의학석사 학위논문

Usefulness of Three Dimensional MR Elastography using the Echo Planar Imaging Technique for Prediction of Esophageal Varices in Cirrhotic Patients

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2014 년 02 월

서울대학교 대학원

임상의과학과 석사과정

신 승 의

3D-MR Elastography for Prediction of Esophageal Varices in Cirrhotic Patients

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A thesis of Master of Science in Clinical Medical Sciences

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February 2014

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이 논문을 의학석사 학위논문으로 제출함

2013 년 10 월

서울대학교 대학원

임상의과학과

신 승 의

신승의의 의학석사 학위논문을 인준함

2013 년 12 월

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Abstract

Introduction: To determine the diagnostic performance of MR elastography and to compare it with that of spleen length and DCE-MRI in predicting the esophageal varices in patients with liver cirrhosis using endoscopy as the reference standard.

Materials and Methods: This retrospective study had institutional review board approval, and informed consent was waived. A total of 139 patients with liver cirrhosis who underwent liver DCE-MRI including MR elastography were enrolled in my study. Hepatic and spleen stiffness values assessed by MRE as well as spleen length were correlated with the presence of esophageal varices and high-risk varices evaluated using Spearman's correlation analysis. The diagnostic performance of MR elastography was compared to that of DCE-MRI and combination of MR elastography plus DCE-MRI using ROC analysis. The reproducibility of MR elastography was prospectively assessed in the other 15 patients using intraclass correlation coefficient.

Results: There were significant positive linear correlations between HS, SS and spleen length and the grade of esophageal varices (rho=0.460; rho=0.482; rho=0.359, all P<0.0001). HS and SS values (>4.81kPa and >7.60kPa) showed better performance than spleen length in predicting the presence of esophageal varices (P=0.0306 and P=0.0064). Diagnostic performances of HS and SS in prediction of high risk varices were comparable to those of DCE-MRI (P=0.1282 and P=0.1371) and the sensitivity was improved when both

MRE and DCE-MRI were considered. MRE was highly reproducible with ICC over 0.9.

Conclusions: HS and SS are associated with the esophageal varices and showed better performance than spleen length in predicting the presence of esophageal varices, and the diagnostic performance of MRE is comparable to DCE-MRI in prediction of presence of esophageal varices and high risk varices.

Keywords:

MR Elastography

Liver cirrhosis

Esophageal varix

Diagnostic accuracy

ROC analysis

Student number: 2012-22703

Contents

Lists for Tables and Figures

List of Abbreviations

DCE-MRI=dynamic contrast enhanced-magnetic resonance imaging

HS=hepatic stiffness

SS=splenic stiffness

ROC=receiver operating characteristic curve

EGD=esophagogastroduodenoscopy

ROI=region of interest

kPa=kilopascal

AUC=area under receiver operating characteristic curve

Introduction

Liver cirrhosis is defined pathologically as fibrosis and inflammation of the liver, mainly caused by chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) and chronic alcohol abuse (1-4). It is known to lead to metabolic hepatic failure as well as portal hypertension. Recently, the population of patients with cirrhosis has been observed to be growing along with the increased incidence of HCV infections and the increased detection of NASH or NAFLD (5, 6).

One of the major complications of portal hypertension is the development of esophageal varices which occurs in approximately 30-70% of cirrhosis patients and has been shown to be correlated with the severity of liver disease (7-9). Considering that the mortality rate of variceal bleeding remains high (10-14), screening endoscopy for esophageal varices is recommended to all patients with established cirrhosis (14, 15). However, it is invasive, uncomfortable, expensive and time consuming as well as it freauently needs sedation. Therefore, there is a significant clinical demand for a noninvasive and sensitive method to assess esophageal varices, particularly high-risk varices.

In this context, there have been several attempts to find noninvasive parameters which may help to identify patients with esophageal varices or suggest the risk of variceal bleeding in patients with cirrhosis such as spleen length, portal vein diameter, Child-Pugh score, platelet count, prothrombin

time, or a combination of multiple indices, and ultrasound elastography (16-22). However, none of these variables has been satisfactorily validated in an independent series of cirrhotic patients (23). A recent meta-analysis of 14 studies examining 10 panels of indirect blood markers in chronic hepatitis C demonstrated that they cannot reliably differentiate stages of fibrosis in individual patients (24). Within the last few years, elastography using ultrasound (USG) and magnetic resonance (MR) imaging has been introduced as a novel noninvasive technology for the diagnosis and monitoring of liver stiffness. As a potential parameter to identify the presence of esophageal varices, hepatic stiffness (HS) and spleen stiffness (SS) measured by MR elastography have been suggested (25, 26). To the best of my knowledge, no studies have been performed to compare the usefulness of liver and spleen stiffness in predicting the presence or absence of esophageal varices in cirrhosis patients. Thus, the purpose of my study were to determine the diagnostic performance of MR elastography to compare it with spleen length and DCE-MRI in predicting the presence of esophageal varices and high-risk varices in patients with liver cirrhosis using endoscopy as the reference standard.

Materials and Methods

Patients

This retrospective study was approved by the institutional review board of Seoul National University Hospital, with waiver of informed consent. The reproducibility of MR elastography is assessed with prospective design, and it is approved by separate IRB with informed consent. This work was partially supported by NIH grant EB001981.

Between November 2010 and March 2012, 533 consecutive patients with liver cirrhosis based on image findings or clinical/laboratory data were referred to the radiology department for liver MR imaging, and 3D MR elastography was performed as a part of the routine liver MRI. Among them, the selected study population met the following inclusion criteria: (a) patients who underwent esophagogastroduodenoscopy (EGD) for variceal screening within 180 days before or after the MRI, and (b) no history of esophageal variceal ligation. Three hundred and fourteen patients who had not had an EGD within 180 days were excluded (27, 28). Another 63 patients who had undergone endoscopic esophageal variceal ligation therapy prior to MR imaging were excluded because prior treatment might have caused a change in lesion characteristics. Seventeen patients were also excluded for suboptimal image quality due to failure to generate a satisfactory mechanical wave through the abdomen for MR elastography. When more than one MR examination was available (n=7), the MR examination closest to the time of EGD was analyzed. The final cohort for my study consisted of 139 patients

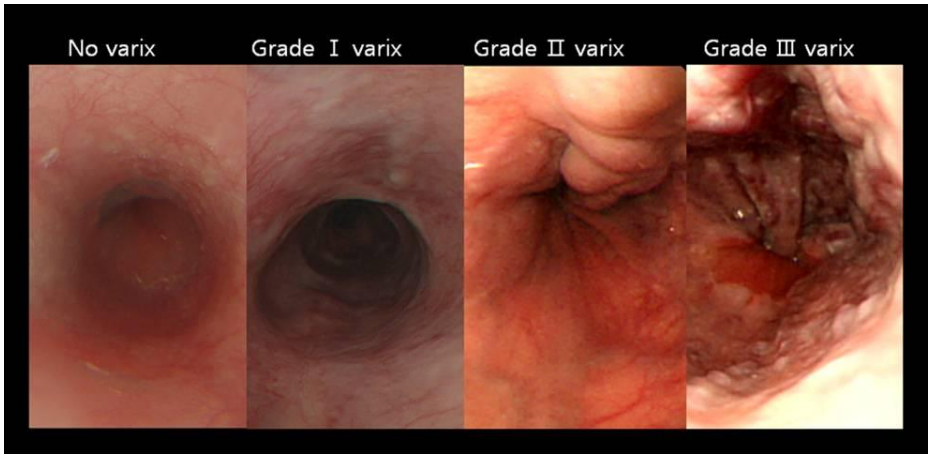
(mean 57.3 years ± 10.5, range 18-80 years; 102 men [mean 55.7 years ± 9.8, range 18-76 years] and 37 women [mean 62.1 years ± 11.1, range 31-80 years]). The diagnosis of cirrhosis was made on the basis of liver pathology findings (n=69) or the combination of typical clinical findings (symptoms and stigmata of cirrhosis and its complications), radiologic findings (morphologic changes of the liver, splenomegaly, ascites, and collateral vessels), and the results of laboratory examinations including Child-Pugh classification (n=70). The causes of liver cirrhosis were hepatitis B (n=84), hepatitis C (n=27), both hepatitis B and C (n=1), chronic alcohol abuse (n=13), primary biliary cirrhosis (PBC, n=3), recurrent pyogenic cholangitis (RPC, n=1), autoimmune hepatitis (n=1) or miscellaneous causes (n=9). Another 15 patients with liver cirrhosis were recruited to evaluate repeatability of liver and spleen stiffness assessed by MR elastography from December 2012 to January 2013.

Esophagogastroduodenoscopy

EGD was performed by one of five attending gastroenterologists and all operators used the following classification of esophageal varices (13): 0, no varices; I, varices run straight; II, varices show a beaded appearance; III, varices run oblique and are tortuous with a tumor-like appearance (Figure 1). Patients were divided into two groups, a low-risk group with no or small varices (grade < II) and with large varices (grade ≥ II) on the basis of their probability for developing esophageal variceal bleeding (29). The mean interval between MR elastography and endoscopy was 23.0 days and the

range was 0 to 168 days.

F**igure 1.** Representative endoscopic findings of esophageal varices in this study



MRI and MR elastography Protocol

All MR images were obtained using a 1.5-T, whole-body MR unit (Signa HDx; GE Healthcare, Milwaukee, WI) using an eight-channel, torso phased-array coil centered over the liver. MR elastography was done at the end of the examination after obtaining standard precontrast liver MR images, prior to gadoxetic acid injection. I used a single-shot, multislice, spin-echo echo planar imaging (EPI) MR elastography pulse sequence to measure tissue displacements and assess tissue mechanical properties throughout the liver and spleen. Imaging was done in the supine position with an acoustic pressure-activated driver placed against the body wall adjacent to the liver. Low-frequency longitudinal mechanical waves of 60Hz were transmitted into

the right liver by a passive driver (synchronized with the imaging sequence) that was placed against the right chest wall over the liver with the center of the driver at the level of the xiphisternum (30, 31). The passive driver was held in place by an abdominal binder. Thirty-two axial slices were obtained for each MR elastography exam from the dome to the tip of the liver.

MR Elastography Analysis

One reader (SSU with 3 years' experience in liver MR imaging) who was blinded to the patients' clinical and biochemical data as well as the grade of esophageal varices measured the spleen length and stiffness of the liver and spleen. The splenic length was obtained by multiplying the number of sections where the spleen was visualized by the thickness of the sections (32-34). Referencing conventional MR images, three geographical, circular- or oval-shaped regions of interest (ROIs) were placed on the right lobe of the liver and carefully adjusted according to the adjacent anatomic landmarks, using three different slices (mean size: 6384.1 mm^2 ± 2919.4). Bile ducts; large vessels within the liver and fissures; artifacts from motion, including pulsation artifacts from the heart and aorta; areas with poor signal-to-noise ratio; the region just below the driver; the left lobe of the liver; and regions without adequate magnitude signal or wave amplitude were avoided (26, 35, 36). ROIs were also placed on the spleen (mean size: 3583.8 mm2 ± 1335.2) at the three levels where the spleen showed a large area, avoiding boundaries and large vessels The overall stiffness of the heterogeneous liver and spleen was

calculated by averaging the mean stiffness values recorded from each slice for the patients. The mean stiffness values were measured in kilopascals (kPa). To assess reproducibility, MR elastography was performed two times repetitively on the same day in the other 15 patients who did not included in the retrospective analysis. The same reader performed the ROI measurement of liver and spleen stiffness applying the same principle as written above. Two sessions of measurement were done with a 2-week separation. Mean liver stiffness and the maximum liver stiffness values within three slices in each session were calculated for further statistical analyses.

In addition, the large amount of ascites at the perihepatic space and whether the liver or spleen had iron deposition were assessed. Iron accumulation was defined as either a presence of definite low signal intensity on T2*-weighted MR images or reduced signal intensity on in phase images compared with the opposed phage images.

Analysis of esophageal varices using DCE-MRI

Two faculty abdominal radiologists (J.H.Y. and M.H.Y, each with 6 years of experience), who were blinded to the patients' physical findings, laboratory values, previous imaging results, and endoscopic results independently interpreted DCE-MRI with portal phase and 3-min delay phase to detect the presence of esophageal varices and high-risk esophageal varices. In the first session, they were blinded to the stiffness values of liver and spleen, and in the second session, they were provided with the stiffness values of liver and

spleen. Before the interpretation session, radiologists underwent a training session using 10 cases with various grades of esophageal varices. The cases in the training session were not included in the interpretation session. Based on the prior study by Kim et al. (37), each radiologist determined the presence of esophageal varices on a 4-point confidence scale (1 = definitely absent, 2 = probably absent, 3 = probably present, 4 = definitely present) and the approximate size by measuring the diameter of the largest observed varix. Sensitivity for the detection of varices was determined using the number of patients with varices assigned a score of 3 or 4. A quantitative cutoff for high-risk varices seen on MRI was chosen as greater than 2 mm in diameter based on previous studies (37).

Statistical analysis

Patient characteristics were expressed as mean values ± standard deviations. The two subject groups were compared using the Student t test (for age) or chi-square test (for subject sex), as appropriate. The relationship between MR elastography values and the variceal grade was assessed using Spearman's correlation analysis. In addition, the correlation between spleen length and variceal grade was evaluated using the Pearson correlation coefficient. A P value of less than 0.05 was deemed to indicate statistical significance. To identify the significant independent predictors of presence of varices, high grade varices and variceal bleeding, multivariate logistic regression analysis with the stepwise selection method was performed; a significance level of P_{in}

< 0.05, P_{out} > 0.10 was established. Variables of age, sex, HBV, HS, SS, and spleen length were put into the analysis. A *P* value of less than 0.05 was considered to indicate a significant difference. To evaluate the diagnostic accuracy for the prediction of the presence of varices (regardless of grade) or high-risk varices (grade ≥ II), the mean area under the receiver operating characteristic curve (AUC), sensitivity, specificity were calculated for HS, SS, spleen length and DCE-MRI. I looked for cutoff values of the HS and SS which maximized the accuracy for predicting the presence of varices and high-risk varices. Accuracy of MR elastography and spleen length was further assessed by means of the leave-one-out cross-validation method to make up for the lack of independence between the training and testing sets due to the limited sample size in my study. To perform leave-one-out cross-validation analysis, the total study population was divided into two groups at random. After a cutoff value was calculated in one group, that cutoff value was applied to the other group and sensitivity and specificity were calculated. The same analysis was carried out by changing the group and the two values were obtained. The weighted mean of these two values of sensitivity, and specificity were then calculated.

To evaluate the added value of MR elastography, the readers were given the stiffness of the liver and spleen, and then requested to predict the presence of varices and high grade varices using DCE-MRI. The AUC, sensitivity and specificity of combined technique were compared with those of DCE-MRI. The differences between the AUC values were compared by the method described by DeLong et al. (38). Sensitivities and specificities were compared

using the McNemar test.

For further evaluation, the mean values of HS and SS were compared between patients with and without variceal bleeding in high grade group. I also assessed the diagnostic performance of HS, SS, spleen length and DCE-MRI for prediction of unprotected variceal bleeding in patient with high risk varices who did not undergo prophylactic variceal ligation, using AUC, sensitivity, and specificity. Additional ROC analysis was performed using HS as a binary variable to predict unprotected variceal bleeding in the high-risk group.

The reproducibility of (a) the mean liver and spleen stiffness over 3 slices, and (b) the maximum liver and spleen stiffness over 3 slices were evaluated by a one-way random model of intraclass correlation coefficient (ICC) and Bland-Altman analysis. The majority of the statistical analyses were supported by the Medical Research Collaborating Center of my institute. All statistical analyses, except ROC curves, were performed using the SPSS software package (version 19.0; SPSS, Chicago, IL, USA). Results from ROC curves were obtained using commercially available software (MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

Among the 139 patients, 78 patients (56.1%) had esophageal varices (33, grade I; 40, grade II; and 5, grade III). Forty five patients had esophageal varices equal to or higher than grade II and were categorized into the high-risk group (32.4%) and the others into the low-risk group (n=94, 67.6%). Among the high-risk group, 15 patients had undergone prophylactic variceal ligation after acquisition of MRI and MR elastography, so they are not included the follow-up group to determine whether bleeding occurred. Another 11 patients experienced unprotected variceal bleeding during the follow-up period. Age, sex, etiology and the interval between MRE and EGD did not show any statistical differences between the two groups. There were 64 patients with iron deposition in the liver and 41 patients with iron deposition in the spleen.

Correlation of MR elastography and spleen length with esophageal varix grade

The mean values of HS and SS values measured by MR elastography were significantly lower in the group without esophageal varices than the group with varices of any grade (4.5kPa vs. 6.6kPa and 6.4kPa vs. 8.8kPa, $P<0.0001$, both). In addition, HS and SS values measured by MR elastography and spleen length were significantly lower in the low-risk group than the high-risk group (5.1kPa vs. 7.1 kPa, $P<0.0001$; 7.1kPa vs. 9.1kPa, $P<0.0001$; 11.9cm vs.

13.9cm, P=0.0014, respectively). On correlation analysis, positive linear correlations were observed between MR elastography values and the grade of esophageal varices (rho=0.460; rho=0.482; rho=0.359, all P<0.0001). As esophageal variceal grade increased, HS, SS and spleen length also increased. Figure 2 summarizes the changes of HS, SS and splenic length for each group with different grades of esophageal varices and the representative images are displayed on Figure 3.

Figure 2. Box and Whisker plot for (A) hepatic stiffness, (B) splenic stiffness and (C) splenic length according to the grade of esophageal varices.

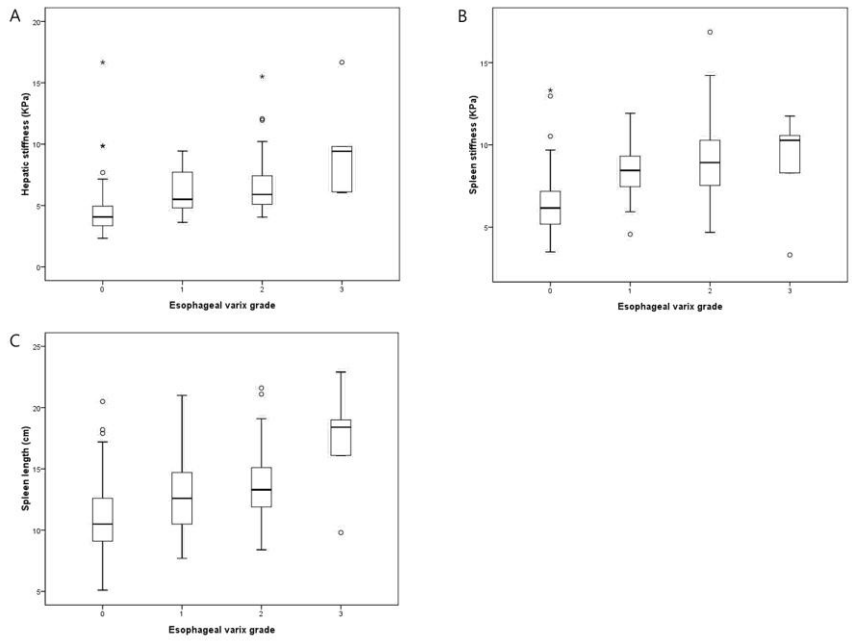
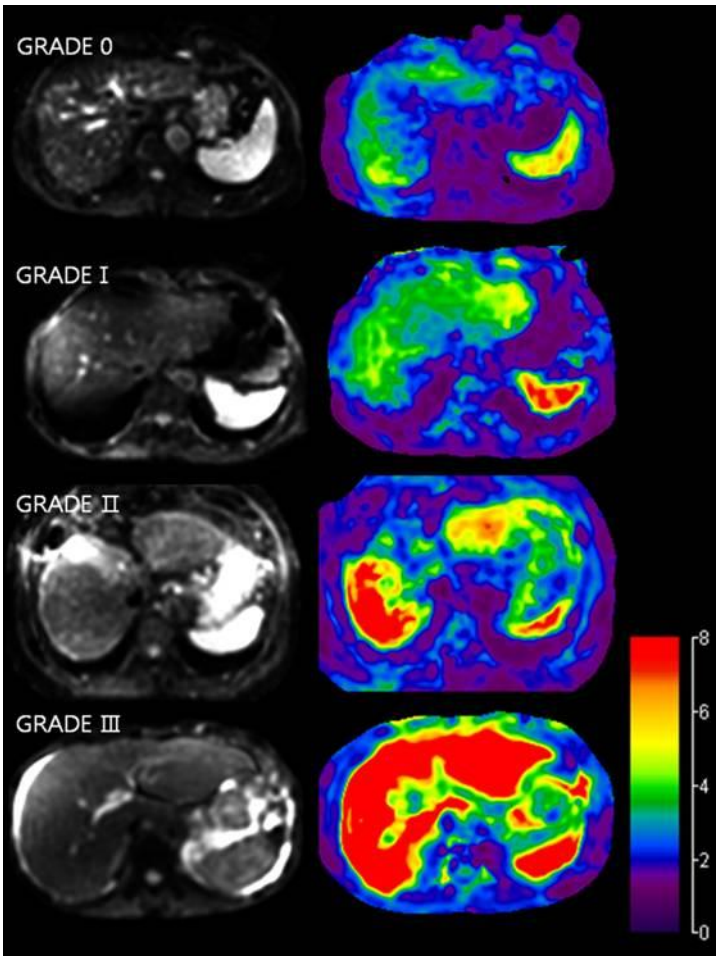


Figure 3. Example of a magnitude image and shear stiffness maps (elastograms) of the liver and spleen in patients with four different grades of esophageal varices proven by endoscopy.



Independent predictive factors for esophageal varices and variceal bleeding

Multivariate logistic regression analysis revealed that HS and SS were the significant independent factors associated with the presence of varices

(P=0.0035 and P<0.0001 respectively) and high grade varices (P=0.0158 and P=0.0026). For prediction of variceal bleeding, only HS was a significant independent predictor (P=0.0038).

Diagnostic performance of MR elastography in identifying the varices and assessing the risk of variceal bleeding compared with DCE-MRI

Table 1 summarizes the sensitivity and specificity of the HS, SS, spleen length and DCE-MRI obtained from ROC curves for the prediction of presence of varices. In pairwise comparisons of ROC curves, three variables of DCE-MRI, HS and SS showed greater capability in predicting the presence of varices compared to spleen length (P=0.0021, P=0.0001, and P=0.0001, respectively). However, there were no statistically significant differences between DCE-MRI and HS or SS (P=0.5493 and P=0.8419, respectively) and between HS and SS (P=0.7665).

The diagnostic performances to detect high-risk varices are summarized in Table 2. In pairwise comparisons of ROC curves, three variables of DCE-MRI, HS and SS showed greater capability in identifying high-risk varices compared to spleen length (P=0.0004, P=0.0430, and P=0.0489, respectively). There were no statistically significant differences between DCE-MRI and HS or SS (P=0.1282 and P=0.1371, respectively) and between HS and SS (P=0.9279).

In the high-risk group without prophylactic variceal ligation, HS was

significantly higher in the patients with variceal bleeding (n=11) than those of patients without variceal bleeding (n=19) (6.4169 vs. 7.9802, P=0.016) but, SS was not (8.9664 vs. 6.6505, P=0.767). In addition, HS, SS and DCE-MRI can be a factor for prediction of unprotected variceal bleeding (P<0.0001, P=0.027, and P<0.0001, respectively), but spleen length was not (P=0.129). The AUC of HS was significantly higher than SS (0.795 vs. 0.673, P=0.0129). However, there were no statistically significant differences between DCE-MRI and HS or SS (P=0.9199 and P=0.0859, respectively). The detailed values are summarized in Table 3. Additional ROC analysis using HS as a binary variable with the cutoff value of HS (>4.81kPa), previously obtained from ROC curve for high-risk varices, revealed that AUC of 0.579 (P=0.0662), sensitivity of 100% and specificity of 15.8%.

Table 1. Diagnostic performance of MR elastography in predicting the presence of varices

	AUC	95% Confidence Interval	Cutoff value*	Sensitivity (%)	Specificity (%)
Before cross-validation					
Hepatic stiffness	0.821	0.746-0.880	4.58 kPa	85.9	72.1
Splenic stiffness	0.833	0.760-0.891	7.23 kPa	84.6	78.7
Spleen length	0.697	0.613-0.772	11.2 cm	74.4	59.0
DCE-MRI Reader 1	0.864	0.795-0.916		74.4	98.4
DCE-MRI Reader 2	0.814	0.740-0.875		74.4	88.5
DCE-MRI Average	0.839	0.790-0.880		74.4	93.4
After cross-validation					
Hepatic stiffness			4.58 kPa	87.4	65.6
Splenic stiffness			7.23 kPa	85.8	65.4
Spleen length			11.2 cm	10.1	96.7

Note.— AUC= area under curve, CI=confidence interval, S=sensitivity, SP=specificity, DCE-MRI= dynamic contrast enhanced MRI

*Best cutoff values chosen via ROC analysis

Table 2. Diagnostic performance of MR elastography in predicting high-risk varices

	AUC	95% Confidence Interval	Cutoff value*	Sensitivity (%)	Specificity (%)
Before cross-validation					
Hepatic stiffness	0.755	0.675-0.824	4.81 kPa	88.9	56.4
Splenic stiffness	0.750	0.670-0.820	7.60 kPa	75.6	66.0
Spleen length	0.670	0.585-0.747	11.2 cm	82.2	51.1
DCE-MRI Reader 1	0.854	0.784-0.908		86.7	84.0
DCE-MRI Reader 2	0.759	0.680-0.828		68.9	83.0
DCE-MRI Average	0.806	0.755-0.851		77.8	83.5
After cross-validation					
Hepatic stiffness			4.81 kPa	84.4	56.7
Splenic stiffness			7.60 kPa	68.3	61.6
Spleen length			11.2 cm	12.3	95.7

Note.— AUC= area under curve, CI=confidence interval, S=sensitivity, SP=specificity, DCE-MRI=dynamic contrast enhanced MRI

*Best cutoff values chosen via ROC analysis

Table 3. Diagnostic performance of MR elastography in predicting unprotected variceal bleeding

	AUC	***P*-value**	**95% Confidence Interval**	**Sensitivity (%)**	**Specificity (%)**
Hepatic stiffness	0.795	<0.0001	0.713-0.863	100	55.9
Splenic stiffness	0.673	0.027	0.582-0.755	54.6	64.9
Spleen length	0.639	0.129	0.847-0.724	63.6	65.8
DCE-MRI Reader 1	0.846	<0.0001	0.770-0.905	90.9	78.4
DCE-MRI Reader 2	0.733	0.0015	0.645-0.809	72.7	73.9
DCE-MRI Average	0.790	<0.0001	0.733-0.839	81.8	76.1

Note.—DCE-MRI=dynamic contrast enhanced MRI

Additional value of MR elastography on DCE-MRI

When both MR elastography and DCE-MRI were taken into account for the analysis, and then compared with the result of DCE-MRI, the AUC were not significantly changed for the group with any grade varices (0.874 vs. 0.839, P=0.0648) and high-risk group (0.832 vs. 0.806, P=0.3361). The sensitivity significantly increased compared with that of DCE-MRI alone for detection of any grade varices (84.6% vs. 74.4%, P=0.0004). But there were no statistical significant differences in the sensitivity for high-risk group (86.7% vs. 77.8%, P=0.1153) and the specificities for the group with any grade varices (90.2% vs. 93.4%, P=0.3438) and high-risk varices (79.8% vs. 83.5%, P=0.1435). These results are summarized in Table 4.

Table 4. Comparison of diagnostic performances between DCE-MRI and combination of DCE-MRI and MR elastography

Parameter	Presence of varices			High-risk varices		
	DCE-MRI	DCE-MRI/MRE	P value	DCE-MRI	DCE-MRI/MRE	P value
AUC *	0.839	0.874	0.0648	0.806	0.832	0.3361
Sensitivity (%) †	74.4	84.6	0.0004	77.8	86.7	0.1153
Specificity (%) †	93.4	90.2	0.3438	83.5	79.8	0.1435

Note.—DCE-MRI=dynamic contrast enhanced MRI, MRE=MR elastography, AUC= area under curve

* The differences between the AUC values were compared by the method described by DeLong et al..

† Sensitivities and specificities were compared using the McNemar test.

Repeatability of MR elastography

The repeatability of the mean stiffness and the maximum stiffness of the liver and the spleen over 3 slices were evaluated by ICC. For both HS and SS, the mean stiffness values were more reproducible than the maximum stiffness values (0.999 vs. 0.997 and 0.981 vs. 0.933, respectively). Bland-Altman analysis revealed that coefficients of repeatability are 0.142, 0.402, 0.679, and 1.538 for HS_{mean}, HS_{max}, SS_{mean}, and SS_{max} repectively.

Discussion

The results of my study indicate that HS and SS values measured from 3D/3-axis MR elastography data obtained using the spin-echo EPI technique well correlated with esophageal varices. In addition, 3D-MR elastography showed comparable diagnostic potential in detecting esophageal varices or identifying high-risk varices with DCE-MRI. Furthermore, the sensitivity significantly increased compared with that of DCE-MRI alone for detection of varices. These results are in good agreement with those of other studies which also demonstrated that liver stiffness values measured by transient US elastography revealed a positive correlation for predicting the presence of esophageal varices (39-42). There is some debate regarding the correlation between HS and SS in patients with chronic liver diseases using MR elastography (26, 43). In my study, there was no statistically significant difference between HS and SS in predicting the presence of varices or identifying high-risk varices. However, the cutoff value of HS (>4.81kPa) revealed that 100% of sensitivity for high-risk varices and there was significant difference in HS in patients who had esophageal varices bleed vs. those who did not. Considering these good sensitivities of MR elastography helping in identify patients at risk of having esophageal varices and variceal bleeding, I should consider measuring HS or SS in all patients with cirrhosis. According to AASLD guidelines, in all patients with cirrhosis, regular screening endoscopy is needed (14, 44). Leaving the invasiveness and expense aside, there are issues with compliance and need of sedation. If I add

MR elastography on routine MRI which is performed for cancer surveillance or management of cirrhosis, the inconvenience of the patients would decrease and may adjust endoscopy schedule.

In my study, MR elastography showed several cases of false positive diagnoses for esophageal varices (18 for HS and 13 for SS) or high-risk varices (41 for HS and 32 for SS). In those patients, although there were neither varices nor high-risk varices, high stiffness values were noted. Interestingly, in all of those cases I found dilated collateral veins other than esophageal varices with contrast-enhanced MR imaging, such as distal splenorenal shunts, retroperitoneal veins, recanalized periumbilical veins and epigastric veins in contrast-enhanced MR imaging of portal and delayed phases coronal images. In severe liver fibrosis or liver cirrhosis with portal hypertension and increased resistance of portal blood flow, it is not surprising that hypertensive portal blood flow could be drained through many other pathways, not only through esophageal varices (42, 45, 46). In addition, the state of hepatic inflammation might overestimate the stiffness value of the liver (47). Also in my study, there were 11 false negative cases which showed low HS values despite of the presence of esophageal varices. Indeed, seven patients had iron deposition in the liver which was present on the T2*-weighted images or the in-and-opposed images, causing a signal drop in the elastogram. Also, two patients had ascites in the perihepatic space that may have possibly interrupted the wave transmission to the liver. Another possibility, as some other studies have suggested, is that the false negative results may be due to portal hypertension which precedes the development of

hepatic fibrosis (21, 26, 48), although I did not have a pathologic evaluation of hepatic fibrosis in those patients.

In my study, I used a 3D/3-axis MR elastography technique using the EPI sequence to measure HS and SS. 3D MR elastography of the liver has been used previously in clinical studies. However, there are still a few problems remaining with this MR elastography approach. First, although the spin-echo nature of this EPI acquisition makes it more resistant to signal losses due to iron deposition than the gradient echo sequence, the measured stiffness values from 3D MR elastography can be erroneously low in cases of severe iron deposition in the liver or spleen (26, 49, 50). This is because iron deposits in the liver and spleen may increase magnetic susceptibility, which can still decrease signal intensity and result in poor wave depiction in the EPI images. However, in my study, many cases showed a good MR elastography signal even though they had parenchyma iron deposition, and therefore further studies are warranted to better explore the relationship between the EPI MR elastography sequence and iron deposition. Second, there were 17 patients with technical failure of MR elastography acquisition. In patients with advanced cirrhosis, the colon may intervene between the abdominal wall and liver surface because the liver parenchyma often shrinks and derangement of liver function frequently causes ascites. Several other previous studies have also demonstrated that patients with ascites, colonic interposition, and excessive subcutaneous or mesenteric fat are likely to have improper propagation of shear waves, even though the technical failure rate of MRE was much lower than ultrasound-based elastography (39, 51-54). There were

several limitations in my study. First, given the retrospective nature of my study, the possibility of selection bias exists. Although my study has a relatively large number of study patients collected in a consecutive manner, the low percentage of patients with high-grade varices patients may affect the negative predictive value to be overestimated. Second, another limiting factor was that the time window between the EGD and MR elastography examinations was relatively long in some patients (range, 0-168 days). However, the maximum time difference between MR elastography and the endoscopic examination was limited to 6 months which is previously used in other studies with tolerance. Third, I tested the reproducibility of MR elastography in another test population (n=15). However, the stiffness values were measured by one reader and the reader variability would be another weakness of my study. Further studies on the reproducibility of MR elastography are warranted, even though other studies have reported high reproducibility (48, 55-58). Lastly, although there were 45 patients of the high-grade varices group, 15 of them had undergone prophylactic variceal ligation to prevent variceal bleeding after acquisition of MRI, and 11 patients experienced variceal bleeding. Therefore, the direct relationship between liver and spleen stiffness and the occurrence of esophageal variceal bleeding was not fully analyzed in my study. In addition, there is a lot of overlap between groups. This suggests that individual patients the technique may be of limited value in grading varices. Also, the following studies are expected for the comparison of the diagnostic accuracy between ultrasound elastography and MR elastography. In summary, the hepatic and splenic stiffness values

assessed by MR elastography are associated with the esophageal varices and the diagnostic accuracy of MR elastographyis comparable to that of DCE-MRI and the sensitivity increases when the MR elastography and DCE-MRI are assessed with combination.

References

1. Jou JH, Muir AJ. In the clinic. Hepatitis C. Ann Intern Med. 2008;148(11):ITC6-1-ITC6-16.

2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4):529-38.

3. Seeff LB, Hoofnagle JH. Epidemiology of hepatocellular carcinoma in areas of low hepatitis B and hepatitis C endemicity. Oncogene. 2006;25(27):3771-7.

4. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371(9615):838-51.

5. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology. 2009;49(1):306-17.

6. Michitaka K, Nishiguchi S, Aoyagi Y, Hiasa Y, Tokumoto Y, Onji M. Etiology of liver cirrhosis in Japan: a nationwide survey. Journal of gastroenterology. 2010;45(1):86-94.

7. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38(3):266-72.

8. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. J Hepatol. 2008;48 Suppl 1:S68-92.

9. National Guideline C. World Gastroenterology Organisation practice guideline: esophageal varices Rockville MD: Agency for Healthcare Research and Quality (AHRQ); [2/13/2012]. Available from: http://www.guideline.gov.

10. Liu CH, Hsu SJ, Liang CC, Tsai FC, Lin JW, Liu CJ, et al. Esophageal

varices: noninvasive diagnosis with duplex Doppler US in patients with compensated cirrhosis. Radiology. 2008;248(1):132-9.

11. D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology. 2003;38(3):599-612.

12. Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, et al. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. Am J Gastroenterol. 2003;98(3):653-9.

13. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med. 1988;319(15):983-9.

14. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3):922-38.

15. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2005;43(1):167-76.

16. Chalasani N, Imperiale TF, Ismail A, Sood G, Carey M, Wilcox CM, et al. Predictors of large esophageal varices in patients with cirrhosis. Am J Gastroenterol. 1999;94(11):3285-91.

17. Barrera F, Riquelme A, Soza A, Contreras A, Barrios G, Padilla O, et al. Platelet count/spleen diameter ratio for non-invasive prediction of high risk esophageal varices in cirrhotic patients. Ann Hepatol. 2009;8(4):325-30.

18. Chang MH, Sohn JH, Kim TY, Son BK, Kim JP, Jeon YC, et al. [Non-endoscopic predictors of large esophageal varices in patients with liver cirrhosis]. Korean J Gastroenterol. 2007;49(6):376-83.

19. Hong WD, Dong LM, Jiang ZC, Zhu QH, Jin SQ. Prediction of large

esophageal varices in cirrhotic patients using classification and regression tree analysis. Clinics (Sao Paulo). 2011;66(1):119-24.

20. Thomopoulos KC. Non-invasive prediction of esophageal varices: is it possible? Saudi J Gastroenterol. 2011;17(1):1-3.

21. Zaman A, Hapke R, Flora K, Rosen HR, Benner K. Factors predicting the presence of esophageal or gastric varices in patients with advanced liver disease. Am J Gastroenterol. 1999;94(11):3292-6.

22. Horvath G. [New non-invasive tool for assessment of liver fibrosis: transient elastography]. Orv Hetil. 2011;152(22):860-5.

23. Berzigotti A, Gilabert R, Abraldes JG, Nicolau C, Bru C, Bosch J, et al. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. Am J Gastroenterol. 2008;103(5):1159-67.

24. Parkes J, Guha IN, Roderick P, Rosenberg W. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. J Hepatol. 2006;44(3):462-74.

25. Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, et al. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. AJR Am J Roentgenol. 2009;193(1):122-7.

26. Nedredal GI, Yin M, McKenzie T, Lillegard J, Luebke-Wheeler J, Talwalkar J, et al. Portal hypertension correlates with splenic stiffness as measured with MR elastography. J Magn Reson Imaging. 2011;34(1):79-87.

27. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, Garcia-Pagan JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology. 2013;144(1):102-11 e1.

28. Morisaka H, Motosugi U, Ichikawa T, Sano K, Ichikawa S, Araki T, et al. MR-based measurements of portal vein flow and liver stiffness for predicting

gastroesophageal varices. Magnetic resonance in medical sciences : MRMS : an official journal of Japan Society of Magnetic Resonance in Medicine. 2013;12(2):77-86.

29. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, et al. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc. 1981;27(4):213-8.

30. Huwart L, Peeters F, Sinkus R, Annet L, Salameh N, ter Beek LC, et al. Liver fibrosis: non-invasive assessment with MR elastography. NMR Biomed. 2006;19(2):173-9.

31. Yin M, Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2007;5(10):1207-13 e2.

32. Bezerra AS, D'Ippolito G, Faintuch S, Szejnfeld J, Ahmed M. Determination of splenomegaly by CT: is there a place for a single measurement? AJR Am J Roentgenol. 2005;184(5):1510-3.

33. Lamb PM, Lund A, Kanagasabay RR, Martin A, Webb JA, Reznek RH. Spleen size: how well do linear ultrasound measurements correlate with three-dimensional CT volume assessments? The British journal of radiology. 2002;75(895):573-7.

34. Ying L, Lin X, Xie ZL, Hu YP, Shi KQ. Performance of platelet count/spleen diameter ratio for diagnosis of esophageal varices in cirrhosis: a meta-analysis. Dig Dis Sci. 2012;57(6):1672-81.

35. Rouviere O, Yin M, Dresner MA, Rossman PJ, Burgart LJ, Fidler JL, et al. MR elastography of the liver: preliminary results. Radiology. 2006;240(2):440-8.

36. Wang Y, Ganger DR, Levitsky J, Sternick LA, McCarthy RJ, Chen ZE, et al.

Assessment of chronic hepatitis and fibrosis: comparison of MR elastography and diffusion-weighted imaging. AJR Am J Roentgenol. 2011;196(3):553-61.

37. Kim H, Choi D, Gwak GY, Lee JH, Park MK, Lee H, et al. Evaluation of esophageal varices on liver computed tomography: receiver operating characteristic analyses of the performance of radiologists and endoscopists. J Gastroenterol Hepatol. 2009;24(9):1534-40.

38. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.

39. Kazemi F, Kettaneh A, N'Kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol. 2006;45(2):230-5.

40. Castera L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol. 2009;50(1):59-68.

41. Lim JK, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: is there still a role for hepatic venous pressure gradient measurement? Hepatology. 2007;45(5):1087-90.

42. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology. 2007;45(5):1290-7.

43. Spina GP, Arcidiacono R, Bosch J, Pagliaro L, Burroughs AK, Santambrogio R, et al. Gastric endoscopic features in portal hypertension: final report of a consensus conference, Milan, Italy, September 19, 1992. J Hepatol.

1994;21(3):461-7.

44. Kang EJ, Jeong SW, Jang JY, Cho JY, Lee SH, Kim HG, et al. Long-term result of endoscopic Histoacryl (N-butyl-2-cyanoacrylate) injection for treatment of gastric varices. World J Gastroenterol. 2011;17(11):1494-500.

45. Matsuo M, Kanematsu M, Kim T, Hori M, Takamura M, Murakami T, et al. Esophageal varices: diagnosis with gadolinium-enhanced MR imaging of the liver for patients with chronic liver damage. AJR Am J Roentgenol. 2003;180(2):461-6.

46. Cho KC, Patel YD, Wachsberg RH, Seeff J. Varices in portal hypertension: evaluation with CT. Radiographics. 1995;15(3):609-22.

47. Vispo E, Barreiro P, Del Valle J, Maida I, de Ledinghen V, Quereda C, et al. Overestimation of liver fibrosis staging using transient elastography in patients with chronic hepatitis C and significant liver inflammation. Antiviral therapy. 2009;14(2):187-93.

48. Hines CD, Bley TA, Lindstrom MJ, Reeder SB. Repeatability of magnetic resonance elastography for quantification of hepatic stiffness. J Magn Reson Imaging. 2010;31(3):725-31.

49. Taouli B, Ehman RL, Reeder SB. Advanced MRI methods for assessment of chronic liver disease. AJR Am J Roentgenol. 2009;193(1):14-27.

50. Adhoute X, Foucher J, Laharie D, Terrebonne E, Vergniol J, Castera L, et al. Diagnosis of liver fibrosis using FibroScan and other noninvasive methods in patients with hemochromatosis: a prospective study. Gastroenterologie clinique et biologique. 2008;32(2):180-7.

51. Kim BK, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol. 2010;105(6):1382-90.

52. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al.

Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol. 2003;29(12):1705-13.

53. Bensamoun SF, Wang L, Robert L, Charleux F, Latrive JP, Ho Ba Tho MC. Measurement of liver stiffness with two imaging techniques: magnetic resonance elastography and ultrasound elastometry. J Magn Reson Imaging. 2008;28(5):1287-92.

54. Huwart L, van Beers BE. MR elastography. Gastroenterologie clinique et biologique. 2008;32(6 Suppl 1):68-72.

55. Yin M, Talwalkar JA, Glaser KJ, Venkatesh SK, Chen J, Manduca A, et al. Dynamic postprandial hepatic stiffness augmentation assessed with MR elastography in patients with chronic liver disease. AJR Am J Roentgenol. 2011;197(1):64-70.

56. Shire NJ, Yin M, Chen J, Railkar RA, Fox-Bosetti S, Johnson SM, et al. Test-retest repeatability of MR elastography for noninvasive liver fibrosis assessment in hepatitis C. J Magn Reson Imaging. 2011.

57. Huwart L, Sempoux C, Vicaut E, Salameh N, Annet L, Danse E, et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology. 2008;135(1):32-40.

58. Kim BH, Lee JM, Lee YJ, Lee KB, Suh KS, Han JK, et al. MR elastography for noninvasive assessment of hepatic fibrosis: experience from a tertiary center in Asia. J Magn Reson Imaging. 2011;34(5):1110-6.

초 록 (국 문)

서론: 간경변 환자에서 자기공명탄성영상을 이용하여 식도정맥류를 예측할 수 있는지 알아보고, 식도정맥류의 예측에 있어서 탄성영상을 역동적자기공명영상 (DCE-MRI)에 추가하는 것이 DCE-MRI 단독 검사법에 비하여 진단능을 향상시키는지를 평가한다.

방법: 이 연구는 윤리 위원회의 승인을 받았다. 간경변 환자중 MRI 를 시행한 139 명의 환자를 대상으로 간탄력도, 비장탄력도, 비장의 크기를 측정하였고, 조영증강 MRI 를 이용하여 식도정맥류를 예측한 결과를 ROC analysis 의 비교를 통해 진단능력을 평가하였다. 또한 조영증강 MRI 만으로 진단하였을 때와 자기공명탄성영상의 정보가 추가로 주어졌을 때의 식도정맥류 진단능력을 비교하였다. 자기공명탄성영상의 reproducibility 는 따로 15 명의 환자를 대상으로 intraclass correlation coefficient 와 Bland Altman analysis 를 이용하여 분석하였다.

결과: 간탄력도, 비장탄력도, 비장의 크기와 식도정맥류의 등급은 양의 상관관계가 있었으며 (상관계수=0.460; 0.482; 0.359, all P<0.0001), 간탄력도, 비장탄력도, 조영증강 MRI는 식도정맥류를 예측하는데 있어서 비장의 크기보다 좋은 결과를 보였다. 또한, 간탄력도, 비장탄력도, 조영증강 MRI의 고위험 식도정맥류를 진단하는 능력은 차이가 없었으나, 조영증강 MRI와 자기공명탄성영상으

로 측정한 탄력도의 정보를 가지고 진단하였을 경우, 조영증강 MRI 만 가지고 진단하였을 때보다 민감도가 증가하였다. 탄성영상의 조직탄성도의 측정은 매우 반복성이 높았다 (ICC>0.9).

결론: 간과 비장의 탄력도는 식도정맥류를 예측하는데 있어서 비장의 크기보다 더 좋은 결과를 보이고 자기공명탄성영상의 진단능력은 조영증강 MRI 의 진단능력과 차이가 없으며 자기공명탄성영상과 조영증강 MRI 를 함께 이용하면 식도 정맥류 예측의 민감도가 증가한다.

주요어: 자기공명탄성영상, 간경변증, 식도정맥류, 진단능력, ROC analysis

학번: 2012-22703