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Magnetic Resonance Elastography for Staging Liver Fibrosis in Chronic Hepatitis C

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Purpose: We evaluated the use of magnetic resonance (MR) elastography (MRE) for staging liver fibrosis in patients with chronic hepatitis C and compared the ability of MRE and serum fibrosis markers for discriminating each stage of fibrosis.

Methods: We evaluated 114 patients with chronic hepatitis C in whom the pathological fibrosis stage was determined (fibrosis stage 0 [F0], 3; F1, 15; F2, 28; F3, 25; and F4, 43). All patients underwent MRE using a 1.5-tesla MR system and pneumatic driver system. We measured stiffness values (kPa) of the liver in a circular region of interest placed on elastograms. We determined the optimal cutoff value and diagnostic ability for discriminating each stage of fibrosis using receiver operating characteristic (ROC) curve analysis and compared the discriminative ability of MRE with that of serum fibrosis markers.

Results: The mean stiffness values of the liver increased with stage of fibrosis: F0, 2.10 ± 0.10 kPa; F1, 2.42 ± 0.29 kPa; F2, 3.16 ± 0.32 kPa; F3, 4.21 ± 0.78 kPa; and F4, 6.20 ± 1.08 kPa. The mean area under the ROC curve (Az) values for discriminating liver fibrosis stages were: $\geq$ F1, 0.984 (95% confidence interval,

0.933–0.996); $\geq$ F2, 0.986 (0.956–0.996); $\geq$ F3, 0.973 (0.935–0.989); and $\geq$ F4, 0.976 (0.945–0.990). The Az values for discriminating fibrosis stages were significantly higher for MRE than serum fibrosis markers.

Conclusion: MRE is a reliable technique for staging liver fibrosis and discriminating liver fibrosis stages in patients with chronic hepatitis C.

Keywords: *hepatitis C, hepatic fibrosis, MR elastography*

Introduction

Chronic liver disease can lead to hepatic fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma. Management of patients with chronic liver disease requires knowledge of the stage of fibrosis because of its close association with prognosis and hepatocarcinogenesis.^{1,2} Liver fibrosis stage is commonly determined by liver biopsy and assessment of the pathology—the only means of direct examination of fibrosis in tissue. However, liver biopsy is associated with such complication risks as hemorrhage and infection and inherent problems that include sampling error, high interob-

server variability, and low patient acceptance.^{3–5} Alternative noninvasive methods for evaluating liver fibrosis have therefore been developed, which include the assessment of such proposed serum fibrosis markers as the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR),⁶ the AST-to-platelet ratio index (APRI),⁷ and the FIB-4 index.⁸

Magnetic resonance (MR) elastography (MRE) was developed as a noninvasive method for measuring liver stiffness and is currently used primarily for staging liver fibrosis in the clinical setting. Though its sufficient reproducibility^{9–11} and high diagnostic ability for staging liver fibrosis are reported,¹² previous studies of liver MRE have included cases of hepatic fibrosis of various causes, including type B and C viral hepatitis and alcoholic hepa-

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titis.^{12–14} Evaluation of cases with a single underlying disease might better elucidate the diagnostic performance of MRE because certain differences in fibrotic patterns may affect stiffness value.¹⁵ For example, pericellular fibrosis is a distinguishing feature of alcoholic hepatitis, while periportal degeneration and fibrosis is believed to be more prominent in type C viral hepatitis than alcoholic hepatitis.¹⁶ Focal necrosis and inflammatory cell infiltration are also believed to be more advanced in type B than type C viral hepatitis.

We evaluated MRE for staging liver fibrosis in patients with type C chronic hepatitis and compared the discriminative ability of MRE and serum fibrosis markers, including the AAR, APRI, and FIB-4 index, at each fibrosis stage.

Materials and Methods

Patients

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki. Our institutional review board approved the study, and written informed consent was obtained from all patients who underwent MRE. Between January 2010 and May 2012, 713 patients with chronic hepatic disease underwent MRE at our institution; all patients had undergone MR for liver cancer screening. Inclusion criteria for the study were: (1) type C chronic hepatitis, (2) available MRE data, (3) pathological determination of liver fibrosis stage within 2 months of MRE, and (4) available laboratory test results within one week of MRE. We excluded 5 patients with severe iron deposits in whom the T_2^* value of the liver was very low, which would preclude signal acquisition by MRE using a gradient-echo sequence. We also excluded patients with both type C and type B hepatitis ($n=4$) or both type C and alcoholic hepatitis ($n=1$). After retrospectively matching radiological and pathological data, we identified 114 patients who met the inclusion criteria (86 men, 28 women; aged 39 to 86 years, mean age 65.8 ± 9.7 years). According to the pathological database of our institution, the diagnosis of fibrosis stage was confirmed by biopsy in 56 cases or resection in 58. Those reports were written by one of 3 diagnostic pathologists with 10 to 16 years' experience used by hematoxylin and eosin stain and Masson trichrome stain. The staging was performed using Metavir scoring system. The pathological stage of liver fibrosis was F0 in 3 patients, F1 in 15, F2 in 28, F3 in 25, and F4 in 43.

Serum fibrosis markers

We calculated the values for the serum fibrosis markers, the AAR, APRI, and FIB-4 index, using the following formulas, where ULN is the upper limit of normal AST level and PLT is the platelet count: $AAR = \text{AST}[\text{U/L}] / \text{ALT}[\text{U/L}]$; $APRI = ([\text{AST}[\text{U/L}] / \text{ULN}] / \text{PLT} [10^9/\text{L}]) \times 100$; and $\text{FIB-4 index} = (\text{age} [\text{years}] \times \text{AST}[\text{U/L}]) / (\text{PLT} [10^9/\text{L}] \times \text{ALT}[\text{U/L}]^{1/2})$.

MR imaging

MRE was performed using a superconducting magnet operating at 1.5T (Signa EXCITE HD; GE Medical Systems, Milwaukee, WI, USA) and an 8-channel phased-array coil and before administration of contrast material. Images were obtained with patients in supine position using a cylindrical passive driver placed across the right chest wall to deliver vibrations via a transcostal approach.¹⁷ The vibrator, placed outside the MR examination room, produced a pneumatic vibration that was delivered to the passive driver via a plastic cylinder. The passive driver was attached using a rubber belt to deliver the vibration to the patient's chest wall and the liver. The vibration generator and passive driver were developed at Mayo Clinic (Rochester, MN, USA).

A 2-dimensional gradient-echo MRE sequence was used. The images were acquired in the transverse plane. Scanning position was set above the gallbladder and below the subphrenic region of the liver. For acquisition of liver images at consistent positions at each phase offset, patients were asked to hold their breath after expiration.¹² The frequency of the driver was 60 Hz and the amplitude was 60%. A parallel imaging technique was not used. Table 1 shows other parameters.

Table 1. Magnetic resonance imaging parameters

Sequence	Two-dimensional gradient-echo T_1 -weighted image
Repetition time/echo time (ms)	100/27
Matrix	256 × 64
Field of view (cm)	30–34 × 40–45
Section thickness/intersection gap (mm)	10/5
Number of signals acquired	1
Flip angle (degrees)	30
Acquisition time (s)	13
Axis of motion-sensitizing gradient pulse	z

Analysis of liver stiffness

The MR scanner automatically generates elastograms by processing the acquired propagating shear wave images according to an inversion algorithm previously described.^{18,19} Shear stiffness of the tissue was determined as a pixel value (kPa).^{19,20} One of the authors (S.I.), with 8 years' radiology experience, referred to elastograms to place a region of interest (ROI) in the right lobe of the liver. We chose a slice near the center of the driver for ROI measurement because the traveling direction of the penetrating wave was considered parallel to the imaging plane around the driver center and because it is necessary to ensure that the wave travels along the imaging plane to avoid overestimation of the wavelength. ROIs were obtained for each patient, and the average value was recorded. As a rule, the ROI was at least 1.5 cm² and exclud-

ed blood vessels, the liver edge, and the area where interference by propagating waves was observed on phase images. One ROI was placed for each patient.

Statistical analysis

We calculated the mean and standard deviation (SD) of liver stiffness and serum fibrosis markers for each liver fibrosis stage, F0, F1, F2, F3, and F4. We used Spearman's rank correlation coefficient to calculate the correlation coefficient between fibrosis stage and these variables. Correlation was considered strong if the absolute value of the correlation coefficient (*r*) was greater than 0.7, moderate if *r* was 0.4 to 0.7, weak if *r* was 0.2 to 0.4, and absent if *r* was 0.2 or less.

We used receiver operating characteristic (ROC) curve analysis to assess the discriminative ability of

Fig. 1. (a) Scattered plot of stiffness values by magnetic resonance elastography (MRE) correlated with pathological liver fibrosis stages in 114 patients. Liver stiffness value increases as the stage of liver fibrosis increases. (b) Scattered plot of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR) correlated with pathological liver fibrosis stages. (c) Scattered plot of AST-to-platelet ratio index APRI correlated with pathological liver fibrosis stages. (d) Scattered plot of FIB-4 index, which is defined as: $(\text{age [years]} \times \text{AST [U/L]}) / (\text{PLT [10}^9/\text{L]} \times \text{ALT [U/L]}^{1/2})$, correlated with pathological liver fibrosis stages. Note: The body of the boxplot consists of a box, which goes from the first (Q1) to the third quartile (Q3). Within the box, a horizontal line is drawn at the median of the dataset. The vertical line goes from Q1 to the smallest data more than $Q1 - 1.5 \times \text{IQR}$ (interquartile range) in the dataset, and the line goes from Q3 to the largest data less than $Q3 + 1.5 \times \text{IQR}$. IQR (interquartile range): $Q3 - Q1$.

MRE and serum fibrosis markers. We calculated the area under the ROC curve (Az value) and optimal cutoff value for differentiating $\geq$ F1 from F0, $\geq$ F2 from $\leq$ F1, $\geq$ F3 from $\leq$ F2, and F4 from $\leq$ F3, and we calculated sensitivity and specificity for the optimal cutoff value. We used a jackknife method to compare Az values of MRE, the AAR, the APRI, and the FIB-4 index for discriminating fibrosis stages.²¹

We used JMP software (Ver. 10; SAS Institute, Cary, NC, USA) for all analyses. $P < 0.05$ was considered statistically significant.

Results

Mean stiffness values of the liver increased as liver fibrosis stage progressed: F0, 2.10 ± 0.10 kPa; F1, 2.42 ± 0.29 kPa; F2, 3.16 ± 0.32 kPa; F3, 4.21 ± 0.78 kPa; and F4, 6.20 ± 1.08 kPa. The pathological stage of liver fibrosis showed significant correlation with liver stiffness values determined by MRE ($r = 0.9149$, $P < 0.0001$) but only moderate correlation with the APRI ($r = 0.6035$, $P < 0.0001$) and FIB-4 index ($r = 0.4374$, $P < 0.0001$) (Fig. 1a, c, d). No significant correlation was observed between the AAR and fibrosis stage ($r = 0.1019$, $P = 0.2806$) (Fig. 1b).

Table 2 shows the mean Az values for discriminating liver fibrosis stages using liver stiffness

values. The Az value for discriminating most liver fibrosis stages was significantly higher for MRE than the serum fibrosis markers.

ROC analysis provided the optimal cutoff values of liver stiffness for discriminating the stages of liver fibrosis, and these values yielded sensitivity and specificity for discriminating fibrosis stage (Table 3).

Figures 2 and 3 show the clinical cases.

Discussion

Staging of liver fibrosis is important in managing chronic liver disease because prognosis diminishes and the risk of developing hepatocellular carcinoma increases as fibrosis progresses.¹ Liver biopsy is

Table 3. Receiver operating characteristic (ROC) analysis of the diagnostic performance of magnetic resonance elastography (MRE) for hepatic fibrosis

Fibrosis score	Optimal cutoff value (kPa)	Sensitivity, % (n/n)	Specificity, % (n/n)
F0 vs F1–4	2.30	95.5(106/111)	100(3/3)
F0–1 vs F2–4	3.20	88.5(85/96)	100(18/18)
F0–2 vs F3–4	4.00	86.8(59/68)	100(46/46)
F0–3 vs F4	4.60	100(43/43)	85.9(61/71)

Table 2. Comparison between magnetic resonance elastography (MRE) and fibrosis tests comprising serum fibrosis markers, AAR, APRI, and FIB-4 index

Variable	MRE	AAR	APRI	FIB-4 index
$\geq$ F1				
Az value	0.984(0.933–0.996)	0.790(0.585–0.909)	0.868(0.674–0.954)	0.520(0.268–0.762)
P value (vs MRE)	NA	0.0212	0.1128	0.0014
$\geq$ F2				
Az value	0.986(0.956–0.996)	0.619(0.462–0.754)	0.846(0.752–0.909)	0.589(0.454–0.711)
P value (vs MRE)	NA	< 0.0001	0.0004	< 0.0001
$\geq$ F3				
Az value	0.973(0.935–0.989)	0.555(0.445–0.659)	0.868(0.776–0.926)	0.744(0.645–0.823)
P value (vs MRE)	NA	< 0.0001	0.0050	< 0.0001
F4				
Az value	0.976(0.945–0.990)	0.624(0.516–0.720)	0.760(0.663–0.836)	0.771(0.673–0.847)
P value (vs MRE)	NA	< 0.0001	< 0.0001	< 0.0001

AAR, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio; APRI, AST-to-platelet ratio index; Az, area under ROC curve; FIB-4 index, (age [years] $\times$ AST [U/L]) / (PLT [10^9 /L] $\times$ ALT [U/L]^{1/2}); NA, not applicable.

Values are mean (95% confidence interval).

Statistical analysis was performed using chi-square test.

Az values of MRE were significantly higher than serum fibrosis markers except for $\geq$ F1 for APRI ($P < 0.05$).

Fig. 2. Magnetic resonance elastography (MRE) images of a 63-year-old man with F1 fibrosis. **(a)** Wave image at 60 Hz. **(b)** MR elastogram. The wavelength of the shear waves is relatively short in the wave image. The elastogram shows a mean stiffness value of 2.4 kPa. The structure ahead of the body projected from the abdomen is due to phase artifact.

Fig. 3. Magnetic resonance elastography (MRE) images of a 69-year-old woman with cirrhosis (F4). **(a)** Wave image at 60 Hz. **(b)** MR elastogram. The wavelength of the shear waves is relatively long in the wave image. The elastogram shows a mean stiffness value of 7.7 kPa.

the gold standard for assessing liver fibrosis but carries some risk of complications, so many noninvasive alternative methods have been proposed. The simplest method for estimating fibrosis stage is to assess the serum fibrosis markers,²² but their reliability decreases when patients have no underlying liver disease or when their serum AST levels are normal.²³ Therefore, serum markers are associated with limited discriminative ability for staging liver fibrosis. Our study elucidated the superior discriminative ability for staging liver fibrosis of MRE compared with serum fibrosis markers, and Huwart and associates reported the significantly higher diagnostic ability of MRE than APRI for this stag-

ing.¹³ A previous systematic review of the performance of serum fibrosis markers showed the median Az values of serum markers for discriminating $\geq$ F2 ranging from 0.73 to 0.88 and for discriminating F4, from 0.73 to 0.94,²⁴ whereas Az values of MRE in our study were consistently above 0.97. We also conclude that MRE is superior to serum markers in its discriminative ability for staging liver fibrosis.

Other imaging-based methods proposed for staging liver fibrosis include diffusion-weighted imaging and an uptake index evaluating gadoxetic acid-enhanced hepatocyte-phase images.²⁵⁻²⁸ These methods do not measure liver stiffness, but other param-

eters, such as molecular diffusivity, tissue microperfusion, and hepatocyte function. However, some authors suggest that the diagnostic abilities of these methods are insufficient compared with those of serum markers or MRE.^{29–31}

Our study has some major limitations. First, we did not analyze other factors that might influence liver stiffness, including steatosis, edema, iron overload, and portal/arterial flow. Although steatosis itself might not affect the stiffness measurement, fat deposition can cause inflammation, which, in turn, can increase liver stiffness even in the absence of fibrosis.^{32,33} The influence of these factors should be further studied in larger series. However, a previous study suggested a significant correlation of liver stiffness measured by transient ultrasound elastography with fibrosis but not with inflammatory activity and steatosis.³⁴ A second limitation was that we had only a small number of cases of F0 and F1 because the clinical requirement for performing biopsy to evaluate fibrosis stage during early-stage liver disease is minimal. Another limitation was the diagnosis of fibrosis stage by only one of 3 pathologists rather than by consensus. Liver biopsy is limited by such factors as high inter- and intraobserver variability,^{3–5} but we could not examine the reproducibility of pathological stage of liver fibrosis. Finally, we did not compare type C viral hepatitis with other hepatitis because there were insufficient cases of other hepatitis. We will try to compare them in the future.

Conclusion

In conclusion, MRE is a reliable technique for staging liver fibrosis and discriminating liver fibrosis stages in patients with chronic hepatitis C.

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