

Liver and Spleen Stiffness Measured by Acoustic Radiation Force Impulse Elastography for Noninvasive Assessment of Liver Fibrosis and Esophageal Varices in Patients With Chronic Hepatitis B

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Abbreviations

ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; HBV, hepatitis B virus; HCV, hepatitis C virus

Objectives—To evaluate the performance of liver and spleen stiffness measured by acoustic radiation force impulse (ARFI) elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B virus.

Methods—Two hundred sixty-four participants, of whom 60 were healthy volunteers (classified as stage 0), 66 were patients with chronic hepatitis B who had undergone liver biopsy, and 138 were patients with hepatitis B-related cirrhosis, were enrolled in this study. Median liver and spleen stiffness values (meters per second) from 10 successful measurements per participant were obtained. Patients with cirrhosis were examined by upper endoscopy.

Results—Significant linear correlations were found between liver (Spearman $\rho = 0.87$; $P < .001$) and spleen (Spearman $\rho = 0.76$; $P < .001$) stiffness and the fibrosis stage. Liver and spleen stiffness values increased as fibrosis progressed; however, overlaps in liver stiffness were detected in stages 0 and 1 and 1 and 2, and overlaps in spleen stiffness were observed in stages 0 and 1, 1 and 2, and 2 and 3. Liver stiffness cutoff values were 1.69 m/s for predicting stage 3 or greater (area under the receiver operating characteristic curve [AUROC] = 0.99) and 1.88 m/s for stage 4 (AUROC = 0.97). The spleen stiffness cutoff value was 2.72 m/s for stage 4 (AUROC = 0.96). Liver stiffness was not correlated with the varix grade, whereas a significant linear correlation (Spearman $\rho = 0.65$; $P < .001$) between spleen stiffness and the varix grade was found. The optimal spleen stiffness cutoff value for predicting varices was 3.16 m/s (AUROC = 0.83).

Conclusions—Liver and spleen stiffness values measured by ARFI elastography are reliable predictors of liver fibrosis. Spleen stiffness measured by ARFI can be used as a noninvasive method for determining the presence and severity of esophageal varices; however, evidence to support a similar role for liver stiffness is lacking.

Key Words—acoustic radiation force impulse; esophageal varices; liver fibrosis; liver stiffness; spleen stiffness

Hepatitis B, which is caused by the hepatitis B virus (HBV), is a potential life-threatening liver infection and the most serious type of viral hepatitis. As the World Health Organization reported,¹ approximately 2 billion people have been infected with HBV worldwide, and more than 350 million people have chronic hepatitis B. In China, the most common viral hepatitis is type B. The final evolutionary stage of chronic hepatitis B is liver cirrhosis. Portal hypertension is a major cause of esophageal varices, which have been reported to occur in up to 90% of patients with cirrhosis.²

The annual incidence of variceal bleeding is almost 5% to 15%, and the mortality rate may reach up to 20% in 6 weeks.³

The management and prognosis of chronic hepatitis B depend on the fibrosis stage. To date, liver biopsy, an invasive technique, is still considered the reference standard. However, its clinical application is limited because of its invasive nature, potential severe complications, sampling errors, and inter-observer and intraobserver diagnostic discrepancies.⁴⁻⁶

In cirrhotic patients, screening for esophageal varices is highly recommended and extremely important because it is closely linked to the scheme of nonselective beta-blocker therapy or endoscopic prophylaxis to prevent variceal bleeding.⁷ The present screening method is endoscopy, which is performed every 2 to 3 years in patients without esophageal varices, every 1 to 2 years in those with mild varices, and annually in those with decompensated cirrhosis. However, this method is invasive, expensive, and not easily accepted by patients.

For the above-mentioned reasons, some noninvasive methods have been proposed to serve as markers for evaluating of the degree of liver fibrosis and that of esophageal varices, including serum markers,⁸⁻¹⁰ transient elastography,⁹⁻¹² magnetic resonance elastography,¹³⁻¹⁵ and acoustic radiation force impulse (ARFI) elastography.^{10,16,17}

Acoustic radiation force impulse imaging^{10,16,18} is a novel technology based on conventional B-mode sonography. An acoustic push pulse excites the tissue and produces shear waves that spread away from the tissue. The propagation of the shear waves can be measured, and their speed depends on the elasticity of the tissue. Therefore, ARFI provides numeric measurements of tissue stiffness as the shear wave velocity, expressed as meters per second. Publications have shown that liver stiffness values correlated well with liver fibrosis staging determined by liver biopsy.^{18,19} Spleen stiffness measured by ARFI elastography in patients with chronic liver disease has also been previously reported.^{16,17} However, those studies focused mostly on patients infected with the hepatitis C virus (HCV).

The aims of this study were to evaluate the accuracy of liver and spleen stiffness measured by ARFI elastography for noninvasive assessment of liver fibrosis in patients with chronic hepatitis B and to investigate whether liver and spleen stiffness values are suitable predictors of the presence and severity of esophageal varices.

Materials and Methods

Study Population

Two hundred sixty-four participants (158 men and 106 women; mean age \pm SD, 39.3 ± 13.7 years; range, 19–74

years) were enrolled in our study between June and November 2011. Of these participants, 60 were healthy control participants (considered to have no fibrosis: stage 0; mean age, 30.0 ± 9.0 years; range, 20–54 years), and 204 had chronic hepatitis B. Informed consent was obtained from all participants, and the local Ethical Committee approved our study.

The control participants were healthy volunteers without any kind of liver disease or patients from other departments of our hospital who had normal liver serologic test results and normal liver sonographic findings. Patients with an enlarged spleen on sonography, diseases affecting the liver, or regular alcohol intake were excluded.

Among the 204 patients, 66 (mean age, 36.5 ± 10.9 years; range, 19–63 years) had undergone liver biopsy, and 138 (mean age, 46.1 ± 10.9 years, range 26–74 years) had been a previous diagnosis of cirrhosis (stage 4) via imaging or biochemical analysis or on the basis of their medical histories. Patients were excluded if they had ascites, carcinoma, a terminal illness, or autoimmune disease, were infected with other liver viruses or the human immunodeficiency virus, or were pregnant.

All patients underwent ARFI elastography in both the liver and spleen, and median values from 10 successful measurements per participant were calculated and expressed as meters per second. Cirrhotic patients underwent upper endoscopy for assessment of esophageal varices. Serologic test results were recorded.

Liver and Spleen Stiffness Measurements

Liver and spleen stiffness measurements were performed with an Acuson S2000 ultrasound system equipped with virtual touch tissue quantification software (Siemens Medical Solutions, Mountain View, CA). A 4C-1 curved linear array transducer was also used. Liver stiffness was measured while the patients were lying in the left lateral decubitus position and with their right arm in maximum abduction, whereas spleen stiffness was measured while the patients were lying in the right lateral decubitus position and with their left arm in maximum abduction. The size of the region of interest was fixed at 10×5 mm. The region of interest was at the parenchyma of the liver and spleen and free of “visible” vessels. Specifically, the location of the region of interest in the liver was the right lobe between the seventh and ninth intercostal spaces, between the midclavian and midaxillary lines, 2 to 3 cm below the liver capsule; that in the spleen was in the middle portion, 1 to 2 cm below the splenic capsule. These measurements were made through an intercostal space. During the procedure, the patients were asked to stop breathing for a moment at

the end of expiration. Two or 3 measurements were made during each breath-holding period, and 4, 5, or more periods were needed to measure in one area. All of the measurements were performed by one experienced sonologist (Figures 1 and 2).

The interval between these measurements and the liver biopsy that 66 of the participants underwent ranged from 1 to 3 days (mean, 2.00 ± 0.84 days). Acoustic radiation force impulse imaging was not immediately performed after biopsy because the patients would not have been able to tolerate the pain caused by the biopsy and scanning immediately after the procedure and because they needed to rest in the dorsal decubitus position with a monitor for the first 6 hours.

The right lobe was chosen because ARFI measurements of the right lobe are reportedly potentially superior to those of the left lobe for diagnosis of liver fibrosis.²⁰ A point 2 to 3 cm under the liver capsule was chosen because a study of 3 points under the liver capsule (0–1, 1–2, and 2–3 cm) found that the most reliable liver elasticity values are obtained when ARFI measurements are made 2 to 3 cm under the liver capsule.¹⁹

Liver Histologic Analysis

Sonographically guided liver biopsy was performed in 66 patients with a Magnum automatic biopsy gun (C. R. Bard, Inc, Murray Hill, NJ) and 16-gauge needles. All of the specimens were at least 1.5 cm long and were analyzed by a single experienced pathologist. Fibrosis was staged on a scale of 0 to 4²⁰ as follows: stage 0, no fibrosis; stage 1, fibrous portal expansion and limited perisinusoidal or lobular fibrosis; stage 2, periportal fibrosis and few fibrous

septa but intact architecture; stage 3, numerous fibrous septa with architectural distortion but no obvious cirrhosis; and stage 4, cirrhosis.

Upper Endoscopy

Seventy-three patients with cirrhosis were willing to undergo endoscopy, and they were examined under intravenous anesthesia. Esophageal varices were evaluated using a GIF-XQ-2400 endoscope (Olympus Optical Co, Ltd, Tokyo, Japan). Varices were graded as follows³: grade 1, mild, characterized as straight varices without a red sign; grade 2, moderate, characterized as straight varices with a red sign or eminence of tortuous varices without a red sign; and grade 3, severe, characterized as eminence of tortuous varices with a red sign or coil-shaped varices.

Serum Biochemical Markers

Venous blood samples were taken from all participants after an overnight fast (8–12 hours) on the same day as the ARFI measurements. The samples were tested in the same laboratory to determine aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels.

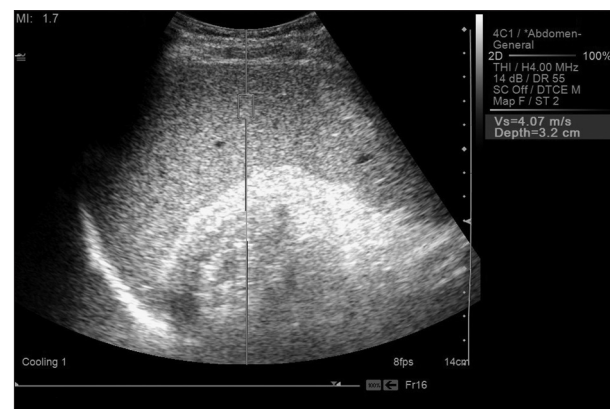
Statistical Analysis

Statistical analysis was performed with SPSS version 19.0 software (SSPS Inc, Chicago, IL); $\alpha = .05$ was considered the significance level. Quantitative liver stiffness variables were expressed as mean \pm SD. Box plots were used to illustrate the distributions of the different parameters. The Levene test was used to investigate the homogeneity of variance. Analysis of variance and the least significant difference *t* test were used to compare the differences in mean liver

Figure 1. Acoustic radiation force impulse elastographic measurement in the right hepatic lobe of a 45-year-old man with stage 4 fibrosis. The region of interest was located 2.1 cm below the liver capsule and 3.2 cm below the skin. The shear wave velocity was 2.03 m/s.



Figure 2. Acoustic radiation force impulse elastographic measurement in the middle portion of the spleen of a 48-year-old man with stage 4 fibrosis. The region of interest was located 1.7 cm below the splenic capsule and 3.2 cm below the skin. The shear wave velocity was 4.07 m/s.



stiffness values in the cirrhotic patients according to the varix grade. The Kruskal-Wallis test and Mann-Whitney *U* test with Bonferroni adjustment (with an adjusted significance level of $\alpha = .005$) were used to compare the differences in mean liver stiffness values according to fibrosis stage. We used the independent *t* test to compare the liver stiffness values between cirrhotic patients with and without varices, as well as that between cirrhotic patients with normal and elevated ALT and AST levels. Quantitative spleen stiffness variables were analyzed in the same manner.

The diagnostic performance was evaluated by sensitivity, specificity, and receiver operating characteristic curves. Optimal cut off values were chosen to maximize the sum of sensitivity and specificity. Correlations between different parameters were analyzed by Spearman correlation coefficients.

Results

Study Population Characteristics

The clinical and biochemical characteristics of the 264 participants are summarized in Table 1. Of the 66 patients who underwent liver biopsy, 17 had stage 1 fibrosis; 23 had stage 2; 23 had stage 3; and 3 had stage 4. The 60 healthy control participants were considered stage 0. The 138 cirrhotic patients were considered stage 4.

Liver Stiffness Measurements for Noninvasive Assessment of Liver Fibrosis

Liver stiffness was measured in all 264 participants. A significant linear correlation (Spearman $\rho = 0.87$; $P < .001$) was found between liver stiffness and the fibrosis stage. On the whole, there was a significant increase in liver stiffness in parallel with the progression of liver fibrosis. However, differences between stages 0 and 1 ($P = .018$) and between stages 1 and 2 ($P = .011$) were not detected. Statistical differences were found in the following groups: stage 0 versus 2 ($P < .001$), stage 0 versus 3 ($P < .001$), stage 0 versus 4 ($P < .001$), stage 1 versus 3 ($P < .001$), stage 1 versus 4

($P < .001$), stage 2 versus 3 ($P = .001$), stage 2 versus 4 ($P < .001$), and stage 3 versus 4 ($P < .001$). The liver stiffness value for each fibrosis stage is shown in Table 2, and a box plot is shown in Figure 3.

Area under the receiver operating characteristic curve (AUROC) analysis showed that liver stiffness measured by ARFI had high predictive values for stage 3 or greater (AUROC = 0.99; Figure 4) and stage 4 (AUROC = 0.97; Figure 5). The optimal cutoff values were 1.69 m/s for stage 3 or greater (sensitivity, 93.9%; specificity, 95.0%) and 1.88 m/s for stage 4 (sensitivity, 95.7%; specificity, 91.8%).

Figure 3. Variations in the shear wave velocity of the liver depending on the fibrosis stage (S). The middle line in each box represents the median. The top and bottom parts represent the first and third quartiles. The error bars show the minimum and maximum values (range). Statistical differences were analyzed by the Kruskal-Wallis test with Bonferroni adjustment. The shear wave velocity of liver increases as the fibrosis progresses.

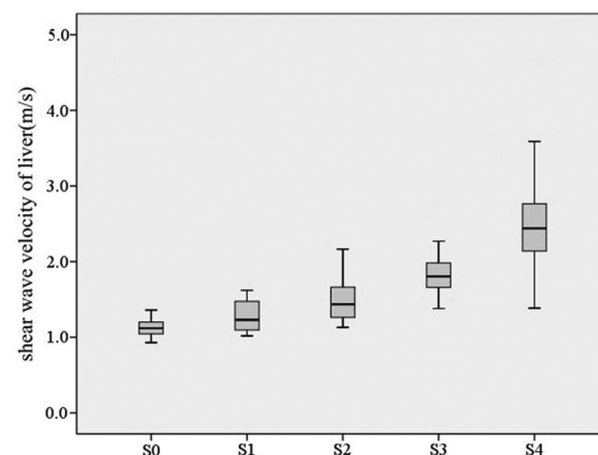


Figure 4. Receiver operating characteristic curve of liver stiffness measured by acoustic radiation force impulse elastography for predicting stage 3 or greater fibrosis (stages 0–2 versus stages 3 and 4).

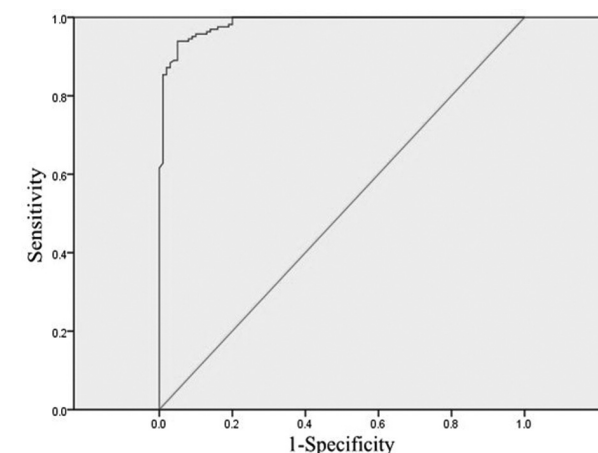


Table 1. Clinical and Biochemical Characteristics of the Participants

Characteristic	Value
Male, n (%)	158 (59.85)
Age, y	39.3 ± 13.7
BMI, kg/m ²	21.90 ± 2.87
AST, U/L	84.14 ± 99.08
ALT, U/L	99.25 ± 120.13

Values are mean ± SD where applicable. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and BMI, body mass index.

Spleen Stiffness Measurements for Noninvasive Assessment of Liver Fibrosis

Spleen stiffness was measured in all 264 participants as well. A significant correlation was observed (Spearman $\rho = 0.76$; $P < .001$) between spleen stiffness and the fibrosis stage. Statistically significant differences between stage 4 and the other subgroups were noted as follows: stage 0 versus 4 ($P < .001$), stage 1 versus 4 ($P < .001$), stage 2 versus 4 ($P < .001$), and stage 3 versus 4 ($P < .001$). In contrast, differences were not found between any two subgroups from stages 0 to 3: stage 0 versus 1 ($P = .374$), stage 0 versus 2

($P = .021$), stage 0 versus 3 ($P = .006$), stage 1 versus 2 ($P = .293$), stage 1 versus 3 ($P = .072$), and stage 2 versus 3 ($P = .620$). The spleen stiffness value for each fibrosis stage is shown in Table 2, and a box plot is shown in Figure 6.

Area under the receiver operating characteristic curve analysis showed that spleen stiffness was highly predictive of the presence of cirrhosis (stage 4; AUROC = 0.96; Figure 7). The optimal cutoff value was 2.72 m/s (sensitivity, 88.4%; specificity, 93.2%).

Combined Analysis of Liver and Spleen Stiffness for Predicting Cirrhosis

The liver and spleen stiffness values were combined for predicting cirrhosis using the cutoff values calculated in this study: the sensitivity and specificity were 99.3% and 92.7%, respectively, when one of the methods yielded positive results and 88.7% and 100% when both methods yielded positive results.

Figure 5. Receiver operating characteristic curve of liver stiffness measured by acoustic radiation force impulse elastography for predicting stage 4 fibrosis (stages 0–3 versus stage 4).

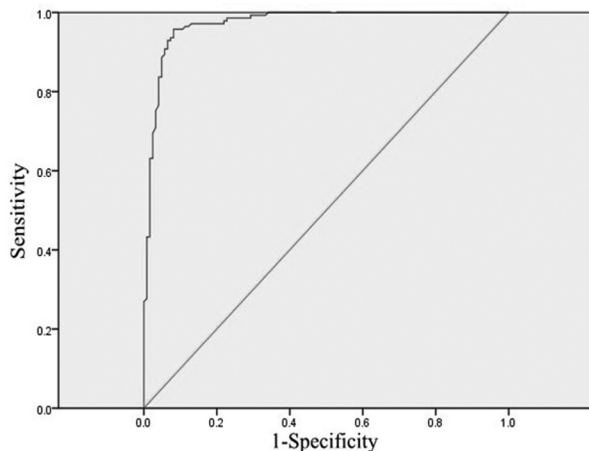


Figure 6. Variations in the shear wave velocity of the spleen depending on the fibrosis stage (S). Statistical differences were analyzed by the Kruskal-Wallis test with Bonferroni adjustment. The shear wave velocity of the spleen changes minimally in stages 0 to 3 but is significantly higher in stage 4 than in any other subgroup.

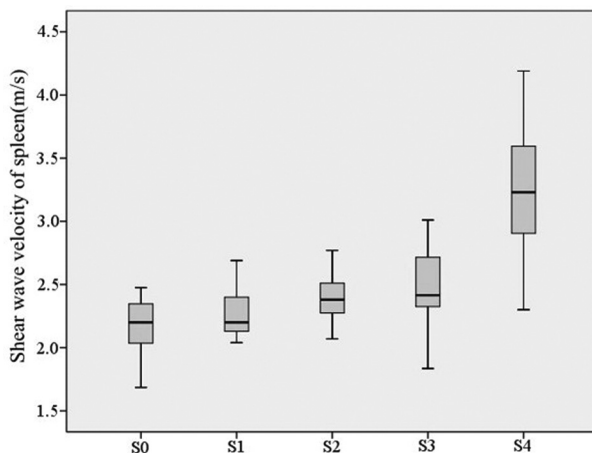
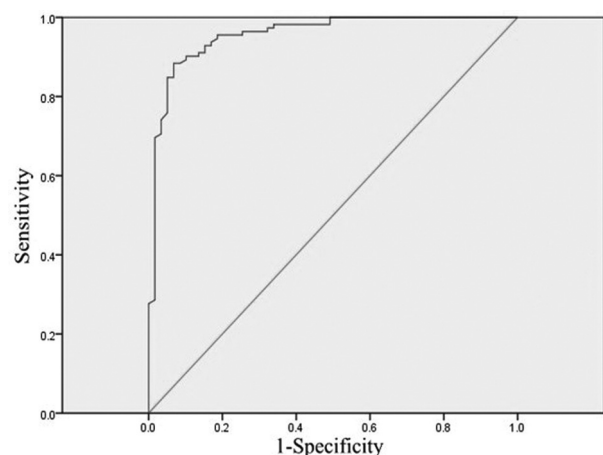


Table 2. Liver and Spleen Stiffness According to Fibrosis Stage

Stage	Cases, n	Liver Stiffness, m/s	Spleen Stiffness, m/s
0	60	1.13 ± 0.12	2.17 ± 0.22
1	17	1.27 ± 0.21	2.27 ± 0.21
2	23	1.50 ± 0.28	2.38 ± 0.31
3	23	1.85 ± 0.34	2.54 ± 0.46
4	141	2.50 ± 0.50	3.24 ± 0.44

Values are mean ± SD.

Figure 7. Receiver operating characteristic curve of spleen stiffness measured by acoustic radiation force impulse elastography for predicting stage 4 fibrosis (stages 0–3 versus stage 4).



Liver and Spleen Stiffness Measurements for Predicting Esophageal Varices

Of the 141 cirrhotic patients, 73 consented to undergo endoscopy. Varices were ruled out in 25 patients, and they were categorized as grade 0. The numbers of patients with varices are shown in Table 3. There was no correlation between liver stiffness and the varix grade. Statistical differences were not observed between the mean liver stiffness values in patients with and without varices ($P = .107$) or between grades 1 and 2 ($P = .985$), grades 1 and 3 ($P = .997$), and grades 2 and 3 ($P = .980$). The mean liver stiffness value for each varix grade is shown in Table 3.

However, a significant direct linear correlation (Spearman $\rho = 0.65$; $P < .001$) was found between spleen stiffness and the varix grade. Statistical differences were found between the groups with and without varices ($P < .001$), between grades 1 and 3 ($P = .001$), and between grades 2 and 3 ($P = .041$), but no difference was found between grades 1 and 2 ($P = .093$). The mean spleen stiffness value for each varix grade is shown in Table 3.

Table 3. Liver and Spleen Stiffness According to the Presence and Degree of Esophageal Varices

Varices	Cases, n	Liver Stiffness, m/s	Spleen Stiffness, m/s
Absent	25 (34.25)	2.46 ± 0.42	2.94 ± 0.35
Present (total)	48 (65.75)	2.65 ± 0.49	3.44 ± 0.38
Grade 1	11 (15.07)	2.65 ± 0.40	3.15 ± 0.35
Grade 2	16 (21.91)	2.65 ± 0.53	3.38 ± 0.29
Grade 3	21 (28.77)	2.65 ± 0.52	3.63 ± 0.37

Values are mean \pm SD.

The AUROCs of spleen stiffness for predicting the presence of esophageal varices (Figure 8) and grade 3 (Figure 9) were 0.83 and 0.83, respectively. The optimal cutoff values were 3.16 m/s for predicting the presence of varices (sensitivity, 84.1%; specificity, 81.0%) and 3.39 m/s for grade 3 (sensitivity, 78.9%; specificity, 78.3%).

Association Between Liver and Spleen Stiffness and Serum Biochemical Markers

To evaluate the influence of ALT and AST levels, we divided the cirrhotic patients into two groups: the first group comprised patients with normal ALT and AST levels, and the second group comprised patients with elevated ALT and AST levels. The mean liver and spleen stiffness values for each group are shown in Table 4.

We found significant difference between the liver stiffness values of the two groups. Table 4 shows that the patients with elevated ALT and AST levels had higher liver stiffness values. Conversely, the difference was not significant between the spleen stiffness values for these groups.

Discussion

The stage of liver fibrosis can be quantified by ARFI elastography. Recent studies have reported that measurement of liver stiffness using ARFI elastography is a novel, accurate, and reliable noninvasive method for assessment of liver fibrosis in patients with chronic liver disease.^{21,22} As liver fibrosis progresses, hemodynamic and pathologic changes can be found in the spleen, especially in late stages of fibrosis. One study²³ found that the size of the spleen increased as

Figure 8. Receiver operating characteristic curve of spleen stiffness measured by acoustic radiation force impulse elastography for predicting the presence of esophageal varices.

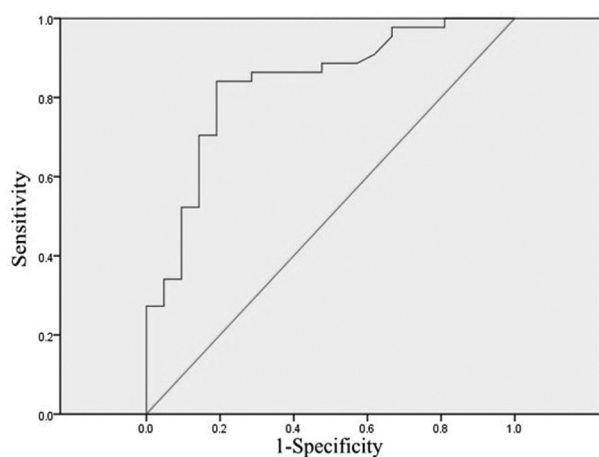
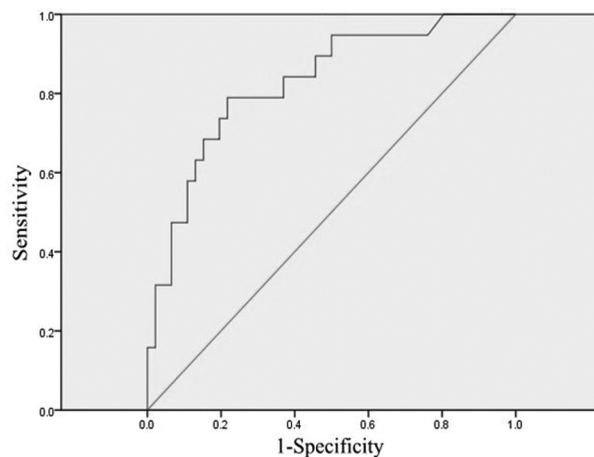


Figure 9. Receiver operating characteristic curve of spleen stiffness measured by acoustic radiation force impulse elastography for predicting the presence of severe esophageal varices (grade 3).



liver fibrosis progressed and was more apparent in late stages. The density of the spleen changes in patients with an enlarged spleen because of tissue hyperplasia, fibrosis, and portal and splenic congestion.¹² Such changes in the spleen are mechanical properties that can be quantified by ARFI elastography. Therefore, we tried to show that liver and spleen stiffness values are useful predictors for evaluation of liver fibrosis in chronic liver disease and to evaluate their performance in predicting the presence of esophageal varices in cirrhotic patients. Moreover, to our knowledge, a study assessing liver fibrosis and esophageal varices specifically in HBV-infected patients has not been reported previously.

Our data clearly showed that liver stiffness correlated well with fibrosis. The stiffness increased with the fibrosis stage. However, overlaps were detected between stages 0 and 1 and stages 1 and 2. Similarly, a study of 112 patients with chronic hepatitis C found overlaps between the consecutive stages F1 and F2 and stages F2 and F3 (METAVIR scores).¹⁸ Another study of 103 patients with chronic hepatitis of different etiologies observed overlaps between stages F0 and F1 and stages F3 and F4 (METAVIR scores).²⁴ These findings suggest that overlaps between consecutive stages occur regardless of etiology. For the healthy volunteers (stage 0), the mean liver stiffness value in our study was 1.13 ± 0.12 m/s which is comparable to those published so far: 1.13 ± 0.23 m/s in healthy volunteers and 1.16 ± 0.17 m/s in stage F0 patients (METAVIR score)¹⁰ and 1.15 ± 0.21 m/s in another group of healthy volunteers.²⁵ For cirrhotic patients, the mean liver stiffness value was 2.50 ± 0.50 m/s, comparable to 2.38 ± 0.74 m/s in 81 patients with HCV or HBV infection¹⁰ and 2.552 ± 0.7782 m/s in patients with HCV infection.¹⁸

We discovered high predictive values of liver stiffness for stage 3 or greater and stage 4, which were similar to the findings in a study of patients with chronic hepatitis C¹⁸ and another study of patients with different etiologies.²¹ The cutoff value for stage 3 or greater was 1.69 m/s, which was the same as the value in a study by Toshima et al²² including 79 patients with different etiologies and similar to the value in a study by Lupsor et al¹⁸ including 112 patients

with chronic hepatitis C (1.61 m/s). The cutoff value for stage 4 was 1.88 m/s, which was slightly higher than the value in the study by Toshima et al²² (1.79 m/s) and lower than the value in the study by Lupsor et al¹⁸ (2.0 m/s).

This study compared the mean spleen stiffness values measured by ARFI elastography among fibrosis stages 0 to 4. There was a correlation between spleen stiffness and fibrosis (Spearman $\rho = 0.76$; $P < .001$). The spleen stiffness values for stages 0 to 3 did not statistically differ, whereas stage 4 had a significantly higher mean value than any other stage. In our study, the mean spleen stiffness value in the healthy volunteers (stage 0) was 2.17 ± 0.24 m/s, which was slightly higher than the previously reported value of 2.04 ± 0.28 m/s in 15 healthy volunteers¹⁷ and lower than the previously reported value of 2.44 m/s in 35 healthy volunteers.²⁶ The mean spleen stiffness value in cirrhotic patients (stage 4) was 3.24 ± 0.44 m/s, which was slightly higher than the value of 3.10 ± 0.55 m/s in a study by Bota et al.¹⁷

To date, only 2 reports have analyzed spleen stiffness for predicting cirrhosis. One¹⁷ showed a cutoff value of 2.55 m/s for predicting cirrhosis with a good AUROC (0.91), and another¹⁶ showed a cutoff value of 2.73 m/s (AUROC = 0.82). Our results showed a high predictive value for the presence of cirrhosis (AUROC = 0.96), with the cutoff (2.72 m/s) being higher than that in the first study and similar to that in the second.

In this study, a combined analysis of liver and spleen stiffness measured by ARFI for predicting the presence of cirrhosis revealed that the sensitivity and specificity were higher when one of the methods in the combined analysis yielded positive results than when only one method was used, and the specificity was significantly elevated when both methods yielded positive results.

In cirrhotic patients, a severe consequence is portal hypertension, which is a contributing factor to the formation of esophageal varices and a direct cause of variceal hemorrhage. Publications have reported that liver stiffness measured using 1-dimensional transient elastography (Fibroscan) showed a statistically significant association with the hepatic venous pressure gradient.^{27–29} Some studies found that liver stiffness measured by 1-dimensional transient elastography was correlated with the esophageal varix grade,³⁰ whereas others showed that liver stiffness correlated with the presence of varices but showed a weak correlation with the varix size³¹ or none at all.²⁷ Acoustic radiation force impulse elastography is a 2-dimensional elastographic technique. To our knowledge, there have been no reports about the correlation between liver stiffness measured by ARFI and the hepatic venous pressure gradient or between

Table 4. Liver and Spleen Stiffness at Different Alanine Aminotransferase and Aspartate Aminotransferase Levels in Cirrhotic Patients

Parameter	Normal ALT and AST	Elevated ALT and AST	P
Liver stiffness, m/s	2.32 ± 0.45	2.61 ± 0.51	.001
Spleen stiffness, m/s	3.19 ± 0.47	3.27 ± 0.46	.368

Values are mean \pm SD. ALT indicates alanine aminotransferase; and AST, aspartate aminotransferase.

liver stiffness measured by ARFI and the presence of esophageal varices. Only 1 study¹⁷ reported a correlation between spleen stiffness measured by ARFI and esophageal varices, in which the authors observed no significant differences in the mean spleen stiffness values between patients with and without varices or between those with different varix grades.

Our data on this issue were confusing. We found a correlation between spleen stiffness and the varix stage, and there was a significant difference between patients with and without varices. We determined a cutoff value of 3.16 m/s for predicting the presence of varices (AUROC = 0.83). We also found a significant difference between grades 2 and 3, but unfortunately, we were not able to distinguish the mean spleen stiffness values between grades 1 and 2. These results may be explained by 3 possible reasons. First, endoscopy was not performed by the same physicians, and the assessment of the varix grade was subjective. Second, not all patients consented to undergo endoscopy and ARFI elastography on the same day; the interval between spleen stiffness measurements and endoscopy ranged from 0 to 30 days, whereas the longest interval in the report by Bota et al¹⁷ reached up to 6 months. Third, the distribution of patients according to varix grades was unequal.

Our article clearly suggests that there was no correlation between liver stiffness measured by ARFI and the esophageal varix grade, and no significant difference was found among the varix grades. The different results between liver and spleen stiffness for assessment of varices may be explained by 2 possible reasons. First, we discovered that the cirrhotic patients with elevated ALT and AST levels had higher liver stiffness values than those with normal ALT and AST levels, whereas the difference was not significant for the spleen stiffness values between the patients with normal ALT and AST levels and those with elevated ALT and AST levels. Some publications have reported a correlation between liver stiffness values measured by ARFI and necroinflammation.^{18,21,32} These reports indicate that elevated ALT and AST levels may affect liver but not spleen stiffness values, which may be the major factor accounting for the above-mentioned findings. Second, the unequal distribution of patients according to varix grades may have led to different numbers in each subgroup.

In conclusion, liver and spleen stiffness values measured by ARFI elastography are reliable predictors of liver fibrosis, especially for patients who are at high risk or not willing to undergo liver biopsy. Spleen stiffness can be used as a noninvasive means for predicting

the presence and grade of esophageal varices and can also be valuable for patients who refuse to undergo endoscopy. Moreover, further studies on liver and spleen stiffness for evaluating liver fibrosis and esophageal varices in a larger population have been planned.

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