Nondiseased Liver Stiffness Measured by Shear Wave Elastography

A Pilot Study

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Objectives—The purpose of this study was to investigate the value of liver stiffness in patients without liver disease using shear wave elastography and to determine the liver stiffness threshold value for identifying patients with chronic liver diseases.

Methods—A total of 150 patients who underwent liver sonography coupled with shear wave elastography were enrolled. On the basis of clinical and pathologic criteria, they were assigned to 1 of 2 groups: nondiseased liver (n = 97) and noncirrhotic chronic liver disease (n = 53). Liver stiffness was measured in the right liver, and the median value of 10 measurements was calculated. Both mean and median values in the nondiseased liver group were compared with those in the noncirrhotic chronic liver disease group. To validate this comparison, liver stiffness of the patients who underwent liver biopsy revealing either no fibrosis (fibrosis score F0; n = 5) or substantial fibrosis (F2; n = 14) was also investigated and compared. To determine the optimal threshold value for determining chronic liver disease, a receiver operating characteristic curve analysis was performed.

Results—The mean liver stiffness value in the nondiseased liver group was 5.4 kPa. In the noncirrhotic chronic liver disease group, the mean value was 8.1 kPa. Differences between the nondiseased liver and both noncirrhotic chronic liver disease groups were statistically significant ($P < .001$). The optimal liver stiffness threshold value for discriminating nondiseased liver from noncirrhotic chronic liver disease was 6.9 kPa. The sensitivity using this threshold was 94%. In the biopsy-proven patients, the mean liver stiffness values were 6.0 kPa in the F0 group and 9.9 kPa in the F2 group.

Conclusions—The range of liver stiffness in patients with nondiseased liver and the optimal threshold value for discriminating these patients from those with chronic liver disease were identified.

Key Words—chronic liver disease; gastrointestinal ultrasound; liver stiffness; nondiseased liver; shear wave elastography

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Abbreviations

CI, confidence interval; ROI, region of interest

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Noninvasive diagnosis of hepatic fibrosis has been a challenge for many hepatologists. Although liver biopsy is the standard method for diagnosing hepatic fibrosis, it is invasive, has been associated with mortality,[1] and represents only a limited area of liver.[2] For these reasons, many studies have been performed to find other markers for diagnosing hepatic fibrosis.[3–5] Grayscale sonography and Doppler sonography are good candidates for noninvasive methods, but there are several limitations such as low interobserver and intraobserver agreement and variability according to the physiologic and pathologic status of the patient.[6–9]

Measurement of liver stiffness using transient elastography, which measures the propagation velocity of the shear wave developed after a mechanical push using a vibrator, was introduced in 2003 and has been performed to evaluate hepatic fibrosis noninvasively in patients with chronic liver disease.[10] Many studies have indicated that transient elastography is a reliable method for liver stiffness measurement,[11–13] and there have been efforts to overcome several limitations that result from the mechanical vibration, such as difficulties in obtaining accurate measurements in patients with hepatic steatosis and a high body mass index.[14,15]

Recently, several new techniques for liver stiffness measurement using the acoustic radiation force impulse[16,17] instead of the mechanical push in transient elastography have been introduced. Shear wave elastography, developed by Supersonic Imagine (Aix-en-Provence, France), is one of these techniques. There are some reports of liver stiffness measurements using this new technique,[18,19] but their use in noninvasive diagnosis of liver fibrosis has not been widely performed compared to the use of transient elastography, and there are a lack of data regarding the normal range of liver stiffness for determining the presence of chronic liver disease.

The purpose of this study was to measure the liver stiffness value in patients without liver disease using shear wave elastography and to determine the optimal liver stiffness threshold value for identifying patients with chronic liver diseases in the absence of liver cirrhosis.

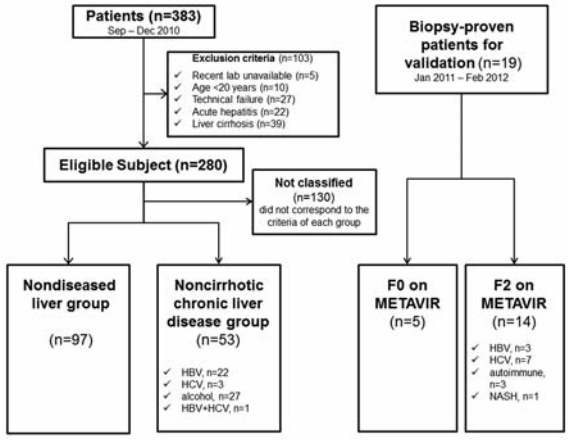
Materials and Methods

Patients

This retrospective study was approved by the Institutional Review Board of Hanyang University Guri Hospital. From September to December 2010, 383 patients underwent liver sonography coupled with shear wave elastography (Figure 1). The reasons for sonographic examination were as follows: viral hepatitis (n = 79); heavy alcoholism (n = 25); other liver abnormalities, including altered liver function test results (n = 59), focal hepatic lesions (n = 11), abdominal pain (n = 24), and suspected biliary disease (n = 18); routine scanning during renal examination in diabetic patients (n = 36); regular assessment for health promotion and postoperative evaluation after surgical procedures such as cholecystectomy (n = 126); and other unspecified reasons (n = 5). Before shear wave elastography was performed, informed consent for clinical application of the new diagnostic tool was obtained from all patients. A total of 367 patients (96%) underwent liver function tests using venous blood samples, with a mean interval between sonography and blood tests of 14 days (range, 0–328 days). We excluded 42 patients from the analysis, using the following exclusion criteria: recent laboratory data (within 3 months) unavailable (n = 5), patients younger than 20 years (n = 10), and failed measurement (n = 27) for the following reasons: inadequate breath holding (n = 8), obesity (n = 4), severe fatty liver (n = 3), small right liver due to liver cirrhosis (n = 9), and unknown reasons (n = 3). We also excluded patients with the probable diagnosis of acute hepatitis associated with hepatitis A or Epstein-Barr virus or other unknown causes (n = 22) and liver cirrhosis (n = 39) because one of the purposes of this study was to reveal the upper liver stiffness threshold in the population without evidence of liver diseases, thus allowing identification of patients with chronic liver diseases that do not progress to cirrhosis. Among the group with cirrhosis, 7 patients had a diagnosis by liver biopsy, whereas the diagnoses in the remaining patients were based on radiologic features such as surface nodularity and hypotrophy of the liver.

All eligible patients (n = 280) were assigned to either the nondiseased liver or noncirrhotic chronic liver disease group to compare the liver stiffness among the groups and to determine the upper cutoff limit for nondiseased liver stiffness. The inclusion criteria for the nondiseased liver group (n = 97) were as follows: (1) no serologic evidence of viral hepatitis B or C; (2) no history of heavy alcohol consumption (>80 g of alcohol per day); (3) serum transaminase and bilirubin levels within normal ranges (aspartate aminotransferase, 5–40 IU/L; alanine aminotransferase, 5–35 IU/L; serum bilirubin, 0.2–1.2

Figure 1. Patient enrollment process. HBV indicates hepatitis B virus; HCV, hepatitis C virus; and NASH, nonalcoholic steatohepatitis.



mg/dL); (4) normal or only slightly high echogenicity compared with that of the renal cortex on grayscale sonography; and (5) body mass index of 25 kg/m^2 or lower. The patients included in the noncirrhotic chronic liver disease group (n = 53) had a clinical diagnosis and were followed for chronic parenchymal liver diseases such as chronic hepatitis B (n = 22), chronic hepatitis C (n = 3), alcoholic liver disease (n = 27), and combined infection by hepatitis B and C viruses (n = 1). The rest (n = 130) were assigned to a "not classified group," which was neither the nondiseased liver nor noncirrhotic chronic liver disease group because they did not correspond to the criteria of those groups.

To validate the result from the comparison of liver stiffness between the nondiseased liver and noncirrhotic chronic liver disease groups, we retrospectively collected information on other patients who had a histologic diagnosis afterward. From January 2011 to February 2012, 51 consecutive patients underwent sonographically guided liver biopsy and shear wave elastography on the same day. Among them, there were 7 patients with no fibrosis (F0 on the METAVIR scoring system), 2 with minimal fibrosis (F1), 14 with periportal fibrosis (F2, substantial fibrosis), 9 with septal fibrosis (F3), and 19 with liver cirrhosis (F4). The F0 patients in whom the laboratory findings were within normal ranges were regarded as having nondiseased liver, so they corresponded to the nondiseased liver group (F0 group; n = 5). To compare the liver stiffness of the F0 group, the patients with substantial fibrosis were also regarded as another group, which corresponded to the noncirrhotic chronic liver disease group (F2 group; n = 14). Patients with a score of F3 were excluded from this comparison because their high liver stiffness values would increase the cutoff for discriminating them from the F0 group, and the specificity would be reduced.

Measurement of Liver Stiffness

A dedicated ultrasound machine (Aixplorer version 3; Supersonic Imagine) was used, equipped with a shear wave elastographic function. The mechanism of shear wave elastography is based on the 2-dimensional transient elastographic technique. Repeated acoustic impulses are sent through the region of interest (ROI) of the liver parenchyma to create mechanical displacement at the focus of the impulses, generating a shear wave that propagates into the ROI. The velocity of the shear wave is measured by ultrafast sonographic scanning (>4000 frames per second), and the liver stiffness in the ROI is calculated from the shear wave velocity.

The liver stiffness measurements were performed after conventional liver sonography by 3 abdominal radiologists with 17, 8, and 6 years of clinical experience in abdominal radiology and liver sonography, respectively, as part of their regular practice. They also had experience in liver stiffness measurement accumulated from more than 50 patients. Scanning parameters were as follows: shear wave elastographic option, standard mode; color map opacity, 50%; displayed elasticity range, 70 kPa; smoothing factor, 5; persistence, medium mode; displayed dynamic range, 62 dB; frame rate, 7 frames per second; mechanical index, 1.5; and soft tissue thermal index, 1.2 to 1.4. Liver stiffness was examined in the right liver through intercostal sonic windows.

The measurement protocol was as follows: The patients fasted for approximately 8 hours before scanning and lay on their backs with their right arms raised for the scan. A broadband convex transducer (1–6 MHz) was positioned on an intercostal space to enable a good view of the liver parenchyma, and a trapezoid color box was positioned on the parenchyma in a location greater than 2 cm from the hepatic capsule and away from large vessels. The patients were asked to hold their breath after exhalation for about 5 seconds, during which a cine loop was obtained, including a shear wave elastographic color map. The sequential frames were then recalled until the elasticity in the color box was judged to have reached a plateau. The round ROI (Q-box) was then positioned in the color box to measure the mean value and standard deviation of elasticity (Figure 2). The diameter of the ROI was as great as 20 mm; it could be changed to take into account the size of measureable parenchyma and the locations of the vessels and hepatic capsule. Referring to the standard method of liver stiffness measurement using transient elastography, the measurement process was repeated 10 times, and the median value was taken as the liver stiffness of the patient.

Statistics

We calculated the means, medians, and 95% confidence intervals (CI) of liver stiffness in the nondiseased liver group, constructed a histogram to investigate the distribution of liver stiffness in this group, and verified the normality of the distribution using the Kolmogorov-Smirnov test. To compare the liver stiffness values between sexes and in different age groups, we performed a Student *t* test and an analysis of variance with the Tukey test as a post hoc analysis. In addition, we calculated the means, medians, and 95% CIs of liver stiffness in the noncirrhotic chronic liver disease group and compared them with those of the nondiseased liver group using *t* tests. In the biopsy-proven

cases (F0 versus F2), we also analyzed the difference in liver stiffness in the same manner described above.

To determine threshold values for discriminating nondiseased liver from noncirrhotic chronic liver disease and F0 from F2 patients, we performed receiver operating characteristic curve analyses and calculated the sensitivity, specificity, accuracy, positive and negative predictive values, and positive and negative likelihood ratios when the optimal liver stiffness cutoff values were applied. Statistical analyses were performed with using SPSS version 17 software for Windows (SPSS Inc, Chicago, IL) and MedCalc version 9.6.3.0 software for Windows (MedCalc Software, Mariakerke, Belgium). $P < .05$ was considered significant.

Results

Clinical Characteristics of the Groups

The mean age ± SD of the nondiseased liver group was 48.7 ± 11.4 years, and the percentage of male patients was 36% (35 male and 62 female). The mean age and percentage of male patients in the noncirrhotic chronic liver disease group were 45.8 ± 9.6 years and 81% (43 male and 10 female), respectively. In the biopsy-proven cases (n = 19), mean ages of the F0 and F2 groups were 39.4 ± 7.7 and 43.0 ± 18.1 years, respectively.

The most common underlying disease in the noncirrhotic chronic liver disease group was alcoholic liver disease (27 of 53 [51%]). However, in the biopsy-proven cases, viral hepatitis was the most common disease (10 of 14 [71%]). Other clinical characteristics are summarized in Table 1.

Nondiseased Liver Stiffness

The mean liver stiffness value in the nondiseased liver group was 5.4 ± 1.2 kPa (range, 2.7–8.5 kPa). The median liver stiffness was 5.6 kPa, and the first and third quartiles were 4.5 and 6.4 kPa, respectively. The distribution of liver stiffness in the nondiseased liver group was shown to be normal ($P = .579$; Figure 3). There was no significant difference in the mean liver stiffness between sexes or among different age groups. Data for the nondiseased liver group are summarized in Table 2.

Threshold Liver Stiffness Value for Determining Diseased Liver

The mean liver stiffness value in the noncirrhotic chronic liver disease group was 8.1 ± 3.0 kPa (Table 3). In the biopsy-proven patients, the values for F0 and F2 patients were 6.0 ± 1.5 and 9.9 ± 5.4 kPa, respectively. The difference in liver stiffness in the noncirrhotic chronic liver disease and nondiseased liver groups was statistically sig-

Figure 2. Sonograms for measurement of liver stiffness using shear wave elastography. **A**, Nondiseased liver. **B**, Noncirrhotic chronic liver disease.

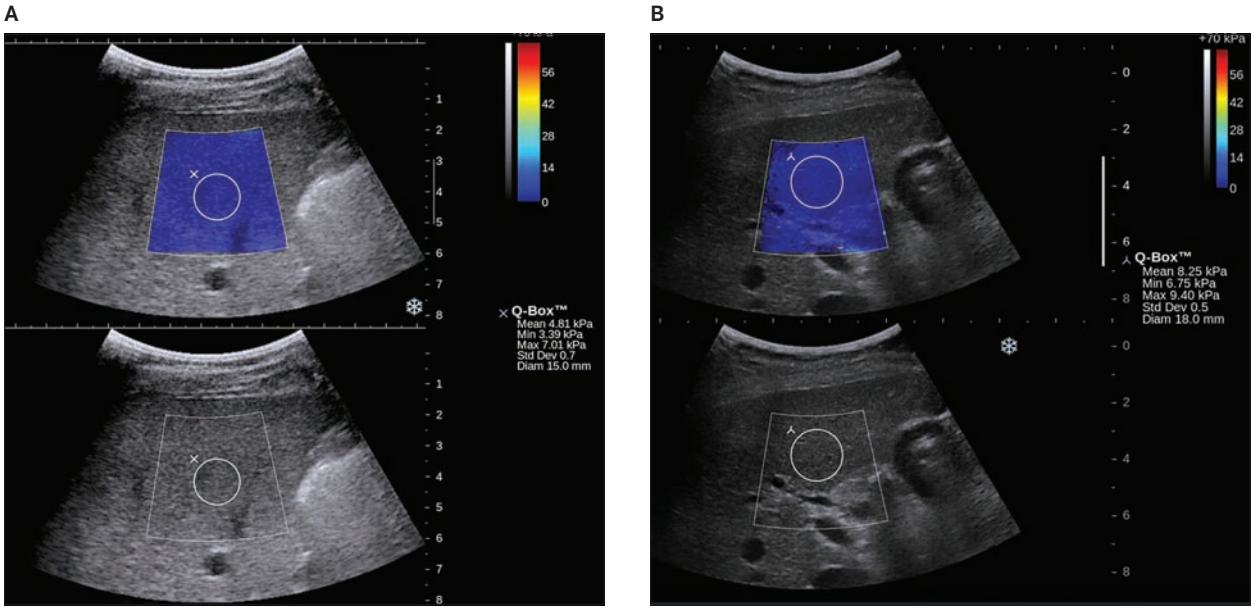


Table 1. Clinical Characteristics of the Patients

Characteristic	Nondiseased Liver (n = 97)	NCCLD (n = 53)	Biopsy-Proven F0 Liver (n = 5)	Biopsy-Proven F2 Liver (n = 14)
Age, y	48.7 ± 11.4	45.8 ± 9.6	39.4 ± 7.7	43.0 ± 18.1
Sex, n				
Male	35	43	2	8
Female	62	10	3	6
Underlying liver disease, n (%)	NA			
HBV		22 (42)	0	3 (21)
HCV		3 (6)	1 (20)	7 (50)
HBV + HBC		1 (2)	1 (20)	0
Alcoholic		27 (51)	0	0
Autoimmune		0	0	3 (21)
NAFLD		0	2 (40)	1 (7)
Unknown		0	1 (20)	0
Laboratory findings				
AST, IU/L	20.8 ± 6.2	50.8 ± 46.5	26.8 ± 16.5	56.0 ± 39.4
ALT, IU/L	19.5 ± 9.2	69.8 ± 137.4	19.4 ± 9.2	101.5 ± 127.9
Bilirubin, mg/dL	0.60 ± 0.35	0.83 ± 0.53	0.38 ± 0.25	0.58 ± 0.28
Platelets, ×1000	172 ± 110	194 ± 72	193 ± 65	203 ± 33
AST-to-platelet ratio	0.24 ± 0.09	0.88 ± 1.24	0.38 ± 0.23	0.72 ± 0.55

Data are presented as mean ± SD where applicable; ALT indicates alanine transaminase; AST, aspartate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; and NCCLD, noncirrhotic chronic liver disease.

nificant ($P < .001$), but the difference between the F0 and F2 patients was not ($P = .131$). The area under the receiver operating characteristic curve value for differentiating the nondiseased liver group from the noncirrhotic chronic liver disease group was 0.813, and that for differentiating the F0 group from the F2 group was 0.757. The optimal liver stiffness threshold was 6.9 kPa for differentiating nondiseased liver from noncirrhotic chronic liver disease. The sensitivity, specificity, and accuracy for differentiating nondiseased liver from noncirrhotic chronic liver disease were 94.1%, 62.3%, and 83.2%, respectively. Applying the same threshold to the biopsy-proven patients, the sensitivity and specificity were 60.0% and 64.3%, respectively, and the accuracy was 68.4% (Figure 4).

Figure 3. Histograms of the liver stiffness values in the nondiseased liver group (**A**) and noncirrhotic chronic liver disease group (**B**). The mean liver stiffness values of the nondiseased liver and noncirrhotic chronic liver disease groups were 5.4 ± 1.2 and 8.1 ± 3.0 kPa, respectively ($P = .467$ and .441, Kolmogorov-Smirnov test).

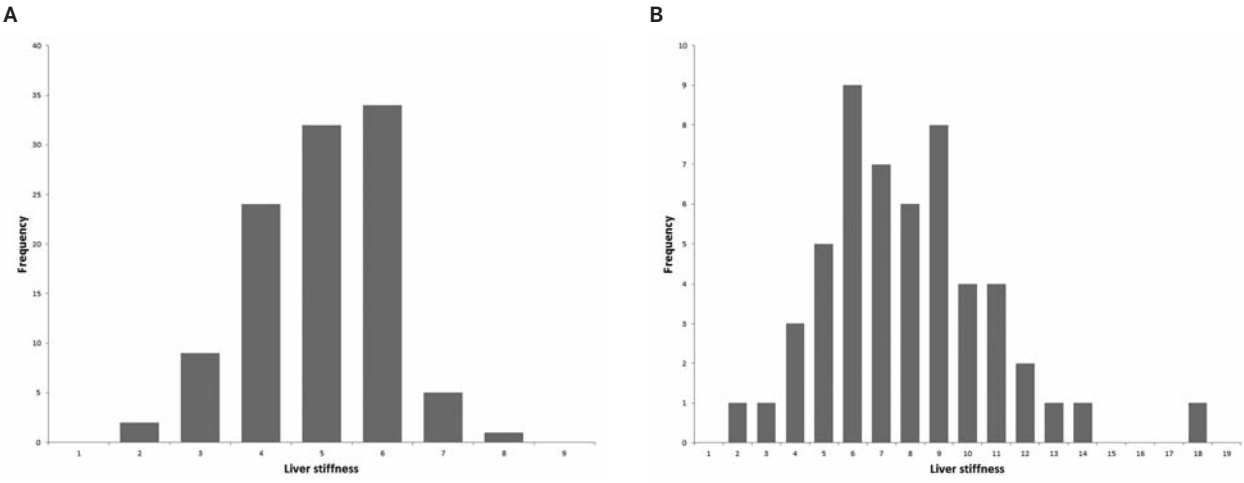


Table 2. Mean Liver Stiffness in the Nondiseased Liver Group

Characteristic	Liver Stiffness, kPa			*P*
	Mean ± SD	Median	95% CI	
Overall	5.4 ± 1.2	5.6	5.2–5.6	
Sex				
Male (n = 35)	5.5 ± 1.3	5.9	5.1–6.0	.490
Female (n = 67)	5.4 ± 1.1	5.5	5.1–5.6	
Age, y				
<40 (n = 19)	5.8 ± 1.1	6.0	5.3–6.3	
41–50 (n = 30)	5.4 ± 1.1	5.7	5.0–5.8	.509
51–60 (n = 37)	5.3 ± 1.2	5.3	4.9–5.7	
>60 (n = 16)	5.4 ± 1.5	5.0	4.6–6.1	

Discussion

The clinical application of shear wave elastography has already been evaluated in the diagnosis of breast cancer,[20–23] measurement of muscular stiffness,[24] and characterization of thyroid nodules.[25] As with these clinical applications, hepatic elastography is a promising technique for diagnosis of hepatic fibrosis. It could be useful in screening patients at high risk of parenchymal liver disease, such as hepatitis B virus carriers and heavy alcoholics, and also in choosing appropriate donors for liver transplantation.[26–28] In this study, shear wave elastography was used to measure liver stiffness in a nondiseased liver population, and the results provide a reference liver stiffness level for patients without liver diseases.

Shear wave elastography is a kind of shear wave-based ultrasound technique using an acoustic radiation force impulse. We propose that using shear wave elastography to evaluate chronic liver diseases has some advantages over previous methods such as transient elastography.[29] The first major advantage of shear wave elastography is that the information on liver stiffness can be obtained in addition to a conventional grayscale sonogram, and it allows precise location of an ROI for liver stiffness measurement in the hepatic parenchyma, avoiding large vessels, ascites, and other structures that could influence the result. The second advantage is that a larger ROI can be used, and liver stiffness can be displayed as a 2-dimensional color map with a look-up table. Such advantages of shear wave elastography may make liver stiffness measurement more reliable than transient elastography.

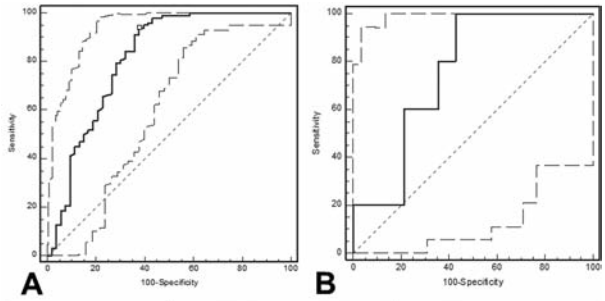
Although there is a lack of sufficient evidence for a firm conclusion, there are some previous clinical studies in which liver stiffness measurements by shear wave elastography and transient elastography were compared for the grading of liver fibrosis in patients with the hepatitis C virus[18,19]; both methods were found to be good indicators for fibrosis staging. The diagnostic performances of the two methods were compared using receiver operating characteristic curve analysis; shear wave elastography was especially superior to transient elastography when identifying substantial fibrosis (≥F2). Although the liver stiffness of healthy individuals was not measured in these studies, the median elasticity of patients with a score of F1 or lower was measured and found to range from 4.8 to 6.2 kPa. In

Table 3. Liver Stiffness Values in the Nondiseased Liver Versus Noncirrhotic Chronic Liver Disease and Biopsy-Proven F0 Versus F2 Liver Groups

Liver Stiffness, kPa	Nondiseased Liver (n = 98)	NCCLD (n = 53)	Biopsy-Proven F0 Liver (n = 5)	Biopsy-Proven F2 Liver (n = 14)
Mean	5.4	8.1	6.0	9.9
Median	5.6	7.9	6.0	9.3
Range	2.7–8.5	2.6–18.3	4.1–7.6	4.4–22.5
SD	1.2	3.0	1.5	5.4
95% CI	5.2–5.6	7.3–9.0	4.1–7.9	6.8–13.0
P[a]	<.001		.131	

NCCLD indicates noncirrhotic chronic liver disease.
[a]Student *t* test.

Figure 4. Receiver operating characteristic curves for differentiating nondiseased liver (NDL) from noncirrhotic chronic liver disease (NCCLD; **A**) and biopsy-proven F0 from F2 liver (**B**) by liver stiffness measured using shear wave elastography. LR indicates likelihood ratio; NPV, negative predictive value; and PPV, positive predictive value.



	NDL from NCCLD	Biopsy-proven: F0 from F2
Az	0.815	0.757
95% CI	0.743 to 0.873	0.509 to 0.920
P-value	.0001	.0288
Optimal cutoff (kPa)	≤6.86	
Sensitivity (%)	93.8	60.0
Specificity (%)	62.3	64.3
Accuracy (%)	82.7	68.4
PPV (%)	82.0	44.0
NPV (%)	84.6	90.0
LR+	2.49	1.68
LR-	0.10	0.62

another study by the same authors evaluating the reproducibility of liver stiffness measurement by shear wave elastography,[29] the mean liver stiffness was 4.87 to 5.39 kPa for 60 healthy volunteers, similar to the results of this study.

On the contrary, there have been more reports about the normal range of liver stiffness on transient elastography. Generally, normal liver stiffness has been reported to be in the range of 4 to 6 kPa. In a large multicenter prospective study performed in Europe,[30] the median value of liver stiffness in F0 patients (n = 113) was 5.6 kPa, and the interquartile range was 4.6 to 7.1 kPa. These results are comparable to our findings that the mean and median liver stiffness values were 5.4 and 5.6 kPa in the nondiseased liver group. However, in a study on potential liver donors,[26] the median liver stiffness values in F0 and F1 patients were 4.10 and 4.30 kPa, respectively. In another study with a similar design but investigating liver stiffness in living liver donors by transient elastography,[27] the mean liver stiffness in healthy participants was 4.6 kPa, and the values did not differ significantly between the sexes or among age groups. In our study, we also investigated differences in liver stiffness between the sexes and among age groups. Liver stiffness in the male group was higher than in the female group, but the difference was not statistically significant. With regard to differences among age groups, liver stiffness in the younger patients was unexpectedly slightly higher than in older patients but again, the difference was not significant. The observed difference could have been an artifact due to the small sample size for younger patients.

Liver stiffness was also measured in the patients with noncirrhotic chronic liver disease in this study, and the median liver stiffness was 8.1 kPa in that group, significantly higher than that in the nondiseased liver group. The threshold value (6.9 kPa) for discrimination of the nondiseased liver group from the noncirrhotic chronic liver disease group could be useful because its sensitivity was high (≈94%) with relatively high accuracy (≈83%); there were fewer false-negative results (noncirrhotic chronic liver disease classified as nondiseased liver) than in previous studies with higher threshold values. In a previous study using shear wave elastography to measure liver stiffness.[18] a liver stiffness threshold value for F2 or higher of 9.12 kPa was proposed. A recent meta-analysis of studies using transient elastography suggested this value to be 7.71 kPa.[31] On the analysis of the biopsy-proven cases in this study, the sensitivity and specificity were relatively low. We thought that this result was because the F0 patients possibly had diseased livers and also because of the small number of patients.

Measuring liver stiffness by shear wave elastography was technically straightforward, but there were problems obtaining accurate objective measurements. First, because the color map indicating liver stiffness changes each second during the examination, it is difficult to decide when to make the measurement. Second, if the color map is heterogeneous, it is also difficult to decide where to locate the ROI for measurement. Therefore, we used a standard protocol for liver stiffness measurement: the measurement was performed when the intensity in the color box reached a plateau, and the ROI was located in a homogeneous area of the color map. However, there was still some subjectivity leading to interobserver variability. In the future, we expect that a standard protocol for liver stiffness measurement by shear wave elastography will be developed by a consensus of researchers.

Our study had several limitations. First, most of the patients did not have liver biopsies, so the nondiseased liver group was defined solely on the basis of the clinical data and laboratory findings. However, since performing liver biopsies on healthy individuals is not ethically justified, we believe that this approach was the best practicable way to define the nondiseased liver group. Second, the sample size for the noncirrhotic chronic liver disease group was relatively small, and the number of cases confirmed histologically was also small. However, our study was only intended to be a preliminary one focused on measuring liver stiffness in nondiseased liver; subsequent studies are required to investigate differentiation of fibrosis stages and liver cirrhosis. Third, the reproducibility of measurements was not assessed because we did not investigate interobserver agreement. Fourth, there were unequal numbers of male and female patients in each group, possibly rendering the sex comparisons inaccurate. However, this factor might not be important, as the differences in liver stiffness between sexes were not statistically significant. Last, it was possible that a bias from the different patient selection periods between the noncirrhotic chronic liver disease and biopsy-proven noncirrhotic chronic liver disease groups—a selection bias that resulted from the recruitment of the patients in the biopsy-proven noncirrhotic chronic liver disease group after the nondiseased liver group and the main noncirrhotic chronic liver disease group—could have affected the results. However, the biopsy-proven noncirrhotic chronic liver disease group was only evaluated adjunctively to validate the primary results from a comparison between nondiseased liver and noncirrhotic chronic liver disease groups.

In conclusion, the mean liver stiffness value measured by shear wave elastography was 5.4 kPa in the nondiseased liver group. The liver stiffness threshold value for differentiation from patients with from chronic liver disease was

6.9 kPa, and the sensitivity was approximately 94% by shear wave elastographic measurement. As a method for measuring liver stiffness, shear wave elastography differs from the currently used technique of transient elastography in that it provides both grayscale sonograms and 2-dimensional elastographic data. For this reason, even though there is still a need to accumulate a large amount of clinical evidence, we expect shear wave elastography to play a role in the clinical diagnosis and management of liver diseases.

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