

# Comparison of the efficacy of Gd-EOB-DTPA-enhanced magnetic resonance imaging and magnetic resonance elastography in the detection and staging of hepatic fibrosis

Wen-Pei Wu, MD<sup>a,b</sup>, Cheng-In Hoi, BS<sup>c</sup>, Ran-Chou Chen, MD<sup>b</sup>, Ching-Po Lin, PhD<sup>d</sup>,  
Chen-Te Chou, MD, PhD<sup>a,b,\*</sup>

## Abstract

The present study compared the efficacy of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) and magnetic resonance elastography (MRE) in the estimation of hepatic fibrosis stages with histopathologic correlation.

This retrospective study included 104 patients (87 men and 17 women; mean age,  $60.6 \pm 10.6$  years) with chronic liver disease who underwent both Gd-EOB-DTPA-enhanced MRI and MRE. The relative enhancement (RE) ratio of the liver parenchyma and the contrast enhancement index (CEI) were calculated as  $(SI_{\text{postliver}} - SI_{\text{preliver}})/SI_{\text{preliver}}$  and  $SI_{\text{post}}/SI_{\text{pre}}$ , respectively, where  $SI_{\text{post}}$  and  $SI_{\text{pre}}$  were the liver-to-muscle signal intensity ratios on the hepatobiliary phase images and noncontrast-enhanced images, respectively. The liver stiffness values were measured using MRE stiffness maps. The diagnostic performance of MRE, RE ratios, and CEI values for hepatic fibrosis staging were compared.

The distribution of fibrosis stages was as follows: F0,  $n=3$  (2.9%); F1,  $n=12$  (11.5%); F2,  $n=17$  (16.3%); F3,  $n=26$  (25.0%); and F4,  $n=46$  (44.2%). MRE, RE ratios, and CEI values correlated significantly with hepatic fibrosis ( $r_s = .79, -.35, -.25$ , respectively,  $P < .05$ ). MRE showed a significantly higher diagnostic performance than did RE ratios and CEI values for each fibrosis stage, except while distinguishing the F1 fibrosis stage (CEI,  $P = .15$ ). A cutoff value of RE ratio = 0.89 can be used to identify patients with significant hepatic fibrosis, with positive predictive value, sensitivity, specificity, and negative predictive value of 93.2%, 61.8%, 73.3%, and 24.4%, respectively.

Gd-EOB-DTPA-enhanced MRI can potentially predict significant hepatic fibrosis. However, the diagnostic performance of MRE for hepatic fibrosis staging was superior to that of Gd-EOB-DTPA-enhanced MRI.

**Abbreviations:** Az = area under the ROC curve, CEI = contrast enhancement index, Gd-EOB-DTPA = gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid, MRE = magnetic resonance elastography, NPV = negative predictive value, PPV = positive predictive value, RE = relative enhancement, ROC = receiver operating characteristic, ROI = region of interest.

**Keywords:** cirrhosis, Gd-EOB-DTPA-enhanced MRI, hepatic fibrosis, magnetic resonance elastography

## 1. Introduction

Hepatic fibrosis is the accumulation of extracellular matrix proteins in response to acute or chronic liver diseases.<sup>[1,2]</sup> Hepatitis B and hepatitis C, which are major causes of chronic liver diseases, such as liver cirrhosis and hepatocellular

carcinoma, are highly prevalent in Taiwan.<sup>[3–5]</sup> The complications of liver cirrhosis and hepatocellular carcinoma are among the 10 leading causes of death in Taiwan annually. Therefore, hepatic fibrosis is very important for diagnosis in clinical situations. Liver biopsy is the gold standard for fibrosis staging in clinical diagnosis. However, it is invasive and is not preferred by patients. Furthermore, it lacks repeatability for tracing patient's status after treatment. In addition, only some of the local liver parenchymal tissues are extracted for pathological analysis; therefore, liver biopsy cannot predict the fibrosis severity of whole liver. Thus, a noninvasive and reliable method is required for fibrosis staging.<sup>[6–8]</sup>

A hepatocyte-specific contrast agent, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), has been widely used. It has been reported to enhance the detection and diagnosis of hepatocellular carcinoma and has been regarded as a functional contrast medium.<sup>[9,10]</sup> Hepatocytes internalize Gd-EOB-DTPA, which allows the signal intensity (SI)-based measurement of the liver parenchyma for quantitative assessment of liver functions.<sup>[11–13]</sup> It may be a potential one-step method for evaluating the liver functions and liver tumor characteristics. Previous studies showed that patients with liver dysfunction presented with reduction of liver parenchymal enhancement by the quantitative methods of direct measurement of liver

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<sup>a</sup> Department of Radiology, Chang-Hua Christian Hospital, Changhua.

<sup>b</sup> Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, <sup>c</sup> Department of Radiology, Centro Medico Pedder, Macau, <sup>d</sup> Brain Connectivity Laboratory, National Yang-Ming University, Taipei, Taiwan.

\* Correspondence: Chen-Te Chou, Department of Radiology, Chang-Hua Christian Hospital, Changhua, Taiwan, No. 135, Nanxiao Street, Changhua, 500 Taiwan (e-mail: 96888@cch.org.tw).

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parenchyma signal intensity.<sup>[14–18]</sup> However, it was still uncertain whether the severity of hepatic fibrosis would correlate the impaired uptake of Gd-EOB-DTPA and in turn the reduced liver parenchymal enhancement due to the damaged severity of hepatocyte function and the decreased number of hepatocytes.

Magnetic resonance elastography (MRE) is a newly developed noninvasive method to predict the stages of hepatic fibrosis, to identify the esophageal varices in patients with liver cirrhosis, and for prognosis of patients with acute liver injury.<sup>[19–22]</sup> To date, liver stiffness measurements obtained through MRE have been reported to accurately predict hepatic fibrosis in patients with chronic hepatitis. However, MRE requires active and passive drivers and is not widely used as yet.

Therefore, the present study compared the diagnostic performances of Gd-EOB-DTPA-enhanced MRI and MRE in hepatic fibrosis staging.

## 2. Materials and methods

### 2.1. Patients

This retrospective study was approved by the institutional review board. The following patients were included in the study: patients with chronic liver disease who received histopathological confirmation for predicting the different stages of hepatic fibrosis and those who underwent Gd-EOB-DTPA-enhanced MRI and MRE within 6 months before histological confirmation. From February 2012 to December 2014, a total of 104 patients (87 men and 17 women; mean age,  $60.6 \pm 10.6$  years; body mass index,  $24.5 \pm 3.5$  kg/m<sup>2</sup>) were included in the present study.

### 2.2. Magnetic resonance imaging

All MRI examinations of the liver were performed using a 1.5-T MRI scanner (Avanto, Siemens Healthcare, Erlangen, Germany) with a 16-channel phased-array body coil for obtaining routine Gd-EOB-DTPA-enhanced MRI and MRE images. All patients were fasted for at least 4 hours before MRI examinations. For Gd-EOB-DTPA-enhanced MRI, all patients received a 0.025 mmol/kg (0.1 mL/kg) peripheral IV bolus of Gd-EOB-DTPA (Primovist, Bayer Schering Pharma, Berlin, Germany) at a speed of approximately 2 mL/s. The line was flushed with 20 mL of 0.9% saline. MRI examinations were performed using dynamic T1-weighted (T1-W) fat-saturated 3-dimensional volumetric interpolated breath-holding sequences (repetition time [TR]/echo time [TE], 3.7 ms/1.4 ms; flip angle, 10°; slice thickness, 3 mm; matrix, 512 × 400; number of excitations, 1) before and 25 to 30 seconds (arterial phase), 55 to 60 seconds (portal phase), 85 to 90 seconds (venous phase), and 20 minutes (hepatobiliary phase) after the injection of Gd-EOB-DTPA.

### 2.3. Magnetic resonance elastography

MRE was performed after Gd-EOB-DTPA-enhanced MRI. MRE was performed with the patient in a supine position using a cylindrical pneumatic passive driver (diameter, 19 cm; thickness, 1.5 cm; Rochester, MN). The passive driver was placed over the right lower chest and anterior abdominal wall of the patient with the center of the driver at the xiphisternum level. The active driver generated continuous low-amplitude mechanical vibrations of 60 Hz. The active and passive drivers were connected by a 7.6-cm long plastic tube. Mechanical waves were transmitted into the liver by the passive driver. The parameters of the MRE sequence were as follows: TR/TE, 50 milliseconds/22.7 milliseconds; flip

angle, 25°; bandwidth, 260 Hz/pixel; imaging frequency, 63.5 MHz; matrix, 256 × 256; slice thickness, 7 mm; field of view, 400 × 400 mm<sup>2</sup>. The scanning time of each axial slice was 21 seconds per breath-hold. A total of 5 slices were acquired for each MRE examination. All postprocessing steps were performed automatically, and the liver stiffness values were presented in kilopascal. The MRE software also generated a confidence map, automatically demonstrating the regions with adequate wave amplitude.

### 2.4. Liver stiffness measurement

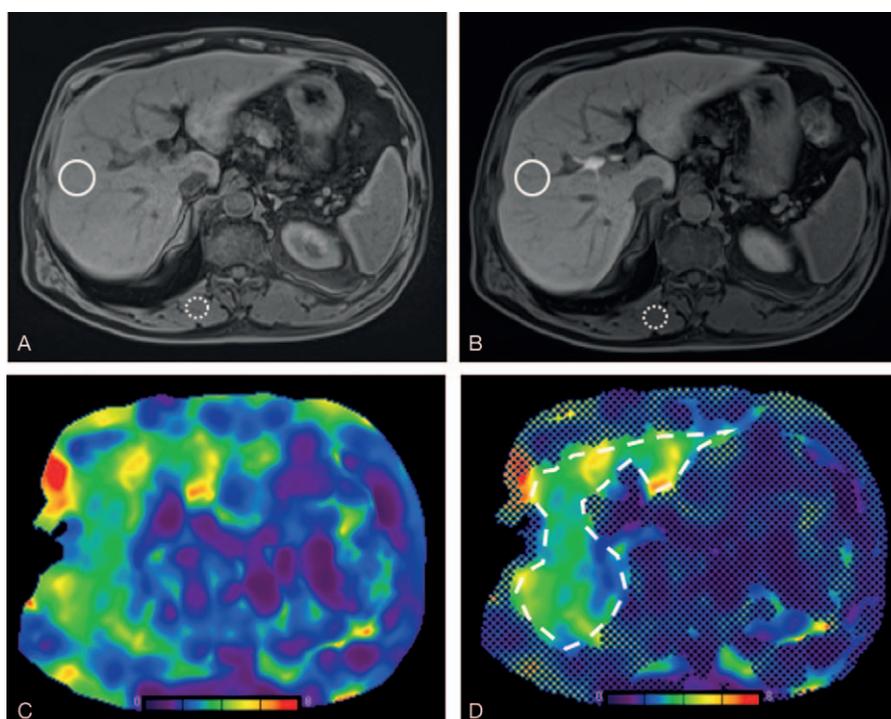
All analyses were performed on a dual-screen diagnostic workstation (GE Healthcare, Milwaukee, WI). Two readers (WPW and CIH, with 8 and 2 years of experience in interpreting liver MR images, respectively), individually analyzed the MRE measurements. The readers were blinded to patients' clinical data and histopathologic results. And to determine the intraclass reliability, 1 reader (CIH) obtained all quantitative MRE measurements 2 times with the time interval of 6 months. For measuring the liver stiffness, the wave images were first evaluated for adequate wave quality. On each axial image of the confidence map, a region of interest (ROI) was manually drawn to include only the liver parenchyma (Fig. 1). The areas on the confidence map that were considered invalid were excluded. In addition, we attempted to avoid artifacts, such as wave interference, liver edges, major blood vessels, and hepatic tumors. The mean liver stiffness values for each MR elastogram were recorded. The stiffness values of the liver parenchyma were calculated by averaging the mean liver stiffness values of the 5 slices in each patient.

### 2.5. Gd-EOB-DTPA-enhanced MRI

The Gd-EOB-DTPA-enhanced MRI SIs were measured on the same workstation 2 times with the time interval of 6 months to determine the intraclass reliability. On the precontrast T1-W images and the Gd-EOB-DTPA-enhanced hepatobiliary phase images, circular ROIs were drawn on the anterior lobe of the liver and paraspinous muscle on the same axial image as large as possible, excluding the major blood vessels, hepatic tumors, liver edges, and artifacts (Fig. 1). Identical ROIs were placed on the images before and after the administration of Gd-EOB-DTPA. Quantitative liver enhancement measurements included the relative enhancement (RE) ratio and the contrast enhancement index (CEI). RE ratios of the liver were calculated using the precontrast and postcontrast hepatobiliary phase SI measurements of the liver parenchyma as follows:  $(SI_{\text{postliver}} - SI_{\text{preliver}}) / SI_{\text{preliver}}$ .<sup>[23]</sup> The CEI values were calculated as  $SI_{\text{post}} / SI_{\text{pre}}$ , and the liver-to-muscle SI ratio was calculated separately as a ratio of the SI of the liver parenchyma to that of the paraspinous muscle on the noncontrast-enhanced images ( $SI_{\text{pre}}$ ) and on the hepatobiliary phase images ( $SI_{\text{post}}$ ).<sup>[24]</sup>

### 2.6. Histopathological analysis

Hepatic fibrosis was diagnosed based on the histopathological analysis of the percutaneous liver biopsy specimens (n=28) or surgical resection specimens (n=76). Liver biopsies were performed using an 18-gauge cutting needle biopsy under sonography or computed tomography guiding. The location of biopsy was in left lobe (n=6) or in right lobe (n=21). Tissue samples were fixed in buffered formalin and embedded in



**Figure 1.** A 65-y-old man with chronic liver disease and F2 hepatic fibrosis (confirmed through pathologic analysis) underwent gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) and MR elastography (MRE): (A) precontrast phase and (B) hepatobiliary phase of the T1-weighted image; the region of interests (ROIs) in the liver parenchyma (solid line) and paraspinous muscle (dotted line) at the precontrast and hepatobiliary phases. (C) MR elastogram and (D) liver stiffness value was determined at the confidence area (dotted line). The mean liver stiffness value, contrast enhancement index (CEI), and relative enhancement (RE) ratio measured through MRE were 3.43, 1.67, and 0.89 kPa, respectively.

paraffin. All specimens were stained with hematoxylin and eosin stain and Masson trichrome stain and were analyzed by an experienced attending hepatopathologist who was blinded to the clinical, biochemical, and MR examination results. All liver samples with specimen size  $\geq 10$  mm and portal tracts  $\geq 5$  were considered adequate. Hepatic fibrosis was staged on a scale of F0 to F4 according to the METAVIR scoring system (F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis with few septa; F3: numerous septa without cirrhosis; F4: cirrhosis).<sup>[25]</sup>

### 2.7. Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (version 20.0 for Windows; Chicago, IL) and MedCalc Programme (MedCalc Software, Mariakerke, Belgium). Spearman correlation analysis was performed to evaluate the relationship between hepatic fibrosis stages, RE ratio, CEI values, and liver stiffness values measured through MRE. To investigate the interobserver reliability and intra-observer reliability, absolute agreement intraclass correlation coefficients were calculated for both MRE, RE ratios, and CEI ratios. The diagnostic performances of RE ratios, CEI values, and MRE were determined through receiver operating characteristic (ROC) analysis. In addition, the sensitivity, specificity, area under the ROC curve (Az), positive predictive value (PPV), negative predictive value (NPV), and accuracy of RE ratios, CEI values, and MRE were demonstrated. The MedCalc ROC curve module was used to compare the significant differences between the Azs for RE ratio, CEI, and MRE.  $P < .05$  was considered statistically significant.

## 3. Results

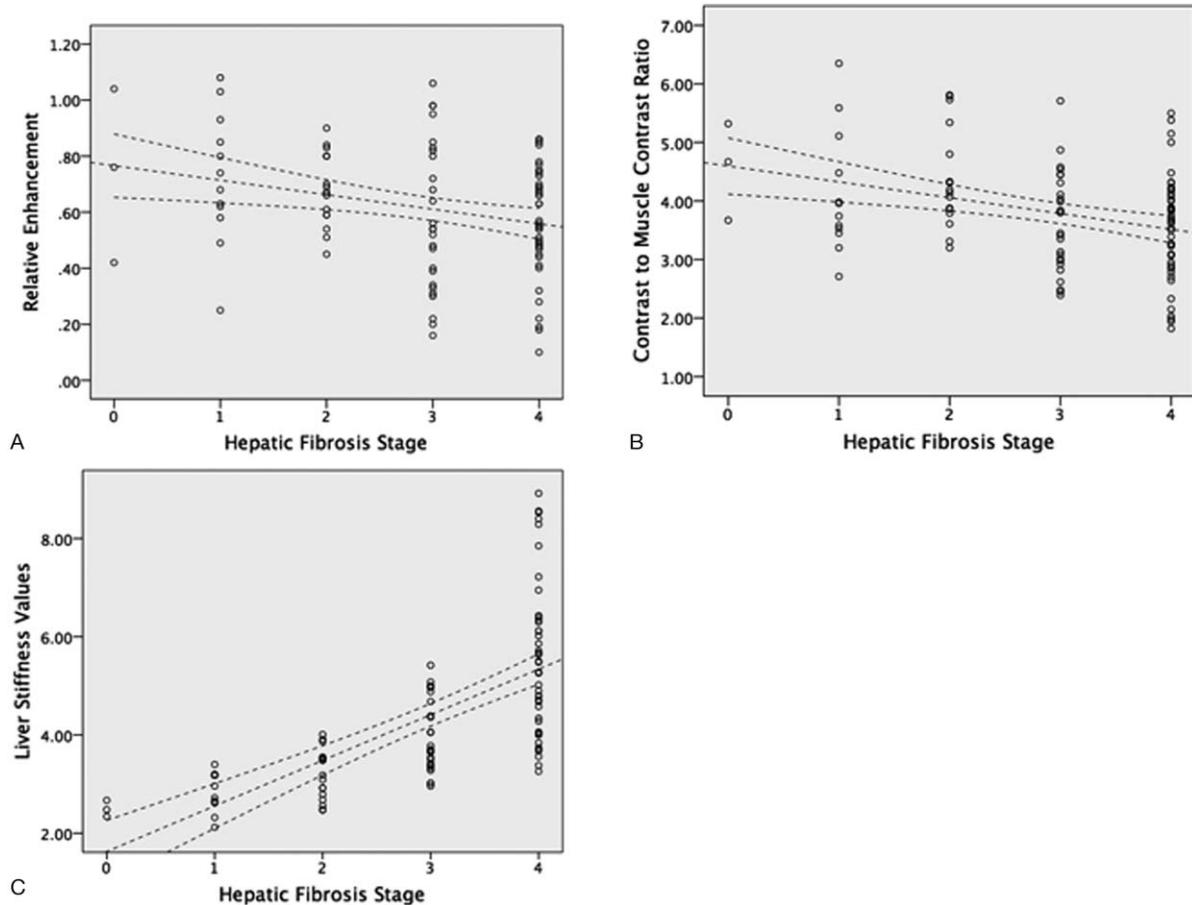
### 3.1. Baseline characteristics of the study patients

Table 1 presents the baseline clinical characteristics of the study patients. The distribution of fibrosis stages among the 104 patients were as follows: F0,  $n=3$  (2.9%); F1,  $n=12$  (11.5%); F2,  $n=17$  (16.3%); F3,  $n=26$  (25.0%); and F4,  $n=46$  (44.2%). No adverse events occurred among these studies.

**Table 1**  
Demographic data of the patients with chronic hepatitis.

Number of patients	104
Gender (male/female)	87/17
Age (mean $\pm$ SD)	60.6 $\pm$ 10.6
BMI, kg/cm <sup>2</sup>	24.5 $\pm$ 3.5
Chronic liver disease	
HBV	54
HCV	32
HBV+HCV	1
Alcoholic liver disease	6
Unknown	11
METAVIR scoring system	
F0	3
F1	12
F2	17
F3	26
F4	46

BMI = body mass index, HBV = hepatitis B virus, HCV = hepatitis C virus, SD = standard deviation. Unknown liver diseases may be caused by nonalcoholic steatohepatitis, autoimmune hepatitis, and cryptogenic hepatitis.



**Figure 2.** Scatterplots for (A) relative enhancement (RE) ratio, (B) contrast enhancement index (CEI), and (C) liver stiffness values measured through magnetic resonance elastography (MRE) at different hepatic fibrosis stages. Spearman correlation demonstrated the relationships between the hepatic fibrosis stages and RE ratios ( $r_s = -0.35$ ;  $P < .001$ ), CEI values ( $r_s = -0.25$ ;  $P = .01$ ), and liver stiffness values ( $r_s = 0.79$ ;  $P < .001$ ).

### 3.2. Diagnostic performance of MRE, RE Ratios, and CEI values in predicting hepatic fibrosis stages

The mean liver stiffness values measured through MRE increased as the hepatic fibrosis stages progressed ( $r_s = 0.79$ ,  $P < .001$ ; Fig. 2C). The interobserver reliability between MRE-reader 1 and MRE-reader 2 was 0.98,  $P < .001$ . The intraobserver reliability of MRE was 0.95, indicating excellent reliability. MRE-measured liver stiffness values differed significantly between all stages of liver fibrosis ( $P < .05$ ). The optimal cutoff values of liver stiffness were 2.68 kPa for  $\geq F1$  (F0 vs F1-F4; sensitivity, 92.1%; specificity, 100%), 3.23 kPa for  $\geq F2$  (F0-F1 vs F2-F4; sensitivity, 86.5%; specificity, 93.3%), 3.56 kPa for  $\geq F3$  (F0-F2 vs F3-F4; sensitivity, 83.3%; specificity, 90.6%), and 4.02 kPa for F4 (F0-F3 vs F4; sensitivity, 82.6%; specificity, 81.0%).

Negative correlations were observed between the RE ratios, CEI values, and the hepatic fibrosis stages independently (RE ratio,  $r_s = -0.35$ ,  $P < .001$ ; CEI,  $r_s = -0.25$ ,  $P = .01$ ), indicating that as the hepatic fibrosis stages progressed, the RE ratios and CEI values decreased (Fig. 2A and B). The interobserver and intraobserver reliability for RE and CEI was 0.85 and 0.84, 0.90 and 0.82, respectively, and the RE ratios and CEI measured values had excellent reliability. RE differed significantly between all stages of fibrosis with the exception of F0 and F1 ( $P = .63$ ). The cutoff values of RE ratio were 1.12 for  $\geq F1$  (sensitivity, 91.1%; specificity, 33.3%), 0.89 for  $\geq F2$  (sensitivity, 61.8%; specificity,

73.3%), 0.81 for  $\geq F3$  (sensitivity, 58.3%; specificity, 84.4%), and 0.79 for F4 (sensitivity, 63.0%; specificity, 72.4%). CEI differed significantly only between F1 and F2 ( $P = .03$ ), and between F2 and F3 ( $P = .004$ ). The cutoff values of CEI were 1.75 for  $\geq F1$  (sensitivity, 74.3%; specificity, 66.7%), 1.57 for  $\geq F2$  (sensitivity, 49.4%; specificity, 80.0%), 1.55 for  $\geq F3$  (sensitivity, 52.8%; specificity, 81.3%), and 1.51 for F4 (sensitivity, 39.1%; specificity, 70.7%; Table 2, Fig. 3).

The diagnostic performances of MRE, RE ratios, and CEI values at corresponding METAVIR hepatic fibrosis stages were compared; RE ratios had a slightly higher Az than did CEI values, except when distinguishing the F1 fibrosis stage. However, the differences were not significant ( $P = .29, .84, .26$ , and  $.10$  for  $\geq F1$ , F2, F3, and F4, respectively; not shown in Table 2).

As shown in Table 2, MRE had an excellent and significantly superior diagnostic ability than that of RE ratio and CEI in predicting each METAVIR hepatic fibrosis stage, except when predicting F0 versus F1 to F4 (CEI,  $P = .15$ ).

## 4. Discussion

Gd-EOB-DTPA is a gadolinium-based contrast agent, which is mediated by a functional hepatocyte through an active transport system that involves factors such as the organic anion-transporting polypeptide. The intracellular uptake of Gd-EOB-DTPA may decrease because of impaired liver

**Table 2**  
**Optimal cutoff values of liver stiffness values measured through MRE, RE ratios, and CEI values for different hepatic fibrosis stages.**

	Cutoff	Az (95% CI)	Sn	Sp	PPV	NPV	Accuracy	P
RE								
≥F1	≤1.12	0.569 (0.469–0.666)	91.1%	33.3%	97.9%	10.0%	89.4%	.04
≥F2	≤0.89	0.672 (0.573–0.761)	61.8%	73.3%	93.2%	24.4%	63.5%	.002
≥F3	≤0.81	0.725 (0.628–0.808)	58.3%	84.4%	89.4%	47.4%	66.4%	<.001
≥F4	≤0.79	0.666 (0.567–0.756)	63.0%	72.4%	64.4%	71.2%	68.3%	<.001
CEI								
≥F1	≤1.75	0.634 (0.534–0.726)	74.3%	66.7%	98.7%	7.1%	74.0%	.15
≥F2	≤1.57	0.661 (0.562–0.751)	49.4%	80.0%	93.6%	21.1%	53.9%	.002
≥F3	≤1.55	0.673 (0.574–0.762)	52.8%	81.3%	86.4%	43.3%	61.5%	<.001
≥F4	≤1.51	0.602 (0.501–0.696)	39.1%	70.7%	52.9%	60.0%	57.7%	<.001
MRE, kPa								
≥F1	≥2.68	0.955 (0.896–0.986)	92.1%	100.0%	100.0%	27.3%	92.3%	
≥F2	≥3.23	0.933 (0.867–0.973)	86.5%	93.3%	98.7%	53.9%	87.5%	
≥F3	≥3.55	0.935 (0.869–0.974)	83.3%	90.6%	95.2%	70.7%	85.6%	
≥F4	≥4.02	0.909 (0.836–0.956)	82.6%	81.0%	77.6%	85.5%	81.7%	

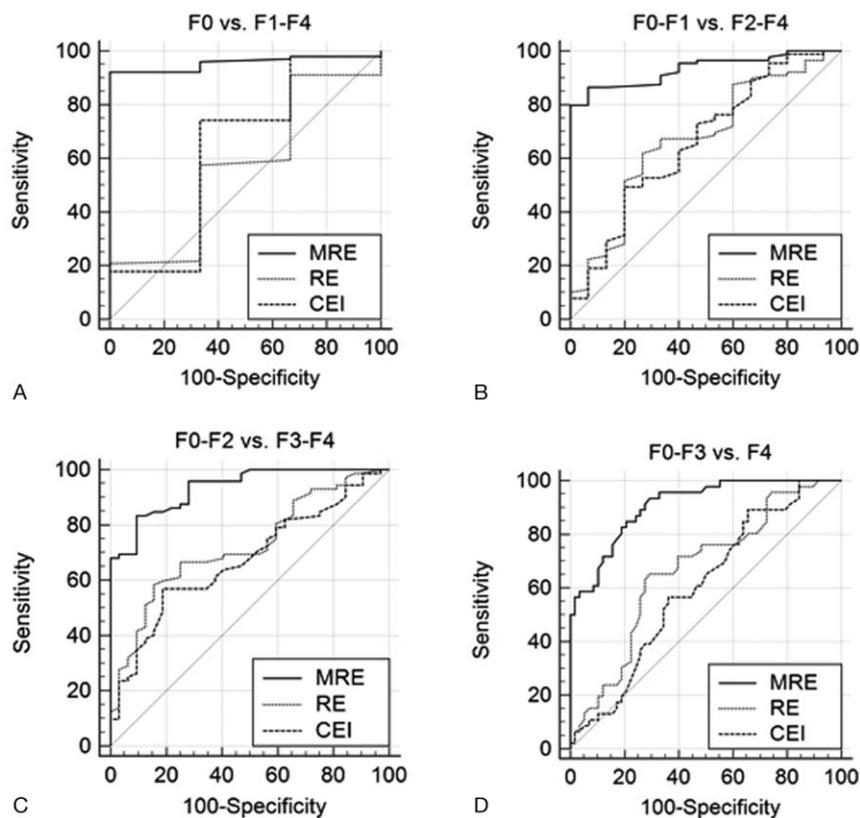
Az=area under the curve, CEI=contrast enhancement index, kPa=kilopascal, MRE=magnetic resonance elastography, NPV=negative predictive value, PPV=positive predictive value, RE=relative enhancement, Sn=sensitivity, Sp=specificity.

Accuracy represents the ratios of patients who were classified appropriately (true positive + true negative).

P value represents the comparison between the area under the curve of RE ratio and CEI with that of MRE at each corresponding fibrosis stage.

functions.<sup>[13]</sup> Therefore, SI measurements of the liver parenchyma in the hepatobiliary phase after the administration of a peripheral IV bolus of Gd-EOB-DTPA could be a direct quantitative method for assessing the degree of hepatocellular

functions. Moreover, Gd-EOB-DTPA-enhanced MRI is based on a routine clinical imaging protocol and could provide additional information in addition to accurate diagnosis of focal hepatic lesions.



**Figure 3.** Receiver operating characteristic (ROC) curve analysis for F<sub>0</sub>≥1 (A), F<sub>0</sub>≥2 (B), F<sub>0</sub>≥3 (C), F<sub>0</sub>≥4 (D) of magnetic resonance elastography (MRE), relative enhancement ratio (RE), and contrast enhancement index (CEI) of liver parenchyma on gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) images.

**Table 3****Comparison of quantitative methods on Gd-EOB-DTPA-enhanced MR images to staging hepatic fibrosis and to predict significant fibrosis in the literature review.**

Author	Year	Journal	N	Disease (n)	Fibrosis (n)	Tesla	Quantitative methods	Correlation	AUC	Cutoff	Sn, %	Sp, %
Watanabe et al	2011	Radiology	114	Chronic Liver disease or focal liver lesion (99) None (15)	F0 (18) F1 (20) F2 (15) F3 (31) F4 (30)	3	CEI Post-liver SI ratio	−0.79 −0.56				
Motosugi et al	2011	Magn Reson Imaging	100	HCV (45) HBV (17) Alcoholism (2) Others (20) None (16)	F0 (16) F1 (17) F2 (10) F3 (21) F4 (36)	1.5	Liver-spleen contrast ratio Corrected liver enhancement ratio Spleen index	−0.393 −0.322 −0.331	0.68	1.76	74.6	56.0
Choi et al	2013	Invest Radiol	168	HBV (120) HCV (13) Alcoholism (6) Others (17)	F0 (23) F1 (14) F2 (32) F3 (39) F4 (65)	1.5	CEI	−0.378	0.622	1.609	46.3	82.4
Feier et al	2013	Radiology	102	HCV (38) HBV (21) Autoimmune hepatitis (14)	F0 (23) F1 (11) F2 (14) F3 (13) F4 (41)	3	RE	−0.65	0.82	1.18	75	77
Jang et al	2013	Ann Hepatol	113	HBV (82) HCV (9) Alcoholism (5) None (17)	F0 (13) F1 (18) F2 (15) F3 (32) F4 (35)	3	CEI	−0.545	0.703	1.32	50	93.5
Nojiri et al	2013	J Gastroenterol Hepatol	224	HCV (224)	F0 (26) F1 (39) F2 (31) F3 (66) F4 (62)	1.5	RE Liver-to-intervertebral disk ratio Liver-to-muscle ratio Liver-to-spleen ratio	−0.478 −0.661 −0.463 −0.376	0.83 0.88 0.83 0.77	1.38	50.9	97.4
Park et al	2014	World J Gastroenterol	42	HBV (16) HCV (4) NAFLD (3) None (19)	Fibrosis (23) Nonfibrosis (19)	3	CEI	−0.321				
Wu et al	Present		104	HBV (54) HCV (32) HBV+HCV (1) Alcoholism (6) Unknown (11)	F0 (3) F1 (17) F2 (17) F3 (25) F4 (42)	1.5	RE CEI	−0.345 −0.246	0.672 0.661	0.89 1.57	61.8 49.4	73.3 80.0

AUC=area under the receiver operating characteristic curve, CEI = contrast enhancement index, HBV=hepatitis B virus, HCV=hepatitis C virus, NAFLD=nonalcoholic fatty liver disease, RE = relative enhancement, Sn=sensitivity, Sp=specificity.

In our study, the RE ratio ( $r_s = -0.35$ ;  $P < .001$ ) and CEI ( $r_s = -0.25$ ;  $P = .01$ ) exhibited mild negative correlations with the hepatic fibrosis stages, indicating that as the hepatic fibrosis stages progress, the patients' RE ratios and CEI values might decrease. Quantitative analysis of the liver parenchyma revealed that the Az of the RE ratio at each fibrosis stage was slightly higher than that of CEI, except at the F1 stage; however, the differences were not significant. The diagnostic performance of different quantitative methods on Gd-EOB-DTPA MR images varied as the correlation ranged from  $-0.32$  to  $-0.79$  (Table 3). Our results are consistent with previous studies.<sup>[11,13,15,24]</sup> By contrast, Watanabe et al<sup>[23]</sup> and Feier et al<sup>[19]</sup> revealed a moderately strong correlation between Gd-EOB-DTPA-enhanced MRI and hepatic fibrosis stages. This inconsistency in the findings may be due to relatively fewer patients with F0 hepatic fibrosis being enrolled in our study, which might

affect the statistical results. However, in clinical practice, patients who undergo Gd-EOB-DTPA-enhanced MRI imaging for focal liver lesions often have chronic liver disease. In addition, differences between the MRI scanners may affect the results; a higher contrast-to-noise ratio of gadolinium chelate-based contrast agents can be achieved with a 3.0-T MRI scanner than with a 1.5-T MRI scanner. Therefore, the differences in the SIs of the liver parenchyma before and after Gd-EOB-DTPA injection may be more pronounced with a 3.0-T MRI scanner than with a 1.5-T MRI scanner.

Our results revealed that RE ratios and CEI values have acceptable PPV (93.2–98.7%) for distinguishing between mild and significant fibrosis and a low NPV (7.1–24.4%). For quantitative assessment of the contrast enhancement in liver parenchyma, Gd-EOB-DTPA-enhanced MRI might be a possible method for predicting significant hepatic fibrosis using the cutoff

values of 0.89 and 1.57 for RE ratio and CEI, respectively. Therefore, Gd-EOB-DTPA-enhanced MRI of the liver might be a potential one-step method for evaluating hepatic fibrosis stages and the characteristics of the focal liver lesions. Recently, optimal personalized treatments have been developed to reduce the risk of chronic liver disease-associated complications. Patients with significant fibrosis have benefited by initiating antiviral therapy according to the latest American Association for the Study of Liver Disease and European Association for the Study of Liver treatment guidelines.<sup>[26–29]</sup> Although noninvasive diagnostic imaging has been used as an initial test for risk stratification of hepatic fibrosis (National Institute for Health and Care Excellence),<sup>[30]</sup> Gd-EOB-DTPA-enhanced MRI cannot replace liver biopsy because of low sensitivity and NPV.

The liver stiffness values measured through MRE ( $r_s = 0.79$ ) had a strong correlation with hepatic fibrosis stages. Our results indicated that diagnostic performance of MRE is significantly higher than that of RE ratios and CEI values, which may be because the liver stiffness values are related to the pathological changes that occur in the liver structure during hepatic fibrosis. By contrast, RE ratios and CEI values are associated with hepatocellular functions. Moreover, a patient with significant fibrosis or liver cirrhosis may have satisfactory liver functions.

In our study, the liver stiffness values measured through MRE not only showed a substantial correlation with the hepatic fibrosis stages but also effectively predicted the hepatic fibrosis stages. MRE predicted significant fibrosis ( $\geq F2$ ) with high sensitivity (86.5%) and specificity (93.3%). Therefore, MRE can possibly predict significant fibrosis and provide early clinical diagnosis.<sup>[27,31]</sup>

The present study had several limitations. First, this study had a retrospective design; therefore, the relatively small number of patients might undermine the reliability. Second, the hepatic fibrosis stages were not equally distributed in our study population; only a few patients with F0 fibrosis were included, which may have affected the statistical results. Moreover, only patients with chronic liver disease who underwent both Gd-EOB-DTPA-enhanced MRI and MRE were included, which might explain the low prevalence of early fibrosis in our study population. Therefore, additional prospective investigations with a larger study population are warranted.

In conclusion, the diagnostic performance of MRE for hepatic fibrosis staging is superior to that of Gd-EOB-DTPA-enhanced MRI. RE ratios and CEI values exhibited a mild correlation with the hepatic fibrosis stages. MRE is a promising noninvasive tool for hepatic fibrosis staging.

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