Multiparametric MR Is a Valuable Modality for Evaluating Disease Severity of Nonalcoholic Fatty Liver Disease

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INTRODUCTION: **Because nonalcoholic fatty liver disease (NAFLD) is becoming a leading cause of chronic liver disease, noninvasive evaluations of its severity are immediately needed. This prospective cross-sectional study evaluated the effectiveness of noninvasive assessments of hepatic steatosis, fibrosis, and steatohepatitis.**

METHODS: **Patients underwent laboratory tests, liver biopsy, transient elastography, and MRI. Multiparametric MR was used to measure MRI proton density fat fraction, MR spectroscopy, T1 mapping, and MR elastography (MRE).**

RESULTS: **We enrolled 130 patients between October 2016 and July 2019. For the diagnosis of moderate-to-severe steatosis (grade ≥ 2), the area under the receiver operating characteristic curve (AUROC) was lower in controlled attenuation parameter (0.69; 95% confidence interval [CI], 0.60–0.76) than MRI proton density fat fraction (0.82; 95% CI, 0.75–0.89; $P = 0.008$) and MR spectroscopy (0.83; 95% CI, 0.75–0.89; $P = 0.006$). For the diagnosis of advanced fibrosis (stage ≥ 3), the AUROC of MRE (0.89; 95% CI, 0.83–0.94) was superior compared with those of the Fibrosis-4 index (0.77; 95% CI, 0.69–0.84; $P = 0.010$), NAFLD fibrosis score (0.81; 95% CI, 0.73–0.87; $P = 0.043$), and transient elastography (0.82; 95% CI, 0.74–0.88; $P = 0.062$). For detecting advanced fibrosis or nonalcoholic steatohepatitis, the AUROC of MRE (0.86; 95% CI, 0.79–0.91) was higher than that of TE (0.76; 95% CI, 0.68–0.83) with statistical significance ($P = 0.018$).**

DISCUSSION: **Multiparametric MR accurately identified a severe form of NAFLD. Multiparametric MR can be a valuable noninvasive method for evaluating the severity of NAFLD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A224, http://links.lww.com/CTG/A225

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is emerging as a major cause of chronic liver disease, with a prevalence of 20%–30% in the general population (1,2). Among patients with NAFLD, 70%–75% of cases have simple steatosis, whereas 20%–25% of cases progress to nonalcoholic steatohepatitis (NASH) (3). Once NAFLD progresses to NASH, progressive inflammatory signaling activates hepatic stellate cells resulting in fibrosis progression (4). Because fibrosis is associated with increased mortality in patients with NAFLD (5), it is important to identify advanced fibrosis. Although liver biopsy is the gold standard for the diagnosis of NAFLD and classification of disease severity, it has several limitations, such as sampling error, inter- and intraobserver variability, and risk for complications (6). Therefore, the development of a noninvasive tool for evaluating hepatic steatosis and fibrosis and distinguishing between simple steatosis and NASH is immediately required.

Biomedical markers have been investigated for their efficacy in diagnosing NAFLD, NASH, and advanced fibrosis. Although the accuracy and reproducibility of biochemical markers are limited for the diagnosis and classification of the severity of NAFLD (7), some biochemical biomarkers are useful for the initial evaluation of patients with NAFLD because of their convenience and

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accessibility. In particular, the Fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS) are useful for evaluating fibrosis in patients with NAFLD because they are easy to obtain and more accurate than other biochemical fibrosis markers, such as aspartate aminotransferase (AST), compared with the platelet ratio index and BARD score (8).

The recent development of imaging modalities has enabled the evaluation of hepatic steatosis and fibrosis. Using the FibroScan, transient elastography (TE) can evaluate hepatic fibrosis by measuring liver stiffness, whereas controlled attenuation parameter (CAP) can measure hepatic steatosis (9,10). Several meta-analyses showed that CAP and TE are useful for assessing steatosis and fibrosis in patients with NAFLD, respectively (8,11,12). MRI can also measure hepatic fibrosis using MR elastography (MRE) and hepatic steatosis using MRI proton density fat fraction (MRI-PDFF) and MR spectroscopy (MRS) (13,14). A recent American Association for the Study of Liver Diseases practice guidance suggested that TE and MRE are useful tools for assessing of advanced fibrosis in patients with NAFLD (15). Comparisons of the diagnostic accuracy of the FibroScan and MRI by Park et al. (16) and Imajo et al. (17) revealed that MRI-PDFF had significantly greater accuracy than CAP for evaluating steatosis and that MRE was more accurate than TE for evaluating fibrosis. Although these 2 studies were well-characterized prospective studies, they did not evaluate other MRI sequences, such as MRS, which is known to be more accurate for measuring hepatic steatosis (18), and T1 mapping, which correlates with myocardial and hepatic fibrosis (19,20).

The development of biomarkers for the diagnosis of NASH among patients with NAFLD remains an important challenge. Many biochemical markers and panels have been developed but have been insufficiently evaluated. Although TE and MRE have been investigated for their ability to discriminate between simple steatosis and steatohepatitis, their clinical applications are still limited (21). This prospective cross-sectional study aimed to evaluate hepatic steatosis, fibrosis, and steatohepatitis using noninvasive tests, such as biochemical markers, FibroScan, and multiparametric MR.

METHODS

Study population

Patients were included when the biopsy result was appropriate for NAFLD and patients agreed for participation in this study. The exclusion criteria were as follows: (1) patients with other chronic liver diseases, (2) patients with excessive alcohol consumption (men >140 g/wk and women >70 g/wk), (3) patients with decompensated liver cirrhosis, (4) contraindications to MRI, (5) patients with malignancy, (6) patients with other severe systemic disease, and (7) pregnant women. All patients underwent biochemical testing, FibroScan, and MRI within 6 months of liver biopsy.

This study was registered at ClinicalTrials.gov (NCT03725631) and approved by the Institutional Review Board of the Korea University Guro Hospital (2016GR0302). Informed consent was obtained from all participants. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Histological evaluation and definitions

Liver specimens were obtained via percutaneous liver biopsy through the intercostal space using an 18-gauge Tru-Cut needle (TSK Laboratory, Tochigi, Japan). Each specimen consisted of 2 pieces of at least 2 cm each in length. The tissues were then fixed in formalin and embedded into paraffin tissue blocks. Four-micrometer sections were stained with hematoxylin and eosin and subjected to Masson's trichrome staining for fibrosis evaluation. Two pathologists (S.Y.L. and B.H.-K.) evaluated each slide using the NASH Clinical Research Network histological scoring system (22). Each pathologist was masked to the other's result and the patients' clinical, laboratory, and imaging data. Disagreements in the results between the pathologists were resolved by discussion and consensus. NASH was defined when >5% of hepatic steatosis and inflammation were seen with hepatocyte ballooning, regardless of the degree of fibrosis (15).

Evaluation of serological fibrosis markers

The FIB-4 index and NFS were calculated for all patients. The FIB-4 index is calculated using age, AST, ALT, and platelet count as follows:

$$\text{FIB-4} = (\text{age (years)} \times \text{AST (IU/L)}) / \text{platelet count } (10^9/\text{L}) \times (\text{IU/L})^{1/2}$$

The NFS is calculated using age, BMI, presence of impaired fasting glucose or diabetes, AST, ALT, platelet count, and albumin as follows:

$$\begin{aligned}\text{NFS} = {} & -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI } (\text{kg/m}^2) \\ & + 1.13 \times \text{IFG/diabetes (yes} = 1,\ \text{no} = 0) \\ & + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet } (\times 10^9/\text{L}) \\ & - 0.66 \times \text{albumin (g/dL)}\end{aligned}$$

Transient elastography

Liver stiffness and hepatic steatosis were measured by 2 experienced operators using the FibroScan (Echosens, Paris, France). The procedure was performed as described previously, and each examination was performed at least 10 times. Liver stiffness measurement values were expressed in kPa, and hepatic steatosis is expressed in dB/m. When the interquartile range >0.3, the result was considered unreliable (25). An XL probe was used if patients were too obese and unable to be measured with an M probe.

MRI-PDFF, MRS, T1 mapping, and MRE

All patients underwent MRI with a 3T MRI scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). MR sequences included PDFF, MRS, T1 mapping, MRE, and other sequences, such as T1-weighted imaging, T2-weighted imaging, and diffusion-weighted imaging. PDFF was measured using the multiecho (6-echo) modified Dixon techniques (26). MRS was measured using 20 × 20 × 20-mm voxels in the segment VI or VIII using a high-speed T2-corrected multiecho technique (27). T1 mapping was acquired by the modified look-locker inversion recovery (28). MRE was acquired by measurement of the elastogram from the wave images (13). To obtain the wave images, a shear wave driver was placed against the right chest wall anterior to the patient's liver. When other incidental findings were detected, additional contrast-enhanced dynamic imaging was performed as required for diagnosis. All the MR parameters were measured and analyzed by an experienced radiologist.

Table 1. Baseline characteristics

Characteristics	Patients, N = 130
Demographics	
Age, median (IQR), years	51 (41–62)
Female, n (%)	77 (59.2%)
DM/HTN/dyslipidemia, n (%)	55/59/44 (42.3%/45.4%/33.8%)
Anthropometrics	
BMI, median (IQR), kg/m^2	29.73 (25.75–32.69)
Circumference, median (IQR), cm	99 (89–105)
Abdominal AP, median (IQR), cm	23 (22–26)
Laboratory findings	
Hb, median (IQR), g/dL	14.0 (13.2–15.1)
PLT, median (IQR), $\times 10^3/\mu L$	218 (174–255)
AST, median (IQR), IU/L	61 (40–87)
ALT, median (IQR), IU/L	82 (50–120)
Bilirubin, median (IQR), mg/dL	0.60 (0.44–0.81)
Albumin, median (IQR), g/dL	4.3 (4.1–4.4)
PT, median (IQR), INR	1.00 (0.95–1.04)
Creatinine, median (IQR), mg/dL	0.70 (0.60–0.83)
CRP, median (IQR), mg/L	2.37 (1.04–3.85)
Glucose, median (IQR), mg/dL	114 (102–142)
Insulin, median (IQR), μIU/mL	19.17 (12.16–31.13)
HOMA-IR, median (IQR)	5.06 (3.55–8.89)
Cholesterol, median (IQR), mg/dL	181 (152–205)
Histological findings	
Steatosis, n (%) 0/1/2/3	3/52/48/27 (2.3/40.0/36.9/20.8)
Lobular inflammation, n (%) 0/1/2/3	1/42/77/10 (0.8/32.3/59.2/7.7)
Ballooning, n (%) 0/1/2	60/32/38 (46.2/24.6/29.2)
Fibrosis, n (%) 0/1/2/3/4	35/33/34/20/8 (26.9/25.4/26.2/15.4/6.2)
Duration between biopsy and TE, median (IQR), d	26 (10–49)
Duration between biopsy and MRI, median (IQR), d	37 (31–61)

AST, aspartate transaminase; ALT, alanine transaminase; BMI, body mass index; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment for insulin resistance; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; PLT, platelet; PT, prothrombin time; TE, transient elastography.

Statistics

The baseline characteristics are summarized as frequencies and percentages for categorical variables and median and interquartile range for continuous variables. The threshold for each steatosis grade, fibrosis stage, and determination of NASH was determined by the receiver operating characteristic (ROC) curve analysis based on histological examination using the Youden index to maximize sensitivity and specificity. Comparisons of the ROC curves among the modalities were performed by the DeLong method using MedCalc (version 17.6; MedCalc Software, Ostend, Belgium) (29). *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 159 patients were diagnosed with NAFLD at the Korea University Guro Hospital from September 2016 to March 2019 (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A224). Twenty-three patients declined to participate, 2 patients checked interquartile range >0.3 in TE, TE failed in 2 patients, and MRE failed in 2 patients. Baseline clinical, laboratory, and histological characteristics are summarized in Table 1. The median age of the patients was 51 years, and female was the predominant sex (59.2%). Diabetes, hypertension, and dyslipidemia affected 42.3%, 43.8%, and 31.5% of patients, respectively. The median BMI was 29.73 kg/m^2. A relatively high number of patients had a more severe form of NAFLD: 75 (57.7%) had moderate-to-severe steatosis, 70 (53.8%) had NASH, and 28 (21.6%) had advanced fibrosis. The median duration between liver biopsy and TE was 26 days; more than 90% of patients underwent the FibroScan within 90 days. The median duration between liver biopsy and MRI was 37 days; more than 90% of patients underwent MRI within 90 days.

Diagnostic accuracy of noninvasive tests for steatosis

Hepatic steatosis was evaluated using CAP, MRI-PDFF, and MRS. The cutoff values for detecting steatosis grades ≥1, ≥2, and 3 were 232, 287, and 293 dB/m, respectively, as measured by CAP, 2.0%, 15.7%, and 16.7%, respectively, as measured by MRI-PDFF, and 4.0%, 12.8%, and 18.3%, respectively, as measured by MRS (Table 2). For the detection of any grade steatosis, the area under the ROC curve (AUROC) values was similar across the modalities (Figure 1 and Table 2). For the detection of moderate-to-severe steatosis (grade ≥2), the AUROC of CAP was 0.69 (95% confidence interval [CI], 0.60–0.76), which was significantly lower when compared with that of MRI-PDFF (0.82; 95% CI, 0.75–0.89; $P = 0.008$) or MRS (0.83; 95% CI 0.75–0.89; $P = 0.006$). For identifying severe steatosis (grade 3), the AUROC of CAP was 0.67 (95% CI, 0.58–0.75), which was also significantly lower when compared with that of MRI-PDFF (0.85; 95% CI, 0.78–0.91; $P = 0.006$) and MRS (0.86; 95% CI, 0.78–0.91; $P = 0.001$). MRI-PDFF and MRS had similar AUROC values for the detection of steatosis grades ≥2 and 3.

Diagnostic accuracy of noninvasive tests for fibrosis

Hepatic fibrosis was evaluated using the FIB-4 index, NFS, TE, and MRE. The cutoff values and AUROC values for detecting each fibrosis stage are summarized in Table 3. Among the noninvasive tests, MRE had the highest AUROC for grading each stage of fibrosis (Figure 2 and Table 3). For the detection of advanced fibrosis (stage ≥ 3), MRE (AUROC 0.89; 95%, CI 0.83–0.94) was more accurate than the FIB-4 index (AUROC 0.77; 95% CI, 0.69–0.84; $P = 0.010$), NFS (AUROC 0.81; 95% CI, 0.73–0.87; $P = 0.043$), and TE (AUROC 0.82; 95% CI, 0.74–0.88; $P = 0.062$). The AUROC values for the detection of each fibrosis stage were similar between the NFS and TE, except for the detection of cirrhosis (F4) for which the AUROC value was higher in TE compared with the NFS but without statistical significance ($P = 0.256$).

Table 2. Diagnostic accuracy of CAP, MRI-PDFF, and MRS for steatosis

Steatosis grade	Cutoff	AUROC (95% CI)	*P* value	*P* value for AUROC comparison		
				vs CAP	vs PDFF	vs MRS
CAP						
S1-3 vs S0	232 dB/m	0.96 (0.91–0.99)	<0.001	—	0.091	0.072
S2-3 vs S0-1	287 dB/m	0.69 (0.60–0.76)	<0.001	—	0.008	0.006
S3 vs S0-2	293 dB/m	0.67 (0.58–0.75)	<0.001	—	0.006	0.001
MRI-PDFF						
S1-3 vs S0	2.0%	1.00 (0.96–1.00)	<0.001	0.091	—	1.000
S2-3 vs S0-1	15.7%	0.82 (0.75–0.89)	<0.001	0.008	—	0.833
S3 vs S0-2	16.7%	0.85 (0.78–0.91)	<0.001	0.006	—	0.926
MRS						
S1-3 vs S0	4.0%	1.00 (0.96–1.00)	<0.001	0.072	1.000	—
S2-3 vs S0-1	12.8%	0.83 (0.75–0.89)	<0.001	0.006	0.833	—
S3 vs S0-2	18.3%	0.86 (0.78–0.91)	<0.001	0.001	0.926	—

AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; MRS, MR spectroscopy; PDFF, proton density fat fraction.

Diagnostic accuracy of T1 mapping, TE, and MRE for NASH

We evaluated the diagnostic accuracy of T1 mapping, TE, and MRE for NASH. The diagnostic accuracy of T1 mapping for NASH was not meaningful (AUROC 0.59; 95% CI, 0.49–0.67; $P = 0.089$), but it showed significant diagnostic accuracy when patients with a severe form of steatosis were excluded (see Table 1, Supplementary Digital Content 2, http://links.lww.com/CTG/A225). By contrast, TE and MRE showed significant diagnostic accuracy for NASH in the whole patients (AUROC 0.70 in TE and 0.77 in MRE), patients with steatosis grade ≤2 (AUROC 0.74 in TE and 0.77 in MRE), and patients with steatosis grade ≤1 (AUROC 0.81 in TE and 0.79 in MRE). MRE had a significantly higher AUROC for the diagnosis of NASH in the whole patients than T1 mapping (0.77 vs 0.58; $P = 0.004$) (see Figure 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A224). Because TE, T1 mapping, and MRE correlated with hepatic fibrosis, we analyzed the AUROC for patients with fibrosis stages 0, 1, and 2. The AUROC was significant in TE (0.70; 95% CI, 0.60–0.78; $P = 0.001$) and MRE (0.80; 95% CI, 0.71–0.87; $P < 0.001$), whereas it was not significant in T1 mapping (0.60; 95% CI, 0.50–0.70; $P = 0.074$).

Accuracy of TE and MRE in detecting advanced fibrosis or NASH in NAFLD

Next, we evaluated the accuracy of TE and MRE for detecting advanced fibrosis or NASH in all patients with NAFLD. The

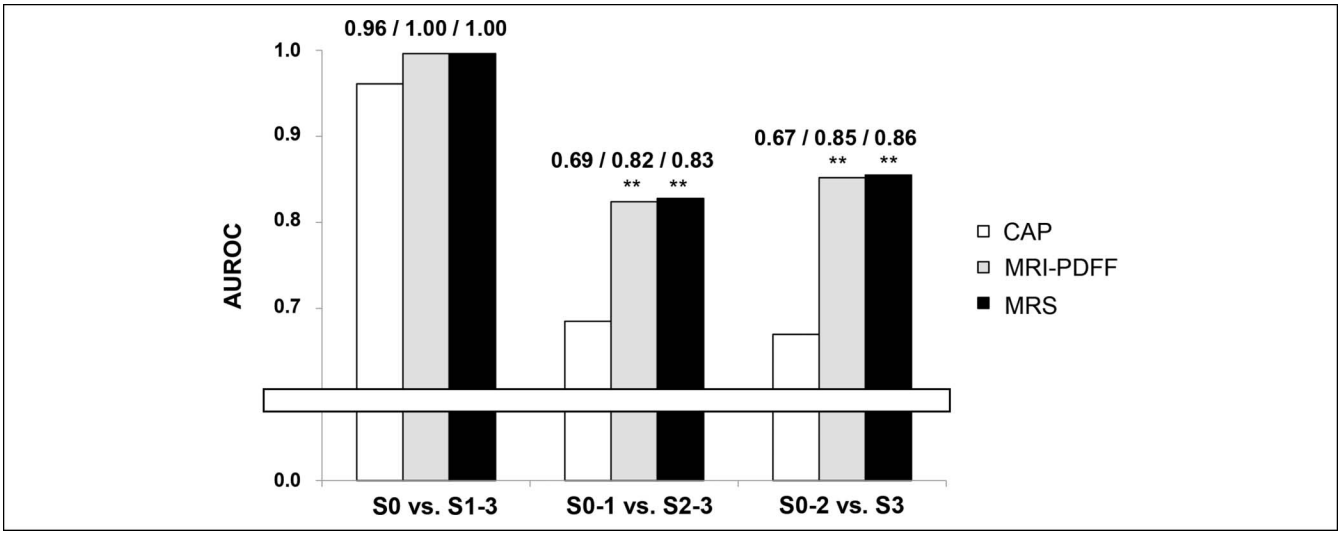

Figure 1. Diagnostic accuracy of noninvasive tests for classifying the severity of hepatic steatosis. The AUROC values are compared among CAP, MRI-PDFF, and MRS for diagnosing any grade of steatosis, steatosis ≥ grade 2, and severe steatosis (grade 3). **AUROC significantly differed from CAP ($P < 0.01$). AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; MRI-PDFF, MRI proton density fat fraction; MRS, MR spectroscopy.

Table 3. Diagnostic accuracy of the FIB-4 index, NFS, TE, and MRE for fibrosis

Fibrosis stage	Cutoff	AUROC (95% CI)	*P* value	*P* value for AUROC comparison			
				vs FIB-4	vs NFS	vs TE	vs MRE
FIB-4 index							
F1-4 vs F0	1.479	0.76 (0.67–0.83)	<0.001	—	0.752	0.426	0.061
F2-4 vs F0-1	1.575	0.73 (0.65–0.81)	<0.001	—	0.103	0.183	0.101
F3-4 vs F0-2	1.852	0.77 (0.69–0.84)	<0.001	—	0.268	0.341	0.010
F4 vs F0-3	2.214	0.83 (0.76–0.89)	<0.001	—	0.314	0.092	0.076
NFS							
F1-4 vs F0	−1.474	0.77 (0.70–0.85)	<0.001	0.752	—	0.511	0.087
F2-4 vs F0-1	−1.474	0.78 (0.70–0.85)	<0.001	0.103	—	0.746	0.535
F3-4 vs F0-2	−0.674	0.81 (0.73–0.87)	<0.001	0.268	—	0.750	0.043
F4 vs F0-3	−0.415	0.88 (0.81–0.93)	<0.001	0.314	—	0.256	0.165
TE (kPa)							
F1-4 vs F0	8.8	0.81 (0.73–0.87)	<0.001	0.426	0.511	—	0.352
F2-4 vs F0-1	11.7	0.80 (0.72–0.86)	<0.001	0.183	0.746	—	0.709
F3-4 vs F0-2	11.8	0.82 (0.74–0.88)	<0.001	0.341	0.750	—	0.062
F4 vs F0-3	16.0	0.94 (0.88–0.97)	<0.001	0.092	0.256	—	0.570
MRE (kPa)							
F1-4 vs F0	3.1	0.85 (0.78–0.91)	<0.001	0.061	0.087	0.352	—
F2-4 vs F0-1	3.6	0.81 (0.73–0.87)	<0.001	0.101	0.535	0.709	—
F3-4 vs F0-2	3.8	0.89 (0.83–0.94)	<0.001	0.010	0.043	0.062	—
F4 vs F0-3	5.1	0.95 (0.90–0.98)	<0.001	0.076	0.165	0.570	—

AUROC, area under the receiver operating characteristic curve; FIB-4, Fibrosis-4; MRE, MR elastography; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; TE, transient elastography.

cutoff values for detecting advanced fibrosis or NASH were 8.4 kPa in TE and 3.56 kPa in MRE. The AUROC was significantly higher in MRE (0.86; 95% CI, 0.79–0.91) than TE (0.76; 95% CI, 0.68–0.83) ($P = 0.018$) (Figure 3).

Other MRI findings

Incidental findings are also summarized in Supplementary Digital Content 2 (see Table 2, http://links.lww.com/CTG/A225). In the liver, 43 cases of hepatic cyst, 5 cases of hemangioma, one case of focal nodular hyperplasia, and one case of hepatocellular carcinoma (HCC) were detected. One case of HCC was found in a 75-year-old female patient, and lesion was not detected by ultrasonography (see Figure 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A224). After examining liver dynamic CT and MRI, she underwent curative resection of a single 3-cm HCC tumor with no recurrence for 2 years.

DISCUSSION

The noninvasive evaluation of disease severity in patients with NAFLD is important for identifying patients who are likely to have progressed to NASH, advanced fibrosis, and cirrhosis. This study evaluated the accuracy of noninvasive biomarkers for classifying steatosis using CAP, MRI-PDFF, and MRS and fibrosis using the FIB-4 index, NFS, TE, and MRE. We also evaluated the diagnostic accuracy of T1 mapping, TE, and MRE for NASH. We found that multiparametric MR is an accurate modality for the classification of steatosis grade and fibrosis stage, especially for identifying advanced stages. Although MRE has moderate accuracy for detecting NASH, we found that MRE had high significant accuracy for identifying NASH or advanced fibrosis, indicating severe forms of NAFLD.

The noninvasive evaluation of hepatic steatosis has been well investigated using imaging modalities, such as CAP, MRI-PDFF, and MRS. CAP estimates hepatic steatosis by quantifying ultrasound attenuation (11), whereas MRI-PDFF and MRS measure hepatic steatosis by quantifying the amount of fat- and water-bound protons (18). Although MRI-PDFF and MRS had similar accuracies for quantifying hepatic fat content and classifying hepatic steatosis grade (30), MRS is theoretically a more accurate method for assessing steatosis than MRI-PDFF because MRS directly measures water and fat peaks, whereas MRI-PDFF estimates hepatic fat by indirectly measuring water and fat peaks (18). In 2 studies that compared diagnostic accuracy of CAP and MRI-PDFF for hepatic steatosis, MRI-PDFF showed significant superiority in distinguishing all grades of steatosis (16,17). Our study showed a similar result that both MRI-PDFF and MRS had significantly higher AUROC values than CAP for classifying moderate and severe steatosis. MRS had a higher AUROC value for grading moderate and severe steatosis than MRI-PDFF, but the difference was insignificant. Because of the limitations of MRS in terms of availability and sampling error, MRI-PDFF would be the preferred modality in a real practice and clinical trial setting (31). Therefore, MRI-PDFF could be an accurate and effective noninvasive modality for evaluating hepatic steatosis.

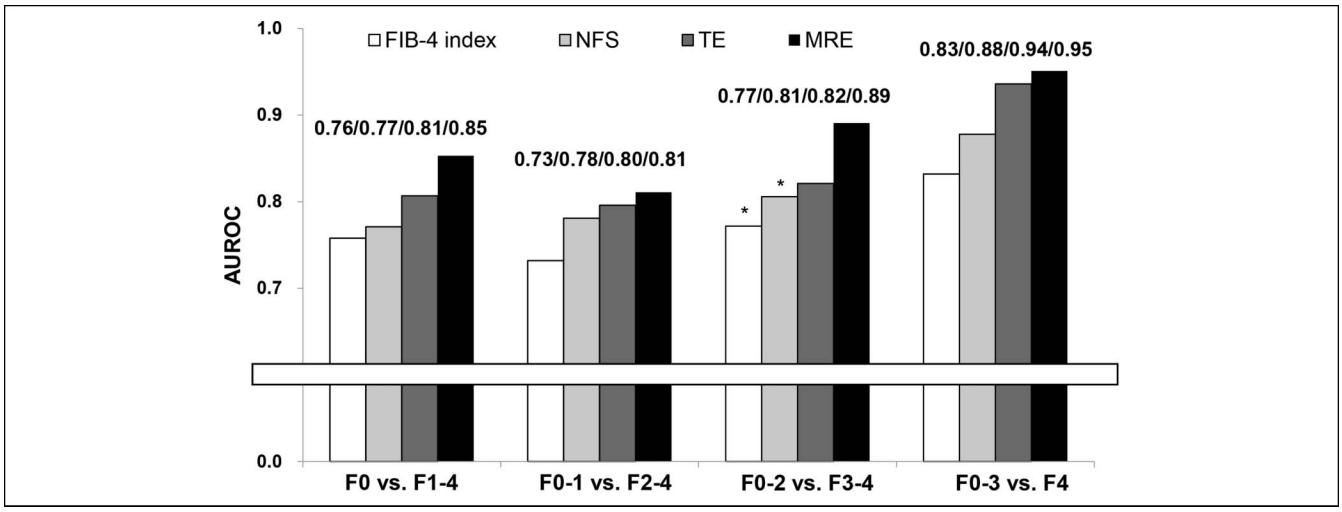

Figure 2. Diagnostic accuracy of noninvasive tests for classifying the severity of hepatic fibrosis. The AUROC values are compared among the FIB-4 index, NFS, TE, and MRE for diagnosing any stage of fibrosis, fibrosis ≥ stage 2, fibrosis ≥ stage 3, and cirrhosis (grade 4). *AUROC significantly different from MRE ($P < 0.05$). AUROC, area under the receiver operating characteristic curve; FIB-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; TE, transient elastography; MRE, MR elastography.

Many biochemical and imaging biomarkers have been developed for the evaluation of hepatic fibrosis. Because the FIB-4 index and NFS have been widely studied and validated for NAFLD (32), we evaluated these biochemical markers and compared them with TE and MRE. TE estimates liver stiffness via measurement of the shear wave velocity, whereas MRE measured liver stiffness by imaging the shear wave propagation (33). Interestingly, the FIB-4 index, NFS, and TE had similar AUROC values for the classification of fibrosis stages 0, 1, 2, and 3. Because the FibroScan is not available at the primary care centers, the FIB-4 index and NFS would be as useful as TE for evaluating fibrosis. MRE was the most accurate method for diagnosing all the stages of fibrosis, and it had a significantly higher AUROC than the FIB-4 index and NFS for the diagnosis of advanced fibrosis. Although there was no statistical significance, MRE had a higher AUROC for grading stage of fibrosis than TE. Several factors, including inflammation, steatosis, and obesity, affect the results of TE, and these confounding factors reduce the diagnostic accuracy of TE (34). As seen in our results, a recently pooled analysis of data from patients with biopsy-proven NAFLD found that MRE has significantly higher diagnostic accuracy than TE (35).

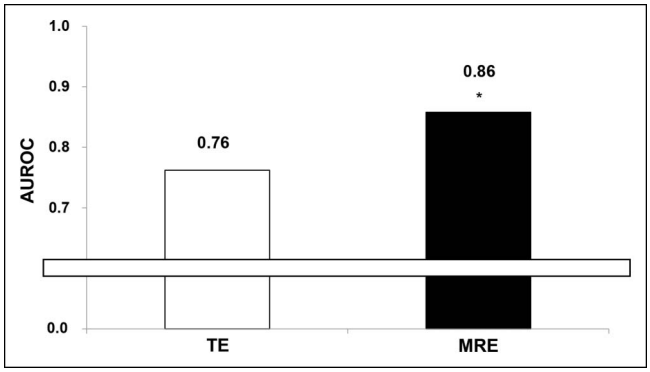

Figure 3. Diagnostic accuracy of noninvasive tests for detecting advanced fibrosis or NASH. The AUROC values are compared among TE and MRE for diagnosing advanced fibrosis (fibrosis ≥ stage 3) or NASH in patients with NAFLD. *AUROC significantly different from TE ($P < 0.05$). AUROC, area under the receiver operating characteristic curve; MRE, MR elastography. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TE, transient elastography.

Noninvasive tests for NASH are more limited. In a study with a small number of patients (n = 58) with NAFLD, MRE showed high accuracy (AUROC 0.93) for the diagnosis of NASH with a threshold of 2.74 kPa (36). Although TE, T1 mapping, and MRE are the indicators of liver fibrosis, liver stiffness was found to increase before the deposition of fibrotic material in an animal study (37). Moreover, it is well known that inflammation and elevation of serum ALT level are correlated with liver stiffness (38). For diagnosing NASH in the present study, the diagnostic accuracy of TE and MRE were significant, and T1 mapping was only meaningful in patients with mild-to-moderate steatosis. When patients with advanced fibrosis were excluded, TE and MRE were still significant for diagnosing NASH, with MRE showing a higher AUROC than TE. In terms of biomarkers for diagnosing NASH with MRE, further studies are needed, and combining MRE and other parameters could be promising.

Multiparametric MR is a promising technique for the evaluation of disease severity in patients with NAFLD (39). A noninvasive evaluation using MRI was the most accurate method for evaluating hepatic steatosis and fibrosis. Moreover, MRE was effective for the diagnosis of NASH, whereas T1 mapping also showed the diagnostic accuracy for NASH in patients with mild-to-moderate steatosis. For detecting advanced fibrosis or NASH, i.e., severe forms of NAFLD, MRE showed high accuracy (AUROC 0.86). Moreover, MRI could detect several lesions that were difficult to find using ultrasound. Indeed, in one female patient, a 3-cm HCC was detected by MRI, which was not detected on ultrasound. Although MRI is an expensive method, Eddowers et al. showed that multiparametric MR could reduce the cost burden of liver biopsy for the risk stratification (40). For accuracy and safety, multiparametric MR could be an attractive choice for evaluating disease severity in patients with NAFLD.

This study has several limitations. First, the diagnosis and identification of disease severity of NAFLD were determined with liver biopsy that has several limitations as described above. Second, there was a time interval between liver biopsy and TE or MRI. Although more than 90% of patients underwent TE and MRI within 90 days of biopsy, it is possible that a change in steatosis and fibrosis occurred during this interval. Finally, the proportions of patients with NASH (51.2%) and advanced fibrosis (21.1%) were high, probably because of the participation of patients with suspected advanced-stage NAFLD. The proportion of patients in this study would differ from that of general patients with NAFLD. However, this study has the strength that more than 100 patients were prospectively enrolled, and various analyses and comparisons were performed.

In conclusion, MRI accurately identified moderate-to-severe steatosis, advanced fibrosis, and steatohepatitis. Therefore, multiparametric MR is a valuable noninvasive method for evaluating disease severity in patients with NAFLD.

CONFLICTS OF INTEREST

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Although liver biopsy is the gold standard for the diagnosis of NAFLD and classification of disease severity, it has several limitations.
- ✓ NASH and fibrosis are important prognostic factors in patients with NALFD.

WHAT IS NEW HERE

- ✓ MRE showed high accuracy for detecting severe forms of NAFLD (advanced fibrosis or NASH).
- ✓ In terms of accuracy and safety, MR with multiparametric sequences could be an attractive choice for evaluating disease severity in patients with NAFLD.

TRANSLATIONAL IMPACT

- ✓ Multiparametric MR can effectively identify severe forms of NAFLD, such as severe steatosis, advanced fibrosis, and steatohepatitis.
- ✓ This valuable modality could be useful in the noninvasive evaluation of disease severity of NAFLD.

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