	68.8	55.9	75.0	**.0017**
Grade 3 (n = 11) vs grades 0–2 (n = 67)							
MRI-PDFF	0.92 (0.84–0.99)	16.37	81.8	83.6	45.0	96.6	
CAP	0.73 (0.58–0.89)	312	63.6	70.1	25.9	92.2	**.0238**

NOTE. Boldface indicates significant *P* values.
[a]AUROC of CAP vs PDFF via Delong test.

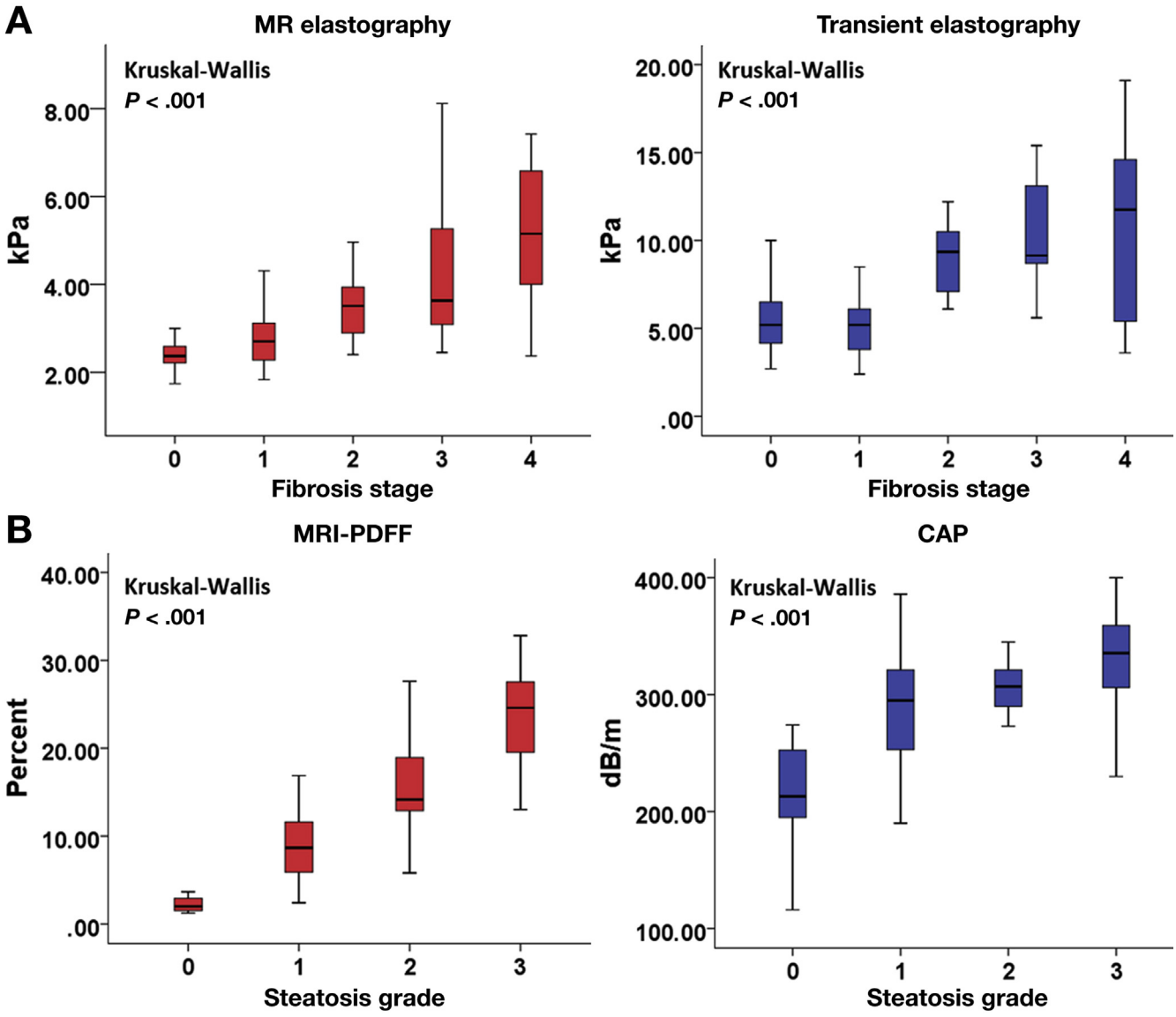

Figure 3. (*A*) Distribution of liver stiffness measurements by MRE and TE stratified by fibrosis stage. Stiffness measurements by both MRE and TE increased with increasing fibrosis stage (Kruskal–Wallis test $P < .001$). (*B*) Distribution of steatosis measurements by MRI-PDFF and CAP stratified by steatosis grade. Steatosis measurements by both MRI-PDFF and CAP (Kruskal–Wallis $P < .001$) increased with increasing steatosis grade.

is more accurate than TE for diagnosing any fibrosis (stages 1–4 vs 0), but not cirrhosis ($P = .0546$) Although Imajo et al assessed TE using the M probe only, we also used the XL probe when indicated during our examination (n = 53). Our cohort's demographic characteristics, such as race and higher BMI (30.5 ± 5.2 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 a larger cohort of patients may be needed to determine the optimal cutoff points for MRI-PDFF vs CAP for the grade of steatosis in NAFLD as well as MRE vs TE for the stage of fibrosis in NAFLD, which may be different for Western NAFLD population vs Asian NAFLD population.

Liver fibrosis and steatosis are clinically important features of NAFLD that have been investigated by noninvasive tests, such as MRI and TE. Steatosis alone is known to progress to NASH and fibrosis.[8] In addition, any fibrosis, even in the absence of severe fibrosis (stages 3–4), compared with no fibrosis was shown to be associated with increased mortality or liver transplantation rates 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-PDFF 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. In addition, 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-PDFF may have utility in short-term trials, as shown previously.[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-PDFF for assessing longitudinal changes in steatosis.[47] Although TE has excellent inter- and intra-operator reproducibility[48] 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 a 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 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. Because this was a single-center study in a highly specialized setting, the generalizability of its findings in other clinical settings is unknown. 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 a mean progression of one stage to take 14.3 years in patients with nonalcoholic fatty liver and 7.1 years in patients with NASH.[6] 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-PDFF, 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, therefore, MRE can also be made available on commercially available MRI platforms throughout the United States. Although TE might be more useful for widespread screening, MRE can 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 before implementing these competing noninvasive approaches in routine clinical practice.

Implication for Future Research

Using prospective, head-to-head comparisons, we found 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 vs TE and/or biopsy must also be evaluated to develop optimal diagnostic strategies for diagnosing NAFLD-associated fibrosis and steatosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.10.026.

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Conflicts of interest
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Supplementary Methods

Histologic Assessment

Hepatic fibrosis was scored from 0 to 4 (0, 1, 2, 3, 4), steatosis and lobular inflammation were scored from 0 to 3 (0, 1, 2, 3), and hepatocellular ballooning was scored from 0 to 2 (0, 1, 2). The sum of these scores, known as the NAFLD Activity Score was calculated. NASH was scored on a 3-point scale (no NASH, borderline NASH, or definite NASH). Patients with borderline or definite NASH were considered as having NASH in this study.

Magnetic Resonance Elastography

A standard 60-Hz shear-wave was generated by an acoustic passive driver attached to the body wall anterior to the liver and coupled with an acoustic active driver outside the MR examination room. A 2-dimensional motion-sensitized gradient-recalled echo MRE pulse sequence synchronized to the shear wave frequency was acquired to obtain 4 noncontiguous axial slices (10-mm thickness, 10-mm inter-slice gap), each during a 16-second breath hold, through the widest transverse section of the liver with short recovery times in between. The acquisition parameters were as follows: repetition time, 50 milliseconds; echo time, 20.2 milliseconds; flip angle, 30 degrees; matrix, 256×64; field of view, 48×48 cm; one-signal average; receiver bandwidth $\pm$ 33 kHz; and parallel imaging accelerating factor, 2. The total acquisition time was approximately 2 minutes.

The wave images from each slice location were automatically processed on the scanner computer using inversion algorithm to generate axial liver stiffness maps called elastograms. The elastograms were transferred and analyzed offline by a trained image analyst (at least 6 months of experience with MRE analysis) blinded to clinical and histologic data. While avoiding liver edges, large blood vessels, and artifacts, the image analyst drew regions of interests on the elastograms using a custom software package in parts of the liver where wave propagation was shown clearly on the wave images. The mean per-pixel liver stiffness values across regions of interests at the 4 slices were calculated and automatically recorded in an electronic spreadsheet.

Supplementary Table 1. Time to Biopsy: Diagnostic Test Characteristics of Transient Elastography and Magnetic Resonance Elastography for the Diagnosis of Fibrosis and Magnetic Resonance Imaging and Controlled Attenuation Parameter for Steatosis Against Models Including Time to Biopsy Overall (n = 94)

Primary analyses	AUROC (95% CI)	Unadjusted vs time, *P* value[a]
Stages 1−4 (n = 51) vs stage 0 (n = 43)		
MRE	0.82 (0.74−0.91)	
MRE+time	0.84 (0.76−0.92)	.1746
Stages 1−4 (n = 51) vs stage 0 (n = 43)		
TE	0.67 (0.56−0.78)	
TE+time	0.62 (0.51−0.74)	.4365
Grades 1−3 (n = 71) vs grade 0 (n = 6)		
MRI	0.99 (0.98−1.00)	
MRI+time	0.99 (0.98−1.00)	1.000
Grades 1−3 (n = 71) vs grade 0 (n = 6)		
CAP	0.87 (0.77−0.98)	
CAP+time	0.91 (0.83−0.99)	.1829

[a]AUROC of unadjusted model vs model with time via Delong test.

Supplementary Table 2. Probe Type: Diagnostic Test Characteristics of Transient Elastography and Magnetic Resonance Elastography for the Diagnosis of Fibrosis and Magnetic Resonance Imaging and Controlled Attenuation Parameter for Steatosis Against Models Including Probe Type

Primary analyses	AUROC (95% CI)	Unadjusted vs probe, *P* value[a]
Stages 1−4 (n = 51) vs stage 0 (n = 43)		
TE	0.67 (0.56−0.78)	
TE+probe	0.62 (0.51−0.74)	.2982
Grades 1−3 (n=71) vs grade 0 (n = 7)		
CAP	0.85 (0.74−0.96)	
CAP+probe	0.85 (0.72−0.98)	.9774

[a]AUROC of unadjusted model vs model with probe type via Delong test.