JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12647

ORIGINAL ARTICLE

Accurate reflection of hepatic venous pressure gradient by spleen stiffness measurement in patients with low controlled attenuation parameter values

Masashi Hirooka, Takaaki Tanaka, Yohei Koizumi, Atsushi Yukimoto, Takao Watanabe, Osamu Yoshida, Yoshio Tokumoto, Masanori Abe and Yoichi Hiasa

Department of Gastroenterology and Metabiology, Ehime University, Graduate School of Medicine, Toon, Japan

Key words
controlled attenuation parameter, high-risk gastroesophageal varices, predictor, spleen stiffness.

Accepted for publication 14 August 2021.

Correspondence
Masashi Hirooka, Department of Gastroenterology and Metabiology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan.
Email: masashih@m.ehime-u.ac.jp

Declaration of conflict of interest: The authors have no conflicts of interest to declare.

Funding support: Japan Agency for Medical Research and DevelopmentJP20fk0210058

Funding support: Japan Society for the Promotion of Science18K0763418K08007

Abstract

Background and Aim: Spleen stiffness measurement (SSM) is useful for assessing portal hypertension. It is unclear whether SSM values are appropriate because vibration-controlled transient elastography (VCTE) does not generate B-mode images. This study aimed to confirm whether the controlled attenuation parameter (CAP) measured in the spleen can predict the accuracy of SSM.
Methods: This retrospective study enrolled 349 patients who underwent SSM using VCTE from January 2012 to December 2020. Consecutive patients were classified into the pilot set (SSM and hepatic venous pressure gradient [HVPG] were measured) and the validation set (SSM was measured without HVPG). In the pilot set, scatter plots with a nonparametric contour line were created. Logistic regression analysis was performed to predict outliers outside the 50% contour line.
Results: The values of CAP could distinguish the outliers in scatter plots between the HPVG and SSM in both univariate and multivariate analyses (cutoff, 118 dB/m). The correlation of SSM with HVPG ($r = 0.718$; $P < 0.001$) was significantly better in the low CAP (≤118 dB/m) group than in the high CAP (>118 dB/m) group ($r = 0.330$; $P < 0.001$). The area under the receiver operating characteristic curve of SSM in predicting high-risk varices was better in the low CAP group than in all patients or in the high CAP group in the pilot set (0.881, 0.854, and 0.843, respectively) and in the validation set (0.893, 0.821, and 0.814, respectively).
Conclusion: For patients with CAP <118 dB/m, SSM is a feasible predictor of HVPG.

Introduction

Portal hypertension (PH) is part of a hemodynamic process triggered by liver cirrhosis, which is mostly induced by alcohol or improper nutrition and less often by viral infections and autoimmune or genetic diseases. In particular, an increase in sinusoidal pressure causes a series of changes in the hepatic microcirculation, which results in the development of esophagogastric varices (EGV), ascites, bleeding, and encephalopathy.[1] Thus, estimation of the portal vein pressure gradient is important. However, direct measurement of portal pressure is invasive, inconvenient, and clinically impractical. Currently, the most commonly used parameter is the hepatic venous pressure gradient (HVPG), defined as the difference between the wedged hepatic venous pressure and the free hepatic venous pressure.[2–4]

Recently, spleen stiffness measurement (SSM) has been shown to be useful for assessing PH.[3,5–9] Hemodynamic changes in PH can cause spleen congestion, which may induce spleen fibrosis and increase SSM.[10] A meta-analysis of nine studies showed that SSM is strongly correlated with HVPG ($r = 0.72$, 95% confidence interval: 0.63–0.80).[11] Colecchia *et al*. showed that SSM is more accurate than other noninvasive parameters in identifying patients with EGV and those with different degrees of PH.[12]

Vibration-controlled transient elastography (VCTE) does not have B-mode imaging; hence, performing SSM is difficult and results in a high rate of inaccurate measurements. Thus, a new transient elastography method is required for SSM. To resolve this limitation, a new three dimensional-printed device, which included transient elastography and ultrasound-fusion methods, was developed.[13] Although the success rate of the SSM has improved, it remains unclear whether the SSM values are appropriate. In addition, for liver stiffness measurements (LSMs), a marker is required to determine the appropriateness of spleen stiffness values.

Thus, by focusing on the image homogeneity of the spleen using B-mode ultrasound, this study aimed to confirm whether

the controlled attenuation parameter (CAP) is a predictive marker of appropriate SSM performance.

Methods

Study design. Our institutional ethics committee approved all study protocols, and the patients provided written informed consent. This was a single-center, retrospective, cross-sectional study. SSM was performed in 376 patients with chronic liver disease between January 2012 and December 2020. The exclusion criteria were obesity (skin-to-capsula distance >25 mm) that prevented measurement of spleen stiffness ($n = 9$) and without esophagogastroduodenoscopy ($n = 3$). Although a history of treatment of hepatocellular carcinoma or gastroesophageal varices were set as the exclusion criteria, no patients met these criteria. The criteria for reliability were 10 validated measurements, a success rate of at least 60%, or failure to satisfy interquartile range (IQR)/median < 0.3 of the obtained spleen stiffness values ($n = 15$). Although previous splenectomy and previous open abdominal surgery were set as the exclusion criteria, no patients underwent these procedures. The final number of participating patients was 349 (Fig. 1). The selection criteria were age 20–90 years and Eastern Cooperative Oncology Group performance status of 0 to 2. Notably, the patient's sex was not considered during selection. VCTE was performed on an empty stomach more than 3 h after eating. The finally selected 349 patients were classified into two groups (pilot and validation sets). In total, 148 consecutive patients were enrolled in the pilot set to evaluate the correlation between the SSM and HVPG measurements. Subsequently, to validate the diagnostic accuracy of transient elastography for SSM, 201 patients in whom SSM was performed without HVPG were enrolled and included in the validation set.

Measurement of liver and spleen stiffness and esophagogastroduodenoscopy. Spleen and liver stiffness were measured using VCTE with an M probe from FibroScan502 (EchoSens, Paris, France) by two operators (Masashi Hirooka and Yohei Koizumi) with more than 10 years of experience in measuring liver and spleen stiffness. The LSM was performed as previously reported.[14] The criteria for reliability were 10 validated measurements and a median (IQR) success rate of at least 60% or <0.3 of the obtained liver and spleen stiffness values. To assess the SSM, the patient was placed in the supine position with the left arm in maximum abduction, and the transducer was placed in the left intercostal space.[15] SSM was assessed on the same day as LSM assessment using the same probe used in the LSM assessment. Ten valid measurements were obtained for the CAP in each patient. According to the criteria proposed at the Baveno VI Consensus Conference, high-risk varices were defined as esophageal varices of grade 1 with red signs or grade 2 or higher, which were deemed clinically significant and required treatment in standard clinical practice.[15] To measure HVPG, the right hepatic vein was catheterized through the right femoral vein, and pressure in both the wedged and free positions was measured using a 5-Fr balloon-tipped catheter. The HVPG was calculated by subtracting the free hepatic venous pressure from the wedged venous pressure. HVPG was measured 2 weeks after LSM and SSM assessments were performed.

Statistical analysis. Data are presented as medians and IQRs. The Kruskal-Wallis test was used for nonparametric data. Spearman's rank correlation coefficient was used to determine the correlation between the SSM and HVPG. Nonparametric density estimation was used to confirm the number of points and the density of the points. Contour lines were plotted for every 5% of all dots. Outliers were defined as those that existed outside the

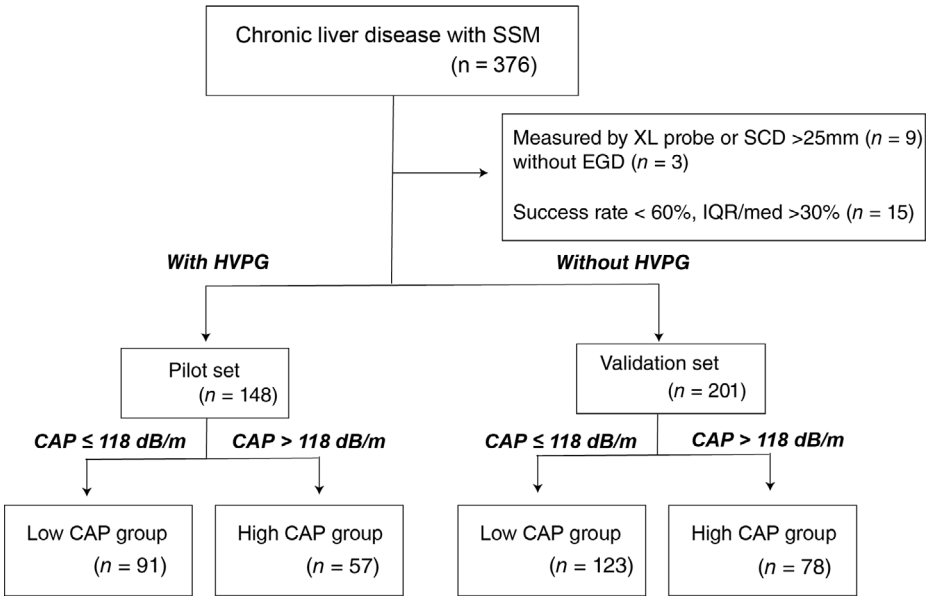

Figure 1 Study design. CAP, controlled attenuation parameter; EGD, esophagogastroduodenoscopy; HVPG, hepatic venous pressure gradient; IQR, interquartile range; SCD, skin-to-capsula distance; SSM, spleen stiffness measurement.

Table 1 Characteristics of the patients

	Pilot set ($n = 148$)	Validation set ($n = 201$)	*P* value
Age (years)	71 (64, 78)	69 (56, 74)	<0.001
Men: Women	107 (72.3%)	41 (27.7%)	0.001
BMI (kg/m^2)	24.3 (21.6, 27.3)	23.1 (20.4, 25.3)	0.003
SCD (mm)	19 (16, 21)	19 (17, 20)	0.898
Etiology			
HBV: HCV: NBNC	16: 57: 75	16: 61: 124	0.120
Liver volume (mL)	1133 (981, 1300)	1106 (917, 1323)	0.304
Spleen volume (mL)	209 (121, 337)	239 (145, 416)	0.026
HVPG (mmHg)	8 (6, 13)	—	
Platelet ($\times 10^3/\mu$L)	125.5 (95.7–166.5)	126.0 (82.5, 183.0)	0.745
PT (%)	84.2 (70.4, 98.7)	79.2 (61.1, 97.2)	0.017
Child-Pugh grade	111: 33: 4	118: 44: 39	<0.001
A: B: C			
LSM (kPa)	18.1 (10.7, 30.1)	18.2 (9.2, 36.3)	0.811
SSM (kPa)	38.1 (23.8, 61.7)	46.4 (29.0, 66.6)	0.028
EGV	66 (44.6%)	94 (46.8%)	0.687
High-risk EGV	38 (25.7%)	63 (31.3%)	0.249

Data are presented as medians and quartiles. High-risk EGV defined as F1 (linear relatively faint varices) with positive red color sign, or F2 (bead-shaped moderate varices), or F3 (nodule or mass-shaped varices).
BMI, body mass index; EGV, esophagogastric varices; HBV, hepatitis B virus s antigen positive; HCV, anti-hepatitis C virus positive; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NBNC, both HBsAg and anti-HCV negative; PT, prothrombin time; SCD, skin-to-capsula distance; SSM, spleen stiffness measurement.

50% contour line. Logistic regression analysis was performed to predict outliers outside the 50% contour line. The optimal cutoff value to predict the outlier was calculated using the Youden index in the receiver operating characteristic (ROC) curve analysis. ROC curve analysis was performed to predict the EGVs. The area under the ROC curve (AUC) was calculated. Optimal cutoff values were selected to maximize the sum of the sensitivity and specificity of the Youden index, and cutoff values with at least 90% sensitivity and specificity were also individually selected. To evaluate the overall accuracy of the SSM in detecting high-risk varices, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated. Differences were considered significant at $P < 0.05$. Statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics. SSM was performed in 376 patients with chronic liver disease; of these, 107 were men, and 41 were women. The median age was 71 years (IQR, 64–78 years). The characteristics of the two independent study groups are shown in Table 1. A flowchart illustrating the study design is shown in Figure 1. Median age, sex, basal metabolic index (BMI), spleen volume, prothrombin time, Child-Pugh grade, and SSM were significantly different between the pilot and validation sets. The validation set included patients with a poor liver functional reserve and a larger spleen volume.

Association of SSM with HVPG. First, we evaluated the correlation between the SSM and HVPG measurements in 148 patients in the pilot set. SSM was significantly correlated with the HVPG ($r = 0.558$; $P < 0.001$, Fig. 2a). In addition, scatter plots with a nonparametric contour line are shown in Figure 2b. Logistic regression analysis was performed to predict outliers outside the 50% contour line. In both univariate and multivariate analyses, CAP was the only significant predictive factor (Table 2). The optimal CAP cutoff for the dots that existed inside the 50% contour line was 118 dB/m. Thus, the correlation between SSM and HVPG was assessed by dividing the low CAP (≤118 dB/m) and high CAP (>118 dB/m) groups. The correlation between SSM and HVPG was significantly stronger in the low CAP group ($r = 0.718$; $P < 0.001$, Fig. 2c) than in the high CAP group ($r = 0.330$; $P < 0.001$, Fig. 2d). The correlation of SSM with platelet counts was significantly stronger in the low CAP group ($r = 0.444$; $P < 0.001$) than in the high CAP group ($r = 0.280$; $P = 0.034$).

Diagnostic accuracy for the presence of high-risk varices. The diagnostic accuracy in predicting high-risk varices in the pilot set is shown in Figure 3a and Table 3. The area under the ROC curve of SSM in predicting high-risk varices was better in the low CAP group than in the high CAP group. According to the Youden index, in the pilot set, the diagnostic accuracy was better in the low CAP group than in all patients or in the high CAP group. For a sensitivity of ≥0.90, LR− was better in the low CAP group than in all patients or in the high CAP group. However, for a sensitivity of ≥0.90, LR+ was better in the high CAP group than in all patients or in the low CAP group. Furthermore, the diagnostic accuracy in predicting high-risk varices in the validation set is shown in Figure 3b and Table 4. In the validation set, according to the Youden index, the diagnostic accuracy was better in the low CAP group than in the high CAP

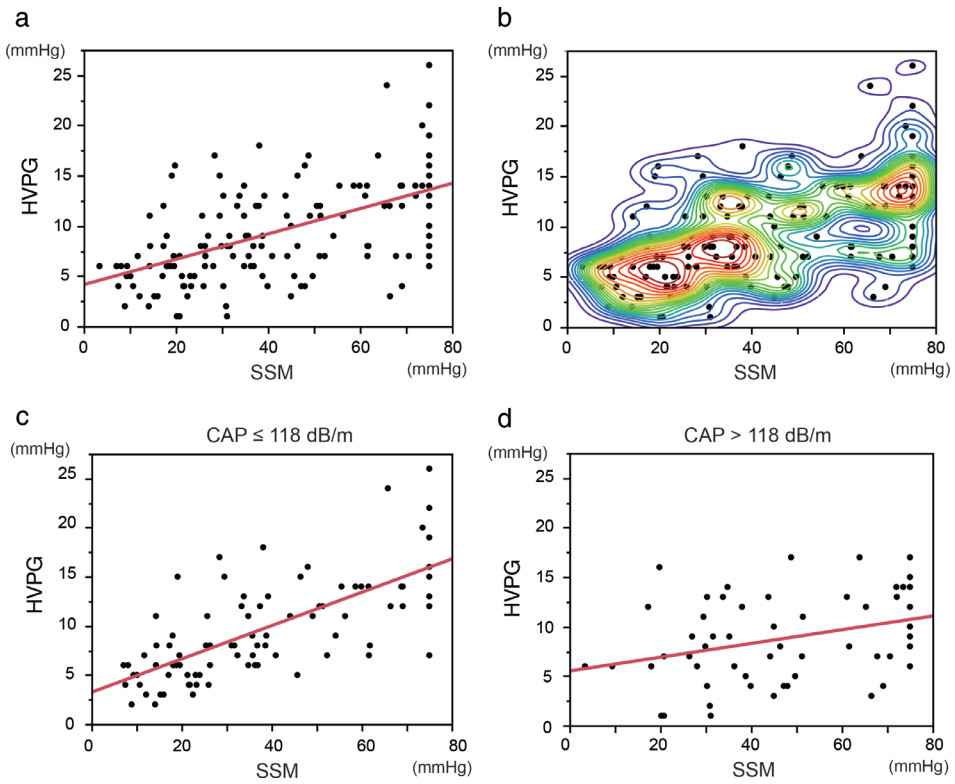

Figure 2 Scatter plots between spleen stiffness measurement and hepatic venous pressure gradient in the pilot set. (a) Scatter plots between spleen stiffness measurement (SSM) and hepatic venous pressure gradient (HVPG) for all patients. SSM was observed to significantly correlate with HVPG ($r = 0.558$; $P < 0.001$). (b) The scatter plots with nonparametric contour lines are shown. The contour line was descripted every 5%. (c) The SSM was observed to more significantly correlate with HVPG ($r = 0.718$; $P < 0.001$) in the low controlled attenuation parameter (CAP) group than in the high CAP group (d).

Table 2 Predictors of outliers in scatter plots between the hepatic venous pressure gradient and spleen stiffness measurement

	Univariate		Multivariate	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Age (years)	1.03 (0.99–1.07)	0.067	1.03 (0.99–1.07)	0.083
Men/Women	1.75 (0.81–3.81)	0.155	1.89 (0.81–4.41)	0.139
HBV or HCV/NBNC	1.24 (0.64–2.41)	0.524	1.32 (0.63–2.75)	0.455
SCD (mm)	0.98 (0.91–1.05)	0.508	0.99 (0.91–1.07)	0.772
BMI (kg/m^2)	1.04 (0.97–1.12)	0.291		
CAP*	0.98 (0.97–0.99)	<0.001	0.98 (0.96–0.99)	<0.001
Splenic volume (mL)	1.27 (0.47–3.56)	0.498	1.00 (0.44–4.47)	0.476
Child-Pugh class C/B or A	5.00 (0.51–49.28)	0.168	3.71 (0.29–47.23)	0.312

**P* value <0.05.

BMI, body mass index; CAP, controlled attenuation parameter; HBV, hepatitis B virus antigen positive; HCV, hepatitis C virus positive; NBNC, both HBsAg and anti-HCV negative; SCD, skin-to-capsula distance.

group. For a sensitivity of ≥0.90, LR− was better in the low CAP group than in all patients or in the high CAP group. For a sensitivity of ≥0.90, LR+ was better in the low CAP group than in all patients or in the high CAP group.

Discussion

It is difficult to determine whether SSM is performed accurately. This study clarified that the CAP was an effective parameter for accurate SSM.

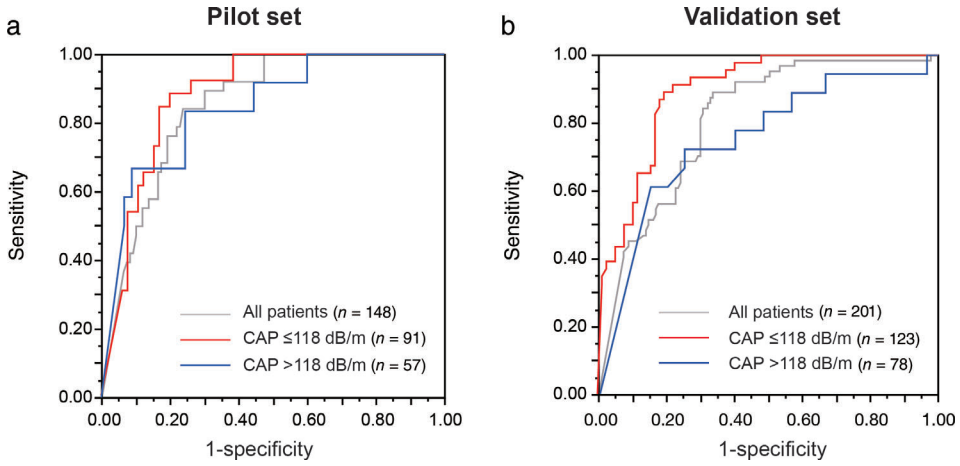

Figure 3 Diagnostic accuracy for predicting esophagogastric varices. Diagnostic accuracy in predicting high-risk varices in the pilot set (a) and validation set (b). The area under the curve of spleen stiffness measurement in predicting high-risk esophagogastric varices was better in the low controlled attenuation parameter (CAP) group (less than 118 dB/m, red line) than in all patients (gray line) or the high CAP group (more than 118 dB/m, blue line).

Table 3 Diagnostic accuracy of the high-risk varices as assessed by spleen stiffness measurement in the pilot set

All patients ($n = 148$)							
Cutoff	Se	Sp	PPV	NPV	LR+	LR−	AUC, 0.854
38.1†	92.1 (35/38)	64.6 (71/110)	47.3 (35/74)	95.9 (71/74)	2.598	0.122	
70.6‡	42.1 (16/38)	90.9 (100/110)	61.5 (16/26)	82.0 (100/122)	4.632	0.637	
48.0§	84.2 (32/38)	76.4 (84/110)	55.2 (32/58)	93.3 (84/90)	3.563	0.207	
CAP ≤ 118 dB/m ($n = 91$)							
Cutoff	Se	Sp	PPV	NPV	LR+	LR−	AUC, 0.881
38.1†	92.3 (24/26)	73.9 (48/65)	58.5 (24/41)	96.0 (48/50)	3.529	0.104	
61.6‡	53.9 (14/26)	92.3 (59/65)	70.0 (14/20)	71.4 (59/71)	5.833	0.508	
44.1§	88.5 (23/26)	80.0 (52/65)	63.9 (23/36)	94.5 (52/55)	4.423	0.144	
CAP > 118 dB/m ($n = 57$)							
Cutoff	Se	Sp	PPV	NPV	LR+	LR−	AUC, 0.843
43.8†	91.7 (11/12)	55.6 (25/45)	35.5 (11/31)	96.2 (25/26)	2.062	0.150	
72.0‡	66.7 (8/12)	91.2 (41/45)	66.7 (8/12)	91.1 (41/45)	7.500	0.366	
51.4§	83.3 (10/12)	75.6 (34/45)	47.6 (10/21)	94.4 (34/36)	3.409	0.221	

†Cutoff for sensitivity ≥0.90.
‡Cutoff for specificity ≥0.90.
§Cutoff based on the Youden index.
AUC, area under the curve; CAP, controlled attenuation parameter; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

In VCTE, one-dimensional images in A-mode are used to guide appropriate transducer placement. An external mechanical vibrator generates shear waves, the velocities of which are detected using A-mode imaging.[14,16] To mitigate measurement variability, at least 10 measurements are obtained, and the median stiffness value (in kPa) has been reported.[17] A successful measurement method was established for LSM. When a shot is unsuccessful, the instrument does not return a value. The entire procedure is considered to have failed when no values are obtained after 10 shots. Successful measurements are validated using the following criteria: (i) the number of valid shots is more than 10; (ii) the ratio of valid shots to the total number of shots is >60%; and (iii) the IQR, reflecting the variability of measurements, is less than 30% of the median LSM value (an IQR/LSM

Table 4 Diagnostic accuracy of the high-risk varices as assessed by spleen stiffness measurement in the validation set

All patients ($n = 201$)							
Cutoff	Se	Sp	PPV	NPV	LR+	LR−	AUC, 0.821
45.0[†]	92.1 (58/63)	63.0 (87/138)	53.2 (58/109)	94.5 (87/92)	2.491	0.126	
69.9[‡]	44.4 (28/63)	90.6 (125/138)	68.3 (28/41)	78.1 (125/160)	4.718	0.613	
45.0[§]	92.1 (58/63)	63.0 (87/138)	53.2 (58/109)	94.5 (87/92)	2.491	0.126	
CAP ≤ 118 dB/m ($n = 123$)							
Cutoff	Se	Sp	PPV	NPV	LR+	LR−	AUC, 0.893
42.7[†]	93.5 (43/46)	74.0 (57/77)	68.3 (43/63)	95.0 (57/60)	3.599	0.088	
61.6[‡]	54.3 (25/46)	90.9 (70/77)	78.1 (25/32)	76.9 (70/91)	5.978	0.502	
42.7[§]	93.5 (43/46)	74.0 (57/77)	68.3 (43/63)	95.0 (57/60)	3.599	0.088	
CAP > 118 dB/m ($n = 78$)							
Cutoff	Se	Sp	PPV	NPV	LR+	LR−	AUC, 0.814
51.4[†]	94.1 (16/17)	52.5 (32/61)	35.6 (16/45)	97.0 (32/33)	1.980	0.112	
67.9[§]	76.5 (13/17)	75.4 (46/61)	46.4 (13/28)	92.0 (46/50)	3.110	0.312	

[†]Cutoff for sensitivity ≥0.90.

[‡]Cutoff for specificity ≥0.90.

[§]Cutoff based on the Youden index.

AUC, area under the curve; CAP, controlled attenuation parameter; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

of less than 30%).[16,18] However, successful SSMs have not been established. Even if we measure spleen stiffness based on the LSM method described above, there are some variations between SSM and HVPG.[3,7,13]

New factors that are not present in liver measurements should be considered when measuring SSM successfully. We focused on the homogeneity of the ultrasound imaging of the spleen. Unlike the liver, the spleen rarely contains fatty deposits. Thus, the attenuation coefficient for the spleen is low. Thus, we focused on CAP, a factor originally used to quantify intrahepatic fat content. This parameter is based on the ultrasonic properties of the radiofrequency backpropagated signals acquired by VCTE. This ultrasonic attenuation coefficient is an estimate of the total ultrasonic attenuation (go-and-return path) at 3.5 MHz and is expressed in dB/m. CAP is evaluated using the same radiofrequency data and in the same region of interest than the radiofrequency data used for LSM. In this study, only CAP was a predictive factor in the univariate and multivariate analyses.

Thus, in addition to the LSM criteria, CAP should be included to adequately perform SSM. The VCTE machine used in this study could not measure stiffness above 75 kPa. Therefore, in this study, nonparametric density estimation was used to define the outliers. At pressures >75 kPa, SSM could be assessed by selecting the dots within the 50% contour line. The best CAP cutoff for the dots that were located inside the 50% contour line was 118 dB/m. Indeed, the SSM with a low CAP better correlated with the HVPG than that with a high CAP.

Finally, it is important to determine whether an adequate SSM identified by CAP can predict clinical outcomes. The HVPG value can be predictive of variceal bleeding.[19] In patients with low CAP, cutoff values were similar in both the pilot and validation sets. According to the Youden index, the cutoff values were 44.1 kPa and 43.7 kPa in the pilot and validation sets, respectively. An approximate cutoff value for predicting high-risk gastroesophageal varices is 44 kPa.

Recent studies have reported that spleen stiffness is more accurate than other noninvasive parameters in identifying patients with EGVs and those with different degrees of PH.[8,20] To detect the high-risk EGV group, the reported cutoff value of SSM was 46 kPa.[12,13] Thus, in patients with low CAP, the cutoff value of 44 kPa is similar to the previously reported cutoff value, while the cutoff value in patients with high CAP is different. In patients with high CAP, NPV and LR+ had a superior specificity of ≥0.90. The reason for this finding is unclear. In the validation set, NPV and LR+ were not superior at a cutoff of 72 kPa. When we assessed the shape of the ROC curve in the pilot set, the curve was not smooth on the left side of the x-axis. Hence, there may have been bias in these instances.

This study has some limitations. First, the HVPG is a referential standard to confirm the successful measurement of spleen stiffness. Optimally, histologic findings of the spleen should be used as a referential marker; however, it is difficult to obtain spleen tissue. Data collection should be performed in a multicenter study, and the study protocol should include patients from whom spleen tissue samples can be obtained. Second, an older version of the VCTE machine was used. Recently, a new version of the VCTE machine was developed in which the shear wave frequency varies from 50 Hz to 100 Hz. Although the stiffness could only be measured up to 75 kPa, in our study, it could be measured up to 100 kPa with a new version of the VCTE machine. Even with a new version of the VCTE machine, the usefulness of CAP as a marker for the successful assessment of SSM should be confirmed. Third, the rate of Child-Pugh class C was higher in the validation set than in the pilot set. Therefore, a

future study, including more patients with Child-Pugh class C, is warranted.

In conclusion, the CAP was a useful marker for accurately measuring spleen stiffness. By using a cutoff of less than 118 dB/m, the SSM can be useful for predicting high-risk gastroesophageal varices.

Acknowledgments

This work was supported in part by JSPS (Japan Society for the Promotion of Science) KAKENHI Grant Number 18K07634 to Masashi Hirooka, Grant Number 18K08007 to Yoichi Hiasa, and from AMED under Grant Number JP20fk0210058 to Yoichi Hiasa.

References

1 Groszmann RJ, Garcia-Tsao G, Bosch J *et al*. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N. Engl. J. Med.* 2005; **353**: 2254–61.
2 Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology*. 2004; **39**: 280–2.
3 Hirooka M, Ochi H, Koizumi Y *et al*. Splenic elasticity measured with real-time tissue elastography is a marker of portal hypertension. *Radiology*. 2011; **261**: 960–8.
4 Merkel C, Montagnese S. Hepatic venous pressure gradient measurement in clinical hepatology. *Dig. Liver Dis.* 2011; **43**: 762–7.
5 Cho YS, Lim S, Kim Y, Sohn JH, Jeong JY. Spleen stiffness measurement using 2-dimensional shear wave elastography: the predictors of measurability and the normal spleen stiffness value. *J. Ultrasound Med.* 2019; **38**: 423–31.
6 Colecchia A, Colli A, Casazza G *et al*. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. *J. Hepatol.* 2014; **60**: 1158–64.
7 Ochi H, Hirooka M, Koizumi Y *et al*. Real-time tissue elastography for evaluation of hepatic fibrosis and portal hypertension in nonalcoholic fatty liver diseases. *Hepatology*. 2012; **56**: 1271–8.
8 Stefanescu H, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. *J. Gastroenterol. Hepatol.* 2011; **26**: 164–70.
9 Takuma Y, Nouso K, Morimoto Y *et al*. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. *Radiology*. 2016; **279**: 609–19.
10 Kondo R, Kage M, Iijima H *et al*. Pathological findings that contribute to tissue stiffness in the spleen of liver cirrhosis patients. *Hepatol. Res.* 2018; **48**: 1000–7.
11 Singh S, Eaton JE, Murad MH, Tanaka H, Iijima H, Talwalkar JA. Accuracy of spleen stiffness measurement in detection of esophageal varices in patients with chronic liver disease: systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* 2014; **12**: 935–945.e4.
12 Colecchia A, Ravaioli F, Marasco G *et al*. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J. Hepatol.* 2018; **69**: 308–17.
13 Tanaka T, Hirooka M, Koizumi Y *et al.* Development of a method for measuring spleen stiffness by transient elastography using a new device and ultrasound-fusion method. *PLoS One*. 2021; **16**: e0246315.
14 Kudo M, Shiina T, Moriyasu F *et al*. JSUM ultrasound elastography practice guidelines: liver. *J. Med. Ultrason. (2001)*. 2013; **40**: 325–57.
15 Wang H, Wen B, Chang X *et al*. Baveno VI criteria and spleen stiffness measurement rule out high-risk varices in virally suppressed HBV-related cirrhosis. *J. Hepatol.* 2021; **74**: 584–92.
16 Ferraioli G, Filice C, Castera L *et al*. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 3: liver. *Ultrasound Med. Biol.* 2015; **41**: 1161–79.
17 Castera L, Forns X, Alberti A. Noninvasive evaluation of liver fibrosis using transient elastography. *J. Hepatol.* 2008; **48**: 835–47.
18 Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. *J. Hepatol.* 2012; **56**: 696–703.
19 Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*. 2017; **65**: 310–35.
20 Colecchia A, Montrone L, Scaioli E *et al*. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology*. 2012; **143**: 646–54.