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HEPATOBILIARY-PANCREAS

MR elastography of the liver at 3.0 T in diagnosing liver fibrosis grades; preliminary clinical experience

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Abstract

Objectives To clarify the usefulness of 3.0-T MR elastography (MRE) in diagnosing the histological grades of liver fibrosis using preliminary clinical data.

Materials and methods Between November 2012 and March 2014, MRE was applied to all patients who underwent liver MR study at a 3.0-T clinical unit. Among them, those who had pathological evaluation of liver tissue within 3 months from MR examinations were retrospectively recruited, and the liver stiffness measured by MRE was correlated with histological results. Institutional review board approved this study, waiving informed consent.

Results There were 70 patients who met the inclusion criteria. Liver stiffness showed significant correlation with the pathological grades of liver fibrosis (rho=0.89, $p<0.0001$, Spearman's rank correlation). Areas under the receiver operating characteristic curve were 0.93, 0.95, 0.99 and 0.95 for fibrosis score greater than or equal to F1, F2, F3 and F4, with cut-off values of 3.13, 3.85, 4.28 and 5.38 kPa, respectively. Multivariate analysis suggested that grades of necroinflammation also affected liver stiffness, but to a significantly lesser degree as compared to fibrosis.

Conclusions 3.0-T clinical MRE was suggested to be sufficiently useful in assessing the grades of liver fibrosis.

Key Points

- *MR elastography may help clinicians assess patients with chronic liver diseases*
- *Usefulness of 3.0-T MR elastography has rarely been reported*
- *Measured liver stiffness correlated well with the histological grades of liver fibrosis*
- *Measured liver stiffness was also affected by necroinflammation, but to a lesser degree*
- *3.0-T MRE could be a non-invasive alternative to liver biopsy*

Keywords MR elastography · 3.0 T · Chronic liver disease · Fibrosis · Necroinflammation

Introduction

In the management of patients with chronic liver diseases and cirrhosis, the assessment of the degree of liver fibrosis is of great importance, because progressive liver fibrosis would result in portal hypertension, liver cancer and finally patient death [1, 2]. The usefulness of ultrasound-based elastography, including transient or shear-wave elastography, has been described and reported for this purpose [3–5]. Shear-wave MR elastography (MRE) has also been reported to be useful in assessing the pathological grades of liver fibrosis [6–19]; however, most of these data have been obtained on 1.5-T systems and those with 3.0-T clinical systems have rarely been presented [20–23]. In particular, clinical application of 3.0-T MRE to patients with chronic liver diseases has been limited [22, 23]. There are several technical differences between MRE systems of 1.5 T and 3.0 T, including the pulse sequences used (gradient-echo vs echo planar), the number of slices obtained (one vs four) and the cross-hatching marks on stiffness maps

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(absent vs present) [6–23]. Because 3.0-T MR systems are increasingly used in the field of body imaging, it is important to show if MRE at 3.0 T works as well as at 1.5 T, as a non-invasive alternative to liver biopsy in the assessment of the grades of liver fibrosis.

We installed a commercially available 3.0-T MRE system and started its clinical application in 2012 after optimization the imaging parameters and establishing the stiffness measurement method [24, 25].

The purpose of this study is to demonstrate our preliminary clinical data of the performance of our 3.0-T MRE system in the assessment of the grades of liver fibrosis with pathological correlation.

Methods and materials

Patient population

Between November 2012 and March 2014, MRE was applied to all patients (over 600) who underwent liver MR in our institute, as part of a routine protocol. All patients fasted for at least 6 h before MR examinations, and MRE was performed before contrast medium administration. Among them, consecutive patients who had pathological confirmation of liver tissue within 3 months from MR examinations were retrospectively recruited. Exclusion criteria were those who had apparent cardiac failure and acute hepatitis, both conditions which are known to cause significant elevation of liver stiffness [26, 27]. Our institutional review board approved this study, waiving informed consent because of its retrospective nature.

MR elastography

The MR equipment used was a 3.0-T clinical system (Discovery 750 W, GE, Milwaukee, USA) along with a 32-element phased-array coil. A 19-cm-diameter passive pneumatic driver was positioned over the centre of the right rib cage at the level of the xiphoid process and attached to an acoustic waveform generator. A 60-Hz waveform was applied to the driver. A 2D spin-echo echo-planar MRE sequence (TR/TE=1000/59, 66×64 matrix, 10 mm slice thickness, 80-Hz magnetization encoding gradient) acquired magnitude and unwrapped phase difference wave images using a 42-cm field-of-view [25]. Four slices were obtained including the level of the hepatic hilum under 16-s breath-holding. Wave images and MRE images (stiffness map) with cross-hatching marks were automatically generated on the operating console. The inversion algorithm used for stiffness map calculation was a multi-scale direct inversion. Liver stiffness was measured by one experienced radiologist (KY) using the fusion image method [24], by placing regions of interest (ROIs) on the stiffness map, mainly in the right hepatic lobe, avoiding apparent pathologies, large vessels, areas with inadequate wave propagation and cross-hatching marks [24]. An average of the four slices was used to represent the liver stiffness of each patient. These data were recorded at the time of routine clinical practice and liver stiffness measurement was not repeated for this study.

Pathological evaluation

The surgically resected or percutaneously biopsied specimens were assessed for the degree of fibrosis and necroinflammatory change using the Metavir system (F0–F4 and A0–A3) [28, 29] by one pathologist (HH) with more than 5 years experience in the field of liver pathology. Although the Metavir system was originally designed to assess liver tissues of patients with chronic hepatitis C, it has also been applied to chronic liver disease of other various aetiologies [30, 31]. Specimens stained with haematoxylin–eosin and Masson's trichrome were assessed. In surgically resected specimens, liver parenchyma farthermost (at least 1 cm apart) from the tumour or apparent pathologies was used for the assessment. Percutaneous biopsy was performed by hepatologists using a 20-gauge needle under ultrasonographic guidance using an intercostal approach, towards the central areas of the right hepatic lobe.

Assessments and statistics

The stiffness measured by MRE was correlated with pathological fibrosis grades (Spearman's rank correlation), and cut-off values for discrimination of each fibrosis grade (F0 vs F1-4, F0-1 vs F2-4, F0-2 vs F3-4 and F0-3 vs F4) were assessed using receiver operating characteristic (ROC) analysis with areas under the curve or Az values as indices. Sensitivities, specificities, accuracies, and positive and negative predictive values were calculated using these cut-off values for each fibrosis grade. The correlation of stiffness values and degree of necroinflammation (A0–A3) was also assessed, and stepwise regression analysis was applied to assess the independency of these factors. The software used for all statistical assessment was JMP version 11 (SAS corporation, Cary, USA). *P* values less than 0.05 were considered significant.

Results

There were 72 patients from whom histological specimens were obtained within 3 months from MR examinations. None of these 72 patients were clinically diagnosed to have acute hepatitis or heart failure. Among them, two patients were excluded because of scanty biopsy specimens, unsuitable for fibrosis staging. Thus, 70 patients with pathological diagnoses formed the final patient population in our study, consisting of 51 men and 19 women, with age ranging from

27 to 87 years (mean 68) (Fig. 1). Of these 70, there were 10, 26 and 2 patients who had chronic hepatitis B, C and both, respectively, and 6 with alcoholic liver disease, 11 with non-B non-C cirrhosis including 6 non-alcoholic steatohepatitis, 2 with autoimmune hepatitis, one each with primary biliary cirrhosis and Wilson disease, and 11 with liver metastases without chronic liver disease. Histological specimens were obtained after MRE in all 70 patients, by percutaneous biopsy (n=46) or by surgical resection (n=24). Liver stiffness measurement was feasible in all 70 patients.

There were 15, 17, 7, 15 and 16 patients with F0, F1, F2, F3 and F4 grades of liver fibrosis. The stiffness of the liver was 2.6±0.4, 3.4±0.6, 3.8±1.1, 6.0±1.4 and 8.2±2.0 kPa for F0, F1, F2, F3 and F4, respectively. Liver stiffness showed significant correlation with the pathological grades of liver fibrosis (rho=0.89, p<0.0001, Spearman's rank correlation) (Fig. 2).

The cut-off values and areas under the curve (Az) calculated from ROC analysis were 3.13 kPa and 0.93 for F0 vs F1-4, 3.85 kPa and 0.95 for F0-1 vs F2-4, 4.28 kPa and 0.99 for F0-2 vs F3-4, and 5.38 kPa and 0.95 for F0-3 vs F4, respectively (Fig. 3). Sensitivity, specificity, accuracy, and positive and negative predictive values of discriminating F0-1 vs F2-4 were 90 % (95 % confidence interval 81–92), 90 % (81–96), 90 % (81–94), 89 % (83–97) and 92 % (78–93); those for discriminating F0-2 vs F3-4 were 97 % (91–100), 94 % (86–96), 96 % (89–98), 95 % (88–97) and 97 % (88–99), respectively.

Sensitivity, specificity, accuracy, and positive and negative predictive values for discriminating F0 vs F1 were 76 % (56–82), 87 % (73–0.96), 81 % (65–91), 87 % (65–95) and 76 % (65–86), respectively, with a cut-off value of 2.98 kPa; those for discriminating F1 vs F2 were 86 % (78–96), 41 % (18–62), 75 % (48–81), 79 % (70–86) and 60 % (26–87), respectively,

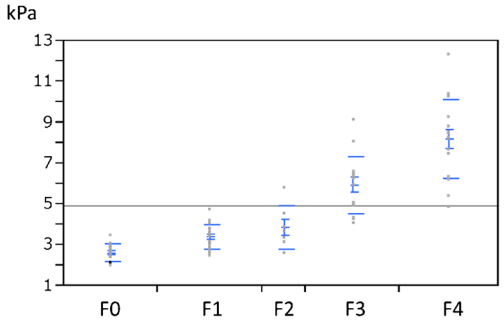

Fig. 2 Liver stiffness (kPa) measured by MR elastography in correlation with pathological fibrosis grades. There was a significant correlation between liver stiffness and the pathological grades of liver fibrosis (rho=0.89, p<0.0001, Spearman's rank correlation). Statistically significant differences were present between F0 vs F1, F2 vs F3 and F3 vs F4 (p<0.05, Tukey–Kramer's HSD test)

with a cut-off value of 3.2 kPa; those for discriminating F2 vs F3 were 100 % (72–100), 73 % (60–73), 82 % (64–85), 64 % (46–64) and 100 % (82–100), respectively, with a cut-off value of 4.1 kPa; those for discriminating F3 vs F4 were 73 % (56–82), 88 % (71–96), 78 % (64–94), 85 % (65–95) and 78 % (63–85), respectively, with a cut-off value of 7.5 kPa.

The degree of necroinflammation (A factor) also showed significant correlation with the measured stiffness of the liver, however, with lower rho values (rho=0.61, p<0.0001) (Fig. 4). The stiffness of the liver was 3.0±0.9, 4.3±1.8, 7.1±2.6 and 7.5±1.4 kPa for A0 (n=13), A1 (n=36), A2 (n=19) and A3 (n=2), respectively.

When stepwise regression analysis was applied, both the degree of fibrosis (F3 vs F4 and F0 vs F1-2) and degree of necroinflammation (A0-1 vs A2-3) were shown to be independently significant factors that affect the stiffness values measured by MRE (Table 1). Representative cases are shown in Figs. 5 and 6.

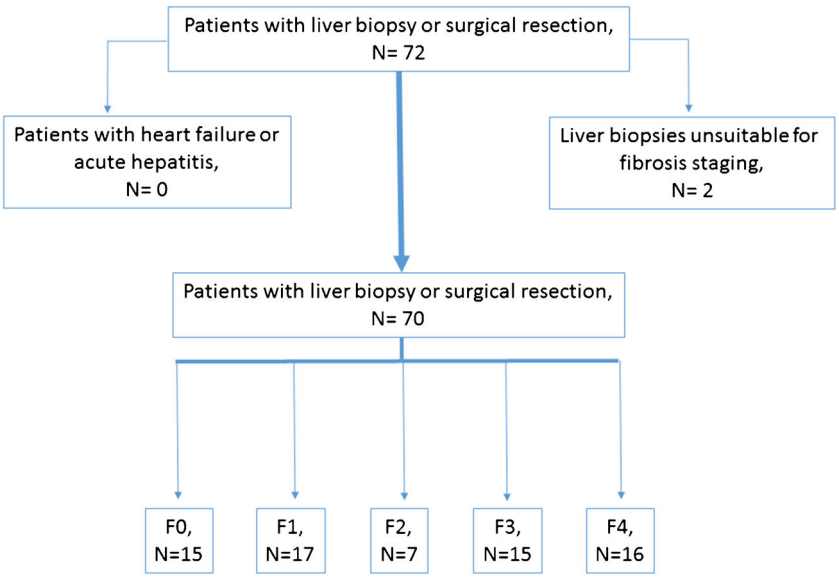

Fig. 1 Flow diagram of patients who underwent MR elastography of the liver between November 2012 and March 2014 and were recruited for this study

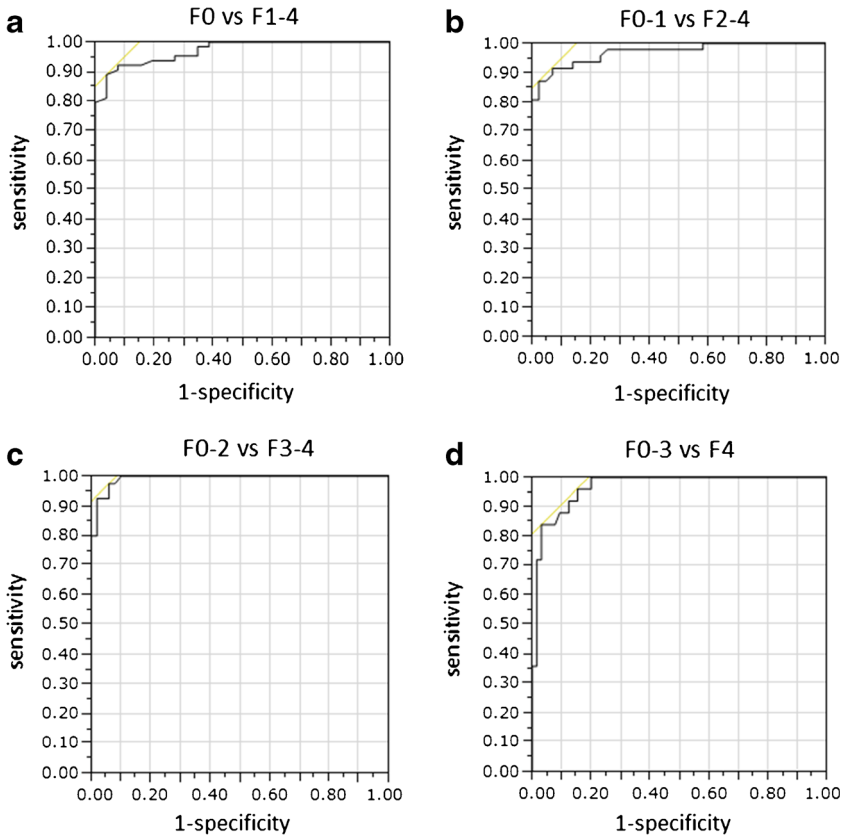

Fig. 3 Receiver-operating characteristic analysis to determine cut-off values in discriminating each pathological fibrosis grade. **a** F0 vs F1-4: area under the curve (Az value) was 0.93 with a cut-off value of 3.13 kPa. Sensitivity, specificity and accuracy were 89 %, 92 % and 89 %, respectively. **b** F0-1 vs F2-4: Az value was 0.95 with a cut-off value of 3.85 kPa. Sensitivity, specificity and accuracy were all 90 %. **c** F0-2 vs F3-4: Az value was 0.99 with a cut-off value of 4.28 kPa. Sensitivity, specificity and accuracy were 97 %, 92 % and 94 %, respectively. **d** F0-3 vs F4: Az value was 0.95 with a cut-off value of 5.38 kPa. Sensitivity, specificity and accuracy were 94 %, 82 % and 85 %, respectively

Discussion

The results confirmed that our 3.0-T MRE works as well as 1.5-T MRE, in terms of the discriminating capability of each pathological fibrosis grade (Az values around 0.93–0.99). However, there appears to be a slight difference in the cut-off values to distinguish each pathological fibrosis grade. The cut-off values for our data are shown in Table 2, along with the reported cut-off values for previously reported MRE for comparison. Apparently, our cut-off values are slightly higher than those previously reported for 1.5-T data [9, 10, 13, 16, 18, 19], although there were no consistencies at all among the previously reported cut-off values obtained with 1.5-T systems. Interestingly, the cut-off values obtained with one of the reported 3.0-T MRE systems [22] were slightly higher than ours, and those with another 3.0-T MRE system [23] were lower. The exact reasons for this difference are unclear, but may be attributable to the heterogeneity of the patient population; most previous studies, including ours, included patient populations with chronic liver diseases of various aetiologies and various numbers. It is of interest that cut-off values

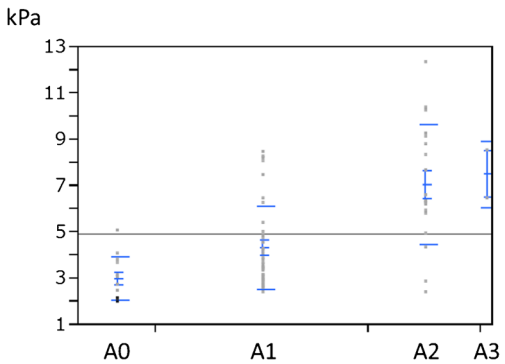

Fig. 4 Liver stiffness (kPa) measured by MR elastography in correlation with pathological grades of necroinflammation. There was a significant correlation between liver stiffness and the pathological grades of necroinflammation of the liver (rho=0.61, $p<0.0001$, Spearman's rank correlation)

Table 1 Results of the stepwise regression analysis

Parameters	Action	*P* value	R^2	AICc	BIC
F3 vs F4	FS	<0.0001	0.74	264.6	273.3
A0-1 vs A2-3	FS	0.01	0.77	262.1	272.9
F0-1 vs F2	FS	0.02	0.78	261.9	272.6
F1 vs F2	FS	0.16	0.78	263.8	278.3

Minimum values of AICc and BIC occur with the first three parameters. *P* values are less than 0.05 for the first three parameters, but larger than 0.05 for the fourth parameter, F1 vs F2. Therefore, the first three parameters, namely F3 vs F4, A0-1 vs A2-3, and F0-1 vs F2, are considered significant

FS forward selection, *AICc* corrected Akaike's information criterion, *BIC* Bayesian information criterion, *F/A* degrees of liver fibrosis and necroinflammation of the liver according to the Metavir system [25, 26]

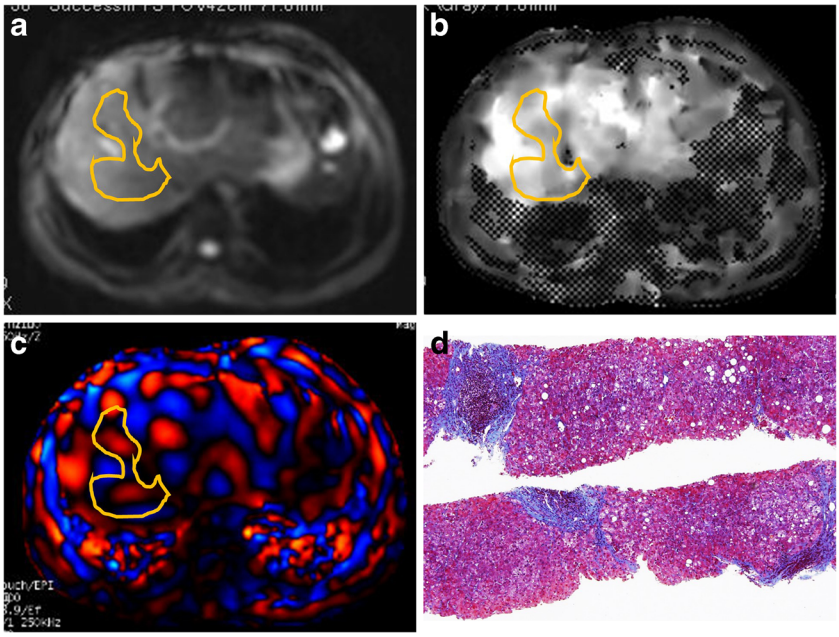

Fig. 5 A 53-year-old male patient with chronic hepatitis C infection and Child–Pugh score 7 points (grade B). **a** Original echo-planar image of MR elastography. A region-of-interest (ROI) is placed avoiding large vessels and cross-hatching marks shown on the stiffness map (**b**). **b** MR elastography (stiffness map) with an ROI. Measured stiffness was 6.5 kPa. **c** Wave image with an ROI. **d** Pathological specimen of percutaneous biopsy (Masson's trichrome stain, original magnification ×200). Marked bridging fibrosis accompanied by destruction of limiting plates, and moderate to severe lymphocytic infiltrates are noted in the portal tracts. Diagnosis of F3/A3 was made according to the Metavir system

obtained exclusively from patients with chronic hepatitis C infection [19] are apparently lower than those for patients with chronic hepatitis B infection [22]. Other possible reasons are technical differences, including those in the pulse sequence used (gradient-echo vs echo-planar), imaging parameters, inversion algorithm, ROI placement method [24] etc. Strictly

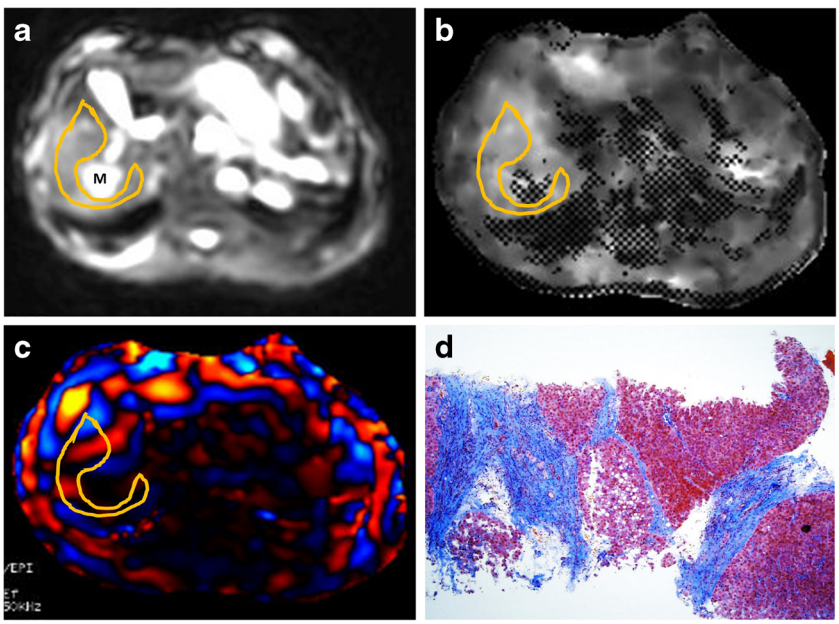

Fig. 6 A 49-year-old male patient with chronic hepatitis C infection and Child–Pugh score 6 points (grade A). **a** Original echo-planar image of MR elastography. A region-of-interest (ROI) is placed avoiding large vessels, cross-hatching marks shown on the stiffness map (**b**), and liver tumor (*M*) which turned out to be an intrahepatic cholangiocellular carcinoma. **b** MR elastography (stiffness map) with an ROI. Measured stiffness was 5.8 kPa. **c** Wave image with a ROI. **d** Pathological specimen of percutaneous biopsy obtained from the vicinity of the liver tumour (Masson's trichrome stain, original magnification ×200). Pseudolobule formation separated by thick fibrous septa and mild inflammatory infiltrates in the portal areas are seen. Diagnosis of F4/A1 was made according to the Metavir system

Table 2 Discrimination of pathological fibrosis grades using MR elastography: comparison with the previous reports

Reference	MR pts #		F0 vs F1-4	F0-1 vs F2-4	F0-2 vs F3-4	F0-3 vs F4	Sen/spec
Our data	3 T	CV	3.13	3.85	4.28	5.38	90/90
	n=70	Az	0.93	0.95	0.99	0.95	
Ref.	1.5 T	CV	2.4	2.5	3.1	4.3	90/100
[9]	*n*=88	Az	0.96	0.99	0.99	1	
[10]	1.5 T	CV	2.93	4.89	6.47	6.47	86/85
	n=85	Az	0.99	0.92	0.92	0.92	
[13]	1.5 T	CV	2.9	3.2	4.0	4.6	NA
	n=72	Az	0.92	0.93	0.98	0.99	
[16]	1.5 T	CV	2.87	3.05	3.57	5.32	90/87
	n=60	Az	0.89	0.94	0.98	0.98	
[18]	1.5 T	CV	5.2	5.37	5.97	5.97	91/97
	n=76	Az	0.92	0.98	0.99	0.95	
[19]	1.5 T	CV	2.3	3.2	4.0	4.6	89/100
	n=114	Az	0.98	0.99	0.97	0.98	
[22]	3.0 T	CV	3.61	4.07	5.45	6.87	95/94.5
	n=113	Az	0.961	0.986	1.000	1.000	

F and *A* factors represent degrees of liver fibrosis and necroinflammation of the liver according to the Metavir system [26, 27]

MR strength of static magnetic field of MR system, *pts#* number of patients studied, *CV* cut-off value, *Az* area under the curve of ROC analysis, *Sen/spec* sensitivity and specificity for diagnosing F0-1 vs F2-4

speaking, even for the two 3.0-T MRE data sets reported so far, detailed techniques are different; one was gradient-echo based [22], and the other was echo-planar based [23]. Furthermore, the parameters used for the latter [23] were different from those for our 3.0-T system. To clarify the exact reasons for these differences in cut-off values and to standardize the MRE technique, imaging the same phantom or same patient population using several MRE systems and direct comparison among them may be needed.

According to our results, the grades of necroinflammation, or A factor, were also correlated with the liver stiffness values, but to a significantly lesser degree as compared to grades of fibrosis (Figs. 2 and 4, Table 1). Although previous reports have suggested that liver stiffness values measured by ultrasound elastography were significantly related to a necroinflammatory process, as well as fibrosis [32, 33], little has been reported on the relationship between liver stiffness measured by MRE and grades of necroinflammation in chronic liver diseases. However, increased liver stiffness has been reported in patients with acute hepatitis [26, 27]. It is reasonable that liver stiffness values measured by MRE are also affected by the grades of necroinflammation, but to a lesser degree than by fibrosis grades, in patients with chronic liver diseases. Degree of necroinflammation is thus a confounding factor for the stiffness values measured with MRE, and therefore MRE cannot replace biopsy completely in this aspect. Similar results have just recently been reported for patients with chronic hepatitis B infection [22]. Ideally, cut-off values may be set not only for F factors, but for the combination of F and A factors, which may require a larger number of cases, and is an issue to be solved in the future.

It has been reported that shear-wave MRE is subject to iron deposition or haemochromatosis [5, 26]. Fortunately, none of our patients had iron overload and MRE was successfully obtained in all of them.

An alternative MR technique to assess liver stiffness would be the cine-tagging method [34–36]. The reported discrimination capability of grades of liver fibrosis, however, does not seem as good as that of shear-wave MRE, at least presently [6–23, 34–36].

Our study has several limitations, in addition to its retrospective nature. One is the anatomical inconsistency between the sites where liver stiffness was measured and those where specimens were obtained from, possibly causing discordance between MRE and pathological results. The liver stiffness as defined in this study was an average of ROI values of four slices, whereas pathological assessment was done only for small areas within the organ. Particularly in surgically resected cases, ROIs for stiffness measurement are to be placed apart from liver tumours and limited to the right hepatic lobe; however, for the pathological assessment of fibrosis or necroinflammation, there was sometimes no other choice but to use the liver parenchymal specimens in the vicinity of liver tumours, even if the specimens were obtained from the left lobe. Another limitation is the relatively small number of patients, particularly those with F2 fibrosis grades, as compared to those with F0-1 and F3-4. This may at least partly explain the lack of significant difference in the liver stiffness and poor

discrimination between F1 and F2 (Fig. 2). Our data, therefore, should be considered as preliminary data, and should be validated in a larger population. Furthermore, although it has been suggested that cut-off values are to be set for each chronic liver disease entity [19, 22, 26], it was not possible in our patient population because of the small number of patients in each chronic liver disease group. A further prospective study with a larger series would be needed to solve these issues. Finally, the setting of the F0 population may be another limitation. Because the majority (11 out of 15) of F0 patients were surgically resected liver metastasis cases, it is theoretically possible that microscopic metastases were present in the measured area of MRE, even though we made sure that there was no pathology at the area of ROI using every other imaging sequence possible, including hepatobiliary phase imaging of gadoxetate enhancement. This could at least be one of the reasons for slightly high cut-off values for F0 vs F1-4.

In conclusion, our preliminary results suggested that 3.0-T clinical MRE yielded sufficiently high diagnostic performance in the assessment of the pathological grades of liver fibrosis, which may be comparable to those reported with 1.5-T clinical MRE systems. It was also suggested that liver stiffness values measured by MRE are affected by the grades of necroinflammation, but to a lesser degree than by fibrosis grades.

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