의학석사 학위논문

Magnetic Resonance Elastography for the Staging of Liver Fibrosis

Comparison of Diagnostic Performance Between Patients with Chronic Hepatitis B and Those with Other Etiologies

간 섬유화 평가를 위한 자기공명탄성영상

만성 B 형 간염 환자군과 기타 원인 환자군 사이의 진단능 비교

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서울대학교 대학원

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장 원

A thesis of the Degree of Master of Science in Medicine

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장 원

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2014년 12월

위 원 장 _____ (인)

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Abstract

Introduction: To evaluate the diagnostic performance of magnetic resonance elastography (MRE) in staging liver fibrosis (LF) in patients with chronic hepatitis B (CHB) and other etiologies.

Methods: This retrospective study was institutional review board approved and the requirement for informed consent was waived. A total of 352 patients with chronic liver diseases (280 with CHB, 26 with chronic hepatitis C (CHC), 17 with alcoholic liver disease (ALD), and 29 patients without definite etiologies) and hepatocellular carcinomas, as well as 63 living liver donors underwent MRE before surgery at our institute. Liver stiffness values (LSVs) were measured on quantitative shear-stiffness maps of MRE, and the diagnostic performance of MRE in staging LF was evaluated using receiver operating characteristic curve (ROC) analysis and the Obuchowski measure on the basis of the histopathologic analysis of LF in the CHB group and in the group comprising other etiologies.

Results: Areas under the curve (AUCs) of LSVs for the diagnosis of significant fibrosis (≥F2), severe fibrosis (≥F3), and cirrhosis (F4) in the CHB group were 0.973 (95% confidence interval [CI], 0.930–0.977), 0.947 (95% CI, 0.918–0.969), and 0.918 (95% CI, 0,883–0.945), respectively. Obuchowski measures were similarly high in the CHB group and in the group comprising other etiologies (0.970 vs. 0.971). However, the estimated cutoff value for F4 in the CHB group was lower than those in other etiologies: 3.56 kPa vs 4.65 kPa, $p< 0.001$.

Conclusions: The diagnostic performance of MRE for the staging of liver fibrosis was similarly high in the CHB and non-CHB groups, but the cutoff LSVs for diagnosing liver cirrhosis were different between the CHB and non-CHB groups.

Keywords: Magnetic resonance elastography, Liver fibrosis, Cirrhosis, Chronic hepatitis B, Necroinflammation
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LIST OF ABBREVIATION

CHB = Chronic hepatitis B

CHC = Chronic hepatitis C

ALD = Alcoholic liver disease

HBV = Hepatitis B virus

HCV = Hepatitis C virus

LF = Liver fibrosis

LSV = Liver stiffness value

MRE = Magnetic resonance elastography

ROC = Receiver operating characteristic curve

AUC = Area under the curve

INTRODUCTION

Chronic liver diseases (CLDs) including viral infections such as the hepatic B virus (HBV) and hepatic C virus (HCV), nonalcoholic fatty liver disease or alcoholic liver diseases, represent a major public health problem often leading to significant morbidity and mortality for patients with this disease (1, 2). In response to liver injuries caused by CLDs, fibrogenesis and necroinflammation can occur, resulting in liver fibrosis which has been shown to progress at variable rates, but ultimately developing into cirrhosis (3). Among the main causes that lead to liver cirrhosis, HBV is the most common cause in most parts of Asia including China and Korea, and subjects with advanced liver fibrosis have been shown to represent the group at greatest risk for developing liver-related complications and mortality, therefore requiring therapy for their underlying etiology (4, 5). Presently, cirrhosis is considered not to be a single disease entity but rather one that can be subclassified into distinct clinical prognostic stages with 1-year mortality ranging from 1% in early cirrhosis to 57% in decompensated disease (5, 6). Thus, recently, strategies formulated to prevent their transition to decompensated stages have been widely adopted in the management of patient with cirrhosis, including specific

antiviral treatment or nonselective beta blockers (7). Therefore, accurate staging of liver fibrosis as well as the diagnosis of early cirrhosis would be of great importance for optimal treatment planning, as the degree of fibrosis has been shown to have prognostic significance in patients with viral infections (6, 8).

For the assessment of liver fibrosis, the current gold standard is percutaneous liver biopsy which is the most commonly used technique today, however, issues such as its invasiveness presenting with the possibility of complications, sampling errors, and intra- or interobserver variability leading to potential under or over staging of liver fibrosis have been raised (9, 10). For these reasons, numerous attempts have been made to evaluate the degree of liver fibrosis using noninvasive options (8, 11-18), such as non-invasive serum markers of aspartate-aminotransferase-to-platelet ratio indexes (APRI), however, their diagnostic performances were shown to be far from optimum (3, 19). More recently, ultrasound based elastography techniques (USE) such as transient elastography (TE) and acoustic radiation force impulse (ARFI) as well as MR elastography (MRE) have been introduced to non-invasively measure liver stiffness (11, 12, 14, 20-25). Among them, MRE has demonstrated high diagnostic performance in staging liver fibrosis, and high reproducibility with a large sample volume, yet previous studies on MRE have reported a wide range of

diagnostic performances for the staging of liver fibrosis with different cutoff values for the various CLDs (26-28). These differences may have originated from heterogeneous study populations in terms of the etiology of chronic liver diseases in their studies. Several studies reported that there were distinguishing histologic features of different types of CLDs, and that fibrotic patterns are different between chronic HBV and HCV infection, and the total amount of fibrotic materials in CHB may be lower than that of CHC(29, 30). Until now, despite that there were several studies focused on a single etiology of CLD, there have been no studies comparing the diagnostic performances of MRE for staging of liver fibrosis between patients with HBV infection and those in other etiologies.

Therefore, the aim of our study is to evaluate the performance of MRE for the staging of liver fibrosis in patients with CHB in comparison to those with other etiologies.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board and written informed consent was waived.

Patient selection

Between October 2009 and August 2013, 830 patients underwent hepatic resection or liver transplantation as treatment for hepatocellular carcinoma (HCC) at our institute. Among them, liver MREs were performed as part of the preoperative MR examination within 3 months prior to surgery in 400 patients. In addition, we enrolled 63 consecutive living liver donor candidates who underwent preoperative MR examinations including MRE for liver transplantations between January 2013 and August 2013. We additionally excluded 23 patients who met at least one of the following exclusion criteria: 1) CLD with combined etiologies such as HBV and HCV co-infection or HBV infections with alcoholic hepatitis (n=9), 2) large tumors replacing the right lobe of the liver (n=6). Twenty-five patients with CLDs were additionally excluded owing to technical failures in acquiring adequate quality MRE. Based on the results of a previous studies on MRE (16, 32), inadequate MRE examinations with technical failures were those at which 1) wave images showed poor wave propagation, 2) anatomic images showed severe respiratory motion artifacts, 3) there was substantial signal loss of the

liver parenchyma compared with that of the muscle and kidneys, suggesting iron overload, or 4) suboptimal measurable areas of less than 1000 mm^2 (n=8). Finally, 352 patients and 63 living donor candidates comprised our study population. Detailed information regarding the patient selection process is presented in Figure 1.

For subgroup analysis according to etiology, donors were classified into either the CHB or non-CHB group by randomized selection considering the population of each subgroup. Fifty donors were included in the CHB group and 13 in the non-CHB group.

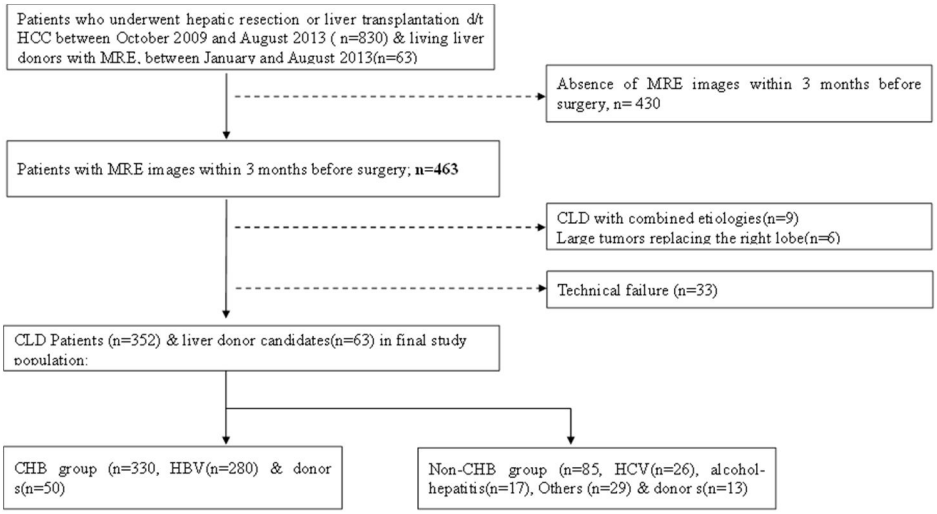

Figure 1. Flow diagram of study population

* Note. – HCC= hepatocellular carcinoma, MRE= magnetic resonance elastography, CLD= chronic liver disease, HBV= hepatitis B virus, HCV= hepatitis C virus, CHB= chronic hepatitis B

MRI techniques

All magnetic resonance examinations including MRE were performed on a 1.5T whole-body MR unit (Signa HDx; GE Healthcare, Milwaukee, WI, USA) with an eight-channel torso phased-array coil. All patients were instructed to fast for 8 hours prior to the examinations. The standard liver imaging protocol was composed of the following sequences: a respiratory-triggered, T2-weighted, fast spin-echo sequence, a T2-weighted, single-shot fast spin-echo sequence, a breath-hold T1-weighted dual echo (in and opposed phases) spoiled gradient-recalled echo (GRE) sequence, and a T2*-weighted GRE sequence. All MRE examinations were performed prior to the injection of contrast material.

Dynamic three-dimensional (3D) fat-saturated GRE sequences (liver acquisition with volume acceleration [LAVA]; GE Healthcare, Milwaukee, WI, USA) including hepatic arterial, portal, venous, late dynamic(3 and 10-minute delayed scans) and hepatobiliary phases (20-minute delayed scan) were obtained before and after intravenous administration of gadoxetate disodium (Primovist®, Bayer Healthcare, Berlin, Germany) at a dose of 0.025 mmol/kg (0.1 mL/kg body weight) at a rate of 1.5 mL/s, followed by a 30 mL saline flush. All images were acquired in either the axial or the coronal plane.

Magnetic Resonance Elastography

Magnetic resonance elastography images were obtained with the patients placed in the supine position with 60 Hz vibrations applied to the abdominal wall using a 19 cm diameter, 1.5 cm thick, cylindrical passive longitudinal pneumatic actuator (MR-Touch; GE Healthcare, Milwaukee, WI, USA) placed against the right anterior chest wall using a two-dimensional (2D) gradient-echo MRE sequence and the direct inversion algorithm (31) as previously described. A two-dimensional MRE sequence was used to acquire axial wave images using the following parameters: repetition time/echo time, 100/26.8 ms; flip angle, 30˚; field of view, 32–37 cm; matrix size, 256 x 64; slice thickness, 10 mm, and a 5 mm interslice gap. Two to four trans axial slices were obtained for each MRE examination.

The 2D MRE protocol used in our study was similar to the one previously described in the literature (25). In brief, the patients were instructed to hold their breath when each slice was being obtained. To maintain a consistent position of the liver, patients were asked to hold their breath at the end of expiration. The MRE acquisition of each slice required two breath-holds, and each breath was held for approximately 16 seconds. After completion of data acquisition, shear wave images

were processed to generate elastograms automatically, which depicted the shear stiffness in kilopascals (kPa) using a inversion algorithm(30, 31). Each MRE examination included MR magnitude images from each MRE acquisition (four slices with four time offsets per slice), phase/wave images used to calculate tissue stiffness, stiffness images, and a confidence map generated by the MRE inversion algorithm to assure the quality of the wave data (25).

Analysis of MRE

Before measuring mean shear stiffness, one author (W.C.) with 4 years of experience in reading MRE images and elastograms, reviewed the MRE images including the anatomic image set, wave image set, and the elastogram set. The reviewer evaluated the quality of the elastograms by referencing the anatomic images and wave images of each patient, and classified them as either adequate or inadequate. We then determined the technical success rate of MRE after excluding cases with inadequate MRE examinations.

In order to measure liver stiffness(LS) values of the liver parenchyma, region of interest(ROI) including the largest part of the liver parenchyma of the right lobe and the left medial segment (S4) was carefully drawn in the anatomic image during MRE acquisition, while

taking care to exclude large hepatic vessels, large bile ducts, liver edges, artifacts and tumors. The reviewer (W.C.) was blinded to each patient's liver histology results. The ROI was then relocated to the corresponding position in the wave images and reassessed that it was placed in the area with adequate wave propagations, regular and relatively free of reflections and interference patterns or in reliable area on the confidence map (32). Finally, the ROI was copied to the corresponding position in the elastograms, providing stiffness values in kPa. The mean LS value (kPa) of the ROI was obtained. In patients who had available confidence maps, tissue shear stiffness was measured in kilopascals (kPa) while referencing the high confidence portion of the segmentation mask with stiffness outliers excluded on the confidence maps (Figure 2).

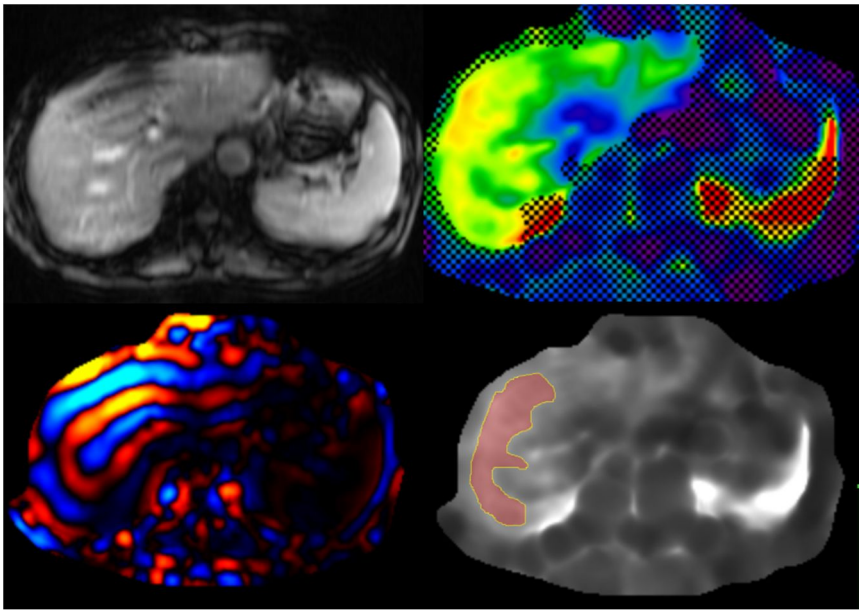

Figure 2. An example of liver stiffness measurement

(Left upper) Anatomic images patient with grade 4 fibrosis

(Right upper) Confidence map of elastogram

(Left bottom) Wave image data

(Right bottom) Elastogram with a free drawn ROI excluding hilar vessels and liver edges

Histopathologic Analysis

All 352 patients enrolled in the study had undergone surgery, and liver biopsy samples were obtained from 63 liver donors. The specimens were fixed in a formalin-alcohol-acetic acid solution and were embedded in paraffin. Thereafter, 4 mm-thick sections were cut and stained with Hematoxylin-Eosin. All specimens were analyzed by one expert hepatopathologist (K.B.L.) who had eight years of clinical experience in interpreting liver pathology examinations, blinded to the MRE results and clinical data. The grade of necroinflammatory activity and fibrosis stage were semi-quantitatively evaluated in the 352 patients. Although fibrosis mainly causes an increase in LS values, severe inflammation such as fulminant hepatitis may affect the LS values. Therefore, we assessed whether there was any impact of necroinflammatory activity on LS measurements using MRE. Necroinflammatory activity in the liver and the liver fibrosis stage in patients with CHB and in patients with non-CHB were assessed according to the Standardized Guidelines proposed by the Korean Study Group for the Pathology of Digestive Diseases (33-35), and according to the METAVIR scoring system. Fibrosis was graded on a scale of 0 to 4, as follows: no fibrosis (F0); mild fibrosis, portal fibrosis without septa (F1); substantial fibrosis, portal fibrosis, and few septa

(F2); advanced fibrosis, numerous septa without cirrhosis (F3); and cirrhosis (F4). In the CHB group, the grade of necroinflammatory activity consisted of lobular activity (L) and porto-periportal activity (P), both of which were graded from 0 to 4 where, 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe, according to the Standardized Guidelines proposed by the Korean Study Group for the Pathology of Digestive Diseases (35). In addition, the non-CHB group, the necroinflammatory activity score was graded on a scale of A0 to A3 according to the METAVIR scoring system as follows: no activity (A0), mild activity (A1), moderate activity (A2), and severe activity (A3) (34).

Serum markers

To evaluate the effectiveness of serum markers as noninvasive parameters for evaluating necroinflammatory activity of the liver, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were obtained within a week from the MRE study.

Statistical analysis

Statistical analyses were performed using commercially available software programs (SPSS, version 21, SPSS Inc., Chicago, IL, USA; MedCalc, version 14, MedCalc Software, Mariakerke, Belgium) as well as a free software program (R, version 2.6.0). Among the patients with successful MRE images and a measurable area of larger than 1000mm2, the diagnostic performance of MRE in detecting any fibrosis (≥ F1), significant fibrosis (≥ F2), advanced fibrosis (≥ F3), and cirrhosis(F4) in CHB patients, was evaluated using receiver operating characteristic (ROC) curves and its 95% confidence interval (36). Results were expressed according to the sensitivity, specificity and area under the receiver operating characteristic curve (Az). To differentiate no fibrosis (F0) from any fibrosis (≥F1) using ROC analysis, living liver donor subject data (n=60 for F0, n=3 for F1) were included and classified into the CHB or non-CHB group.

As the METAVIR scoring system is not a binary gold standard, the use of only ROC analysis may have led to overestimation of diagnostic performance. Thus, we additionally obtained the Obuchowski measure as a performance parameter. Spearman's correlation coefficients (r) and their associated probability (p) were also used to assess the correlations between stiffness values (measured by MRE), fibrosis scores, and inflammatory scores. A p value of less than 0.05 was considered to

indicate statistical significance.

RESULTS

Success Rate and Patient Characteristics

In 33 of the 463 patients (7.1%, 33/463) who underwent MRE within 3 months prior to surgery, MRE examinations were classified as cases of technical failure; thus, the technical success rate of MRE was 92.9%. The causes of technical failures were poor wave propagation seen on wave images (n=13), severe respiratory motion along the z-axis (n=2), the presence of iron deposits in the liver as seen on T2*-weighted gradient echo images (n=10) or suboptimal measurable areas of less than 1000mm2 (n=8). Mean age was significantly older in patients without chronic hepatitis B (CHB) ($p<0.001$), but other epidemiologic factors including sex and BMI were not significantly different. According to the histopathologic evaluation of hepatic fibrosis, 67 (16.1%) of the 415 study patients with technical success were in the F0 stage, 35 patients (8.4%) in the F1 stage, 52 patients (12.5%) in the F2 stage, 70 patients (16.8%) in the F3 stage, and 191 patients (46.0%) were in the F4 stage.

Table 1. Baseline characteristics in patients and donors

	CHB	Non-CHB	Donors	CHB vs. Non-CHB
Sex, males (%)	75.5	85.1	61.5	p=0.108
Age (mean, range, years)	56.8(27~82)	64.5(35~84)	33.7(18~59)	p<0.001
BMI (mean, ±SD, kg/㎡)	22.8±3.17	23.4±3.09	23.0±2.86	p=0.152
LS values	3982.3±1666.4	4461.5±2029.1	1904.3±297.0	p=0.064
Mean interval between MRE and surgery/biopsy (mean, ±SD, days)	14.0±16.2	11.7±14.6	15.7±18.0	p=0.253

*Note. – CHB = chronic hepatitis B, non-CHB = chronic liver diseases other than CHB, BMI =body mass index, LS= liver stiffness

Relationship between Histopathologic Results and Liver Stiffness Measured by MRE

There was a statistically significant positive correlation between LS values of MRE and the fibrosis stages evaluated by histology ($r = 0.818$, $p < 0.001$) in patients. However, the degree of correlation between porto-periportal activity ($r = 0.253$, $p < 0.001$) and LS values was not strong. In addition, lobular activity did not correlate to the LS values significantly ($r = 0.060$, $p = 0.267$). The mean LS values of F3 and F4 were significantly lower in the CHB group than in the non-CHB group: 3333.7 ± 768.7 vs. 3831.61 ± 626.5 kPa ($p = 0.03$) for F3 and 4789.6 ± 1719.9 vs. 5984.6 ± 1894.7 kPa ($p = 0.001$) for F4 (Table 2)

Table 2. Relationship between fibrosis stage and liver stiffness values according to etiology

	Total		CHB		Non-CHB		Donors		CHB vs. Non-CHB
Fibrosis Stage	LS Value	No.	LS Value	No.	LS Value	No.	LS Value	No.	*p*-value
F0	1962.4±360.7	67	2558.3	1	2534.7±357.9	6	1895±301.3	60	N/A
F1	2310.3±599.1	35	2178.5±369.6	21	2622.1±887.3	11	2087±70.2	3	0.138
F2	2835.9±662.7	52	2779.3±686.2	42	3073.3±515.4	10	N/A	0	0.148
F3	3411.9±766.1	70	3333.7±768.7	59	3831.61±626.5	11	N/A	0	0.033
F4	5002.3±1806.1	191	4789.6±1719.9	157	5984.6±1894.7	34	N/A	0	0.001

* Note. – CHB= chronic hepatitis B, No.= number of patients, LS= liver stiffness, N/A= Not available

Diagnostic Accuracies of the LS measurement in patient groups

The cutoff values, sensitivity, specificity, and AUC values of both groups are shown in Table 3. ROC analysis revealed that MRE showed high accuracy in diagnosing fibrosis in all groups (values in all areas are > 0.9). Obuchowski measures were similarly high in both groups (0.970 and 0.971). In patients with CHB and living liver donors, optimal cutoff values of liver stiffness value for ≥F1, ≥F2, ≥F3 and F4 were 2.56, 2.57, 2.92 and 3.56 kPa, respectively; in patients without CHB and donors, those values were 2.90, 2.90, 3.47 and 4.65 kPa, respectively (Table 3). The mean liver stiffness values were significantly different between all possible combinations of two fibrosis stages, except for the differences between F1 vs. F0 and F2 vs. F1 in the non-CHB group (p =0.070 and 0.115, respectively) (Table 4).

Additional subgroup analysis was done for patients without moderate or severe necroinflammation (A2 or A3) to consider the effect of necroinflammation on LS values. The diagnostic performance of these patients in this regard are shown in Table 5. In both groups, Obuchowski measures were similarly high (0.967 and 0.964), but not higher than the values for the total study population (0.967 < 0.970 and 0.964 < 0.971, respectively). For the population with normal AST and ALT levels measured within a week from the MRE exam (n=188), Obuchowski measures were 0.966 in the CHB group and 0.968 in the non-CHB group.

Table 3. Highest discriminating cut-off values with MRE in staging liver fibrosis

	Parameter	≥F1	≥F2	≥F3	F4	Obuchowski measure
CHB group	Criterion (kPa)	2.56	2.57	2.92	3.56	0.97
	Sensitivity (%)	85.8	90.7	89.4	79	
	Specificity (%)	100	95.6	89.5	90.8	
	AUC	0.958	0.973	0.947	0.918	
	Standard error	0.010	0.008	0.013	0.015	
	95% CI	0.930-0.977	0.949-0.987	0.918-0.969	0.883-0.945	
Non-CHB group	Criterion (kPa)	2.90	2.90	3.47	4.65	0.971
	Sensitivity (%)	79.1	90.9	93.3	85.3	
	Specificity (%)	100.0	90.0	95.0	98.0	
	AUC	0.929	0.950	0.962	0.958	
	Standard error	0.027	0.023	0.020	0.026	
	95% CI	0.852-0.973	0.879-0.985	0.897-0.992	0.891-0.990	

* Note. – CHB= chronic hepatitis B, MRE= magnetic resonance elastography, AUC= area under the receiver operating characteristic curve, CI= confidence interval

Table 4. Mean differences in liver stiffness values between all possible combinations of two fibrosis stages

	Total (n=415)			CHB group (n=330)			Non-CHB group (n=85)		
	Mean difference in LSV	AUC (Estimate ± S.E.)	*p*-value	Mean difference of LSV	AUC (Estimate ± S.E.)	*p*-value	Mean difference in LSV	AUC (Estimate ± S.E.)	*p*-value
F1 vs F0	347.8	0.698 ± 0.053	0.003	242.1	0.690 ± 0.065	0.007	521.4	0.704 ± 0.097	0.07
F2 vs F0	873.5	0.892 ± 0.029	<0.001	853.2	0.902 ± 0.032	<0.001	1012.2	0.933 ± 0.047	<0.001
F3 vs F0	1449.5	0.985 ± 0.007	<0.001	1407.5	0.993 ± 0.005	<0.001	1770.5	1.000 ± 0.000	<0.001
F4 vs F0	3040.0	0.995 ± 0.003	<0.001	2863.5	0.999 ± 0.001	<0.001	3923.5	0.984 ± 0.017	<0.001
F2 vs F1	525.7	0.756 ± 0.055	<0.001	611.1	0.792 ± 0.058	<0.001	490.8	0.725 ± 0.118	0.115
F3 vs F1	1101.7	0.907 ± 0.037	<0.001	1165.5	0.961 ± 0.020	<0.001	1249.17	0.894 ± 0.079	<0.001
F4 vs F1	2692.1	0.967 ± 0.016	<0.001	2621.5	0.994 ± 0.004	<0.001	3402.2	0.966 ± 0.027	<0.001
F3 vs F2	576.0	0.731 ± 0.048	<0.001	554.3	0.736 ± 0.054	<0.001	758.3	0.845 ± 0.095	0.007
F4 vs F2	2166.5	0.921 ± 0.019	<0.001	2010.29	0.919 ± 0.023	<0.001	2911.4	0.962 ± 0.031	<0.001
F4 vs F3	1590.5	0.824 ± 0.028	<0.001	1456.0	0.821 ± 0.032	<0.001	2153.0	0.904 ± 0.047	<0.001

* Note. – CHB= chronic hepatitis B, LSV= liver stiffness values measured from magnetic resonance elastography, AUC= area under the receiver operating characteristic curve, S.E.= standard error

Table 5. Highest discriminating cutoff values with MRE for staging fibrosis in patients without significant necroinflammation

	Parameter	≥F1	≥F2	≥F3	F4	Obuchowski measure
CHB group (n=264)	Criterion (kPa)	2.56	2.57	2.78	3.67	0.967
	Sensitivity (%)	82.9	89.2	93	73	
	Specificity (%)	100	95.7	85.1	94.1	
	AUC	0.948	0.967	0.941	0.918	
	Standard error	0.013	0.009	0.015	0.016	
	95% CI	0.914 to 0.971	0.938 to 0.985	0.906 to 0.966	0.878 to 0.948	
Non-CHB group (n=56)	Criterion (kPa)	2.63	2.63	3.47	4.01	0.964
	Sensitivity (%)	82.1	93.8	91.7	88.9	
	Specificity (%)	94.1	87.5	96.9	94.7	
	AUC	0.91	0.956	0.961	0.942	
	Standard error	0.037	0.025	0.030	0.042	
	95% CI	0.802 to 0.970	0.864 to 0.993	0.872 to 0.995	0.845 to 0.987	

* Note. – CHB= chronic hepatitis B, MRE= magnetic resonance elastography, AUC= area under the receiver operating characteristic curve, CI= confidence interval

DISCUSSION

Our study results showed that MRE provided excellent performance in determining the liver fibrosis stage in both patients with HBV infections and patients with CLDs from other etiologies, and LS values measured from MRE demonstrated good correlation with the pathologic liver fibrosis stages of the liver specimen. The AUC values of MRE were 0.973 for significant fibrosis (≥ F2) and 0.918 for liver cirrhosis (F4) in CHB patients, while they were 0.950 and 0.958, respectively, in non-CHB patients. These results regarding the diagnostic accuracy of MRE and LS values in both non-CHB patients and CHB patients are in good accordance with the results of previous studies dealing with patients with CHC or nonalcoholic fatty liver disease (37-39) and with those of a recent meta-analysis study (40). Therefore, based on our study results, we believe that MRE may provide high accuracy for the diagnosis of significant (stage 2) or advanced fibrosis (stage 3) and cirrhosis, independent of the etiology of CLD.

In addition, we also found that the mean LS values of F3 and F4 were significantly lower in the CHB group than those of the non-CHB group (p =0.03 for F3 and p =0.001 for F4). These results are also similar to the results of previous studies on USE (41, 42). Our results in

this regard can be explained by the fact that the histological features of hepatitis B are different from those of hepatitis C (27, 41, 42). CHB tends to make the liver macronodular and heterogeneous, and the total amount of fibrotic material in CHB may be lower than that in CHC. Furthermore, both the different types and the different extents of inflammatory infiltrates within the liver in patients with CHB and CHC may account for the difference in the cutoff values for each stage of HF (27, 41, 42). In our study, when excluding patients with significant necroinflammation, mean stiffness values between F1 and F2 in the non-CHB group became significantly different, suggesting the possible influence of necroinflammation on LS values. Indeed, Shi et al. demonstrated that in patients without advanced fibrosis, necroinflammation may cause an increase in LS values and that the values of F1 with significant necroinflammation were not different from those of F2 without significant necroinflammation (39). Our study results were consistent with their finding. However, according to the results of additional analysis on the diagnostic performance of MRE for patients without significant necroinflammation, the diagnostic performances of MRE were not superior to that of the total study population. Furthermore, as previously mentioned, as high AST and ALT values have been shown to be related to necroinflammatory activity, we additionally analyzed the diagnostic performance of MRE

in patients with measured AST and ALT levels within a week from the MRE exam, but found that the performance values presented as Obuchowski measures were not improved. Therefore, we believe that the differences in pattern and the amount of fibrotic materials in CHB and non-CHB patients could be a major factor for the differences in mean LS values between the two groups.

Of note, despite of the excellent performance of MRE in our study, the cutoff values of liver stiffness for differentiating F0 to ≥F1 and for differentiating F1 to ≥F2 were similar. These similarities in cut-off values were possibly due to the relatively small population of F1 patients (8.4% for F1) in our study, which could have led to bias in cut off values (Table 3). However, despite of the limitation of MRE in differentiating F1 vs. F2, considering its high diagnostic performance in detecting F1 and relatively low false positive rates for significant fibrosis (F2) in the study groups (4.4% for the CHB group and 10.0% for the non-CHB group), the clinical impact of this limitation in differentiating F1 from F2 may be minimal.

The key in therapeutic decision in chronic viral hepatitis is an assessment of liver injury and liver biopsy has the main role in the assessment. But its invasiveness hinders adopting this approach as a routine procedure for the evaluation and current treatment guidelines

for chronic viral hepatitis B mainly uses ALT level, HBV DNA titer and presence of hepatitis B e antigen in decision making(43-46). But significant fibrosis or inflammation has been shown to occur in a group with low HBV DNA titer and in these patients, antiviral treatments would be denied by current guidelines. So considering the high diagnostic accuracy of MRE in staging fibrosis, MRE could additionally identify the patients who would have benefit form treatment(47).

Finally, in our study, we adopted the Obuchowski measure as performance values for liver fibrosis staging in addition to standard ROC analysis (48). The Obuchowski measure is a single value which represents the probability that the values will correctly classify two randomly selected patient samples from different fibrosis stages with a weighting penalty scheme for misclassifying patients. In traditional ROC analysis, the binary gold standard exists; when the gold standard is multinomial or ordinal, ROC curve analysis can be used by constructing a binary scale from the multinomial or ordinal gold standard, however, this method could have led to biased estimates of accuracy and cutoff values according to factors such as the distribution of the study population, making it harder to interpret the results.

Our study has several limitations. First, the population size of non-CHB patients in our study was not large enough to evaluate the

performance of MRE in each etiology. Second, the time interval between the MRE exam and surgery/biopsy/sampling were heterogeneous. This could have potentially hindered the exact evaluation and validation of MRE according to pathologic confirmation and serologic tests. Third, all liver MRE studies were performed on a single MR scanner, and therefore, it might not be possible to extrapolate our study results to an actual clinical situation in which various MR scanners and other scanning parameters are used. Therefore, further studies with a larger number of patients using more than one MR scanner may be required to apply LS measurements to various etiologies.

In conclusion, the diagnostic performance of MRE in staging liver fibrosis is similarly high in CHB and non-CHB patients, while liver stiffness values differentiating liver cirrhosis are different between patients with CHB and non-CHB.

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국문 초록

서론: 이 연구에서는 만성 B 형 간염 환자와 그 이외의 원인에 의한 만성 간염 환자에서 자기공명탄성영상을 이용한 간 섬유화 평가의 진단능을 평가하고자 하였다.

방법: 이 후향적 연구는 기관감사위원회의 승인을 받았으며 고지에 의한 동의의 필요를 면제받았다. 총 352 명의 간 세포 암을 동반한 만성 간질환 환자 (만성 B 형 간염 280 명, 만성 C 형 간염 26 명, 알콜 성 간염 17 명, 기타 29 명)와 63 명의 간 공여자를 대상으로 수술 전 우리 기관에서 간 자기공명탄성영상을 시행하였다. 간 강도 값은 전단 강성도에서 정량적으로 측정되었다. 간 섬유화 평가에 있어 MRE 의 진단능은 간 섬유화의 조직 병리 소견을 기준으로 하여 리시버 작동 특성 커브 분석과 Obuchowski measure 를 통해 평가되었다.

결과: 만성 B 형 간염 환자에서 간 강도 값에 대한 곡선 하 면적은, 의미 있는 섬유화(F2), 심한 섬유화(F3), 간 경변(F4)에 대해 구하였을 때 각각 0.973 (95% 신뢰 구간 0.930−0.977), 0.947 (95% 신뢰 구간 0.918−0.969), 0.918 (95% 신뢰 구간 0.883−0.945)이었다. Obuchowski measure 는 만성 B 형 간염 환자 군과 다른 원인에 의한 환자군 사이에서 비슷하게 높았다 (0.970 대 0.971). 하지만 간 경변에 대한 간 강성 값의 절단 값

은 만성 B 형 간염 환자 군에서 다른 환자 군에 비해 낮았다. (3.56 대 4.65 kPa,p<001).

결론: 간 섬유화 평가에 대한 간자기공명탄성영상의 진단능은 만성 B 형 간염 환자 군과 그 외의 원인에 의한 환자 군에서 비슷하게 높으나 간 경변을 진단하는 간 강도값의 절단값은 만성 B 형 간염 환자 군과 다른 환자 군 사이에서 다르다.

주요어 : 자기공명탄성영상, 간 섬유화, 간 경변, 만성 B 형 간염, 괴사염증

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