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Spleen stiffness-spleen size-to-platelet ratio risk score as noninvasive predictors of esophageal varices in patients with hepatitis B virus-related cirrhosis

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Abstract

This study was conducted to evaluate the predictive value of spleen stiffness-spleen size-to-platelet ratio risk score (SSPS) as a noninvasive predictor of esophageal varices (EVs) and to compare it with others.

In this retrospective study, from April 2017 to October 2018, a total of 65 patients with hepatitis B virus-related cirrhosis who underwent the liver and spleen stiffness (LS, and SS) measurements by 2 dimensional-shear wave elastography and endoscopic evaluation for EVs were enrolled. Liver stiffness-spleen size-to-platelet ratio risk score (LSPS) and SSPS were calculated. The prognostic values were assessed by the area under the receiver operating characteristic curve (AUC).

Twenty-six patients had no EV on endoscopy. Among 39 patients who had EVs, 12 patients had high risk EVs. The AUCs of the LS value, SS value, LSPS, and SSPS for predicting EVs were 0.72, 0.77, 0.80, and 0.85, respectively. The AUCs of the LS value, SS value, LSPS, and SSPS for predicting high-risk EVs were 0.55, 0.78, 0.67, and 0.80, respectively. SSPS had the highest specificity, at 96.15%, for predicting EVs.

SSPS may be beneficial to exclude from having EVs and it is expected that the frequency of performing endoscopies for screening EVs can be reduced.

Abbreviations: 2D-SWE = two-dimensional-shear wave elastography, AUC = area under the receiver operating characteristic curve, EV = esophageal varix, LS = liver stiffness, LSPS = liver stiffness-spleen size-to-platelet ratio risk score, SS = spleen stiffness, SSPS = spleen stiffness-spleen size-to-platelet ratio risk score.

Keywords: elasticity imaging techniques, esophageal and gastric varices, liver, liver cirrhosis, predictive value of tests, spleen

1. Introduction

An esophageal varix (EV) is one of the critical accompanying complications of portal hypertension in liver cirrhosis patients.[1] According to previous studies, the average risk of variceal bleeding in cirrhotic patients without previous hemorrhage is 30% and the mortality rate ranges from 17% to 57%.[2–6] Therefore, predicting and appropriately treating EVs in patients with liver cirrhosis is important. Current guidelines recommend endoscopic surveillance of EVs every 2 to 3 years for all compensated cirrhosis patients with or without small EVs, as well as preventing the first variceal bleeding for patients with medium or large varices using either nonselective beta blockers or endoscopic band ligation.[7]

The diagnosis of EVs using endoscopy is still invasive and needs specific expertise, resulting in increased medical workloads and limited compliance by asymptomatic patients.[8] There have been many attempts to identify noninvasive, reproducible and accurate parameters to predict EVs. Over the years, liver

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This retrospective study was approved by the Institutional Review Board and granted a waiver of written informed consent for use of data.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors have no conflicts of interest to disclose.

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stiffness (LS) and spleen stiffness (SS) measured by variable tissue elastography methods have been proven to be significantly correlated with EVs. Some reports have shown promising results for predicting EV and bleeding using LS–spleen diameter-to-platelet ratio score (LSPS), which is a combination of LS measured by transient elastography and platelet-to-spleen ratio.[9,10]

Thus, the purpose of this study was to evaluate the predictive value of spleen stiffness-spleen size-to-platelet ratio risk score (SSPS) as a noninvasive predictor of EVs and to compare it with other noninvasive ultrasound elastography derivatives including LS, SS, and LSPS.

2. Methods

2.1. Study populations

This retrospective study was approved by the Institutional Review Board and granted a waiver of written informed consent for use of data. Between April 2017 and October 2018, a total of 2540 consecutive patients underwent 3377 sessions of LS and SS measurements for hepatic fibrosis evaluation. A search of the electronic medical records and picture archiving and communication system records identified 88 potentially eligible treatment-naive patients for EV with hepatitis B virus-related cirrhosis, who underwent both LS and SS measurements using two dimensional-shear wave elastography (2D-SWE) and endoscopy for evaluation of EV within 1 month. The diagnosis of liver cirrhosis was established by means of histopathologic proof (n = 8) or radiologic evidence (liver cirrhosis either on US, CT, MRI, or 2D-SWE, n = 80) combined with clinical and laboratory findings. We excluded patients who had a history of treatment for hepatic malignancy: either hepatic surgery, transarterial chemoembolization, local ablation, or chemotherapy (n = 15); were diagnosed as having portal vein thrombosis (n = 4); had been prescribed a ß-blocker as a prevention for EV bleeding or any other cause (n = 4). Finally, 65 patients were enrolled (mean age, 58.6 years ± 8.7 [standard deviation]; range, 41−78 years; 44 men [mean age, 58.4 years ± 8.8; range, 41−76 years], and 21 women [mean age, 58.6 years ± 8.7; range, 51−78 years]) (Fig. 1).

The baseline characteristics of the patients in terms of age, sex, body mass index; the laboratory findings including platelet count, aspartate aminotransferase, alanine aminotransferase, albumin, prothrombin time; spleen size, Child-Pugh classification, EV grades, LS values, and SS values were obtained from the electronic medical records and picture archiving and communication system records.

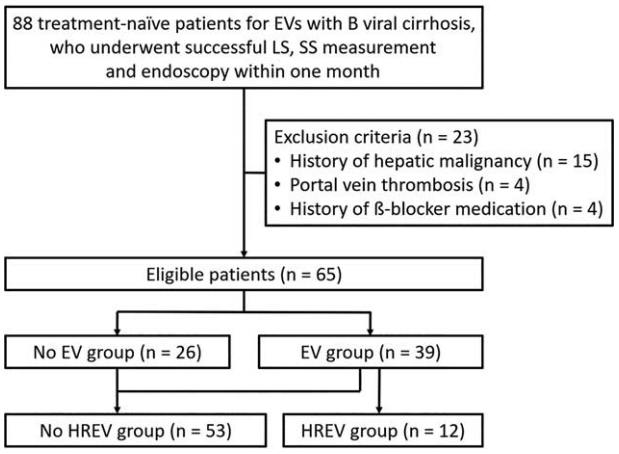

Figure 1. Flowchart of the study population. EV = esophageal varix, HREV = high-risk esophageal varix, LS = liver stiffness, SS = spleen stiffness.

2.2. Liver, spleen stiffness measurements and their derivatives

Along with conventional liver ultrasonography, LS and SS measurements were performed by 1 of 3 experienced operators (YK, SL, and YSC) as part of their regular practice. All operators were certified abdominal radiologists and had used 2D-SWE to measure LS in at least 300 cases at the onset of this study. Liver and spleen stiffness measurements were performed as described previously.[11,12] 2D-SWE studies of the liver and spleen were performed with an Aixplorer US system (SuperSonic Imagine SA, Aix-en-Provence, France). For scanning, a broadband convex transducer (1–6 MHz) was used. Scanning parameters were as follows: SWE 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/s; mechanical index, 1.5; and thermal index of soft tissue, 1.2 to 1.4.

All patients underwent 5 sequential LS and SS measurements in a single session by 2D-SWE. Patients were fasted for approximately 8 hours prior to the measurements. LS measurements were performed on the right lobe of the liver, through the intercostal spaces, with the patient lying in a supine position and the right arm in maximal abduction. They were asked to hold their breath after moderate exhaling, and a cine loop was obtained including a 2D-SWE color map. A trapezoidal color box (3.5 × 2.5 cm in size) was positioned greater than 2 cm below the hepatic capsule and away from large vessels. Sequential frames were recalled when the elasticity in the color box was judged to reach a plateau. A round region of interest (also referred to as the Q-box) was then positioned in the color box to measure the mean elasticity and its standard deviation. The stiffness value was expressed in kilopascals (kPa). The round region of interest was up to 2 cm in diameter, and its size was changed if necessary, according to the amount of measurable parenchyma and the locations of large vessels. Each LS value was the median of 5 sequential measurements. Invalid results were defined as those having an interquartile range divided by median value of 0.3 or greater, the index of validity used for transient elastography.[13]

After the liver stiffness measurement, the size and stiffness of the spleen were measured with the same transducer. The size of the spleen was measured at the left intercostal or subcostal space with the left arm at maximum abduction. After measuring the longitudinal diameter of the spleen, spleen stiffness was measured in the same way as liver stiffness. The depth of respiration was controlled individually to a level at which the elasticity signals were constant and without artifacts. Artifact-like signals underneath the splenic capsule and the major vessels of the spleen were avoided. We defined spleen stiffness values with an interquartile range divided by median of less than 0.3 as valid, and a measurement was considered to be successful when a valid spleen stiffness was obtained.

LSPS and SSPS were calculated using the following formulas: LSPS = LS value × spleen diameter (cm)/platelet count (10^9/L)[9]; SSPS = SS value × spleen diameter (cm)/platelet count (10^9/L).

2.3. Endoscopic evaluation for esophageal varices

Endoscopy was performed within 1 month of the LS measurement by 1 of 2 experienced endoscopists. Both endoscopists had

Table 1

Participant characteristics (N = 65).

Characteristic	Standard value (range)	Value
Age (yr) *	NA	58.6 ± 8.7
Male sex	NA	44 (67.7%)
Body mass index (kg/m^2) *	NA	24.8 ± 3.4
Platelet count (×10^9/L) *	150–400	111.5 ± 45.3
Aspartate aminotransferase (IU/L)	15–45	37 (29.0–52.0)
Alanine aminotransferase (IU/L)	10–45	26.0 (20.0–36.5)
Albumin (g/L)	4.2–5.0	4.2 (3.7–4.5)
Prothrombin time (INR)	0.8–1.2	1.1 (1.1–1.2)
Spleen size (cm)	NA	11.3 (9.9–12.9)
Child-Pugh classification*		
A	NA	63 (96.9)
B	NA	1 (1.5)
C	NA	1 (1.5)
Esophageal varix†		
None	NA	26 (40)
F1	NA	20 (30.8)
F2	NA	10 (15.4)
F3	NA	9 (13.8)
LS (kPa)	NA	12.2 (8.7–17.6)
SS (kPa)	NA	30.8 (24.8–37.7)
LSPS	NA	1.42 (0.70–2.51)
SSPS	NA	3.02 (1.90–5.66)

Unless indicated otherwise, data are numbers of patients, with percentages in parentheses, or medians, with first-third quartile values in parentheses.

INR = international normalized ratio, LS = liver stiffness, LSPS = liver stiffness-spleen size-to-platelet ratio risk score, NA = not applicable, SS = spleen stiffness, SSPS = spleen stiffness-spleen size-to-platelet ratio risk score.

* Data are means ± standard deviation.

† The grades for esophageal and gastric varices were assigned according to the criteria of the Japanese Research Society for Portal Hypertension.

more than 10 years of experience in esophagogastroscopy, which is considered to be the gold standard technique for evaluating EVs. All endoscopies were performed in an endoscopy unit using a video endoscope system (Olympus GIF-Q145; Olympus, Tokyo, Japan). EV grading was performed according to previously published criteria. They were classified into 4 groups according to their shape and size: F0, no varicose appearance; F1, straight, small-caliber varices; F2, moderately enlarged, beady varices; and F3, markedly enlarged, nodular or tumor-shaped varices. High-risk EV was defined as equal to or greater than grade F1 EV with the red dot sign or EV equal to or greater than grade F3.[14,15]

2.4. Statistical analysis

The normality of the distribution of quantitative variables was evaluated using the Shapiro–Wilk test and was expressed as median with IQRs or as mean ± standard deviation, as appropriate. Nonparametric variables including LS, SS, LSPS, and SSPS of the patient groups (no EV group vs EV group and no high-risk EV group vs high-risk EV group) were compared by using the Mann–Whitney *U* test. The diagnostic performance for predicting EVs and high-risk EVs of LS measured by 2D-SWE, SS measured by 2D-SWE, LSPS, and SSPS were assessed by an area under the receiver operating characteristic curve (AUC) analysis. The optimal cut-off values for predicting EVs and high-risk EVs of each parameter were defined as the value maximizing the sum of sensitivity and specificity on the basis of the Youden index. All *P* values less than.05 were considered significant. Statistical analyses were performed with Medcalc, version 19.0.3 (Medcalc software, Ostend, Belgium).

3. Results

2.5. Patient characteristics

The patients' characteristics are summarized in Table 1. The majority of patients (97.0% [63 of 65]) had been diagnosed with Child-Pugh class A cirrhosis. The other 2 patients were diagnosed as either Child-Pugh class B or Child-Pugh class C cirrhosis, respectively. Endoscopy showed that 39 of the 65 patients (60%) had EVs (any grade), whereas no varices were found in 26 of the 65 patients (40%). Twelve patients (18.5% [12 of 65]) were assigned to the high-risk EV group, because of F2 grade EVs with the red dot sign (n = 3) and F3 grade EVs (n = 9), whereas 53 patients (81.5% [53 of 65]) were assigned to the not high-risk EV group, because the EVs were equal to or less than F2 grade without the red dot sign (n = 27) or an EV was not found (n = 26). There was no F1 grade EV with a red dot sign.

2.6. Comparison of LS, SS, LSPS, and SSPS values in each group

Median values for each parameter according to the groups are summarized in Table 2. All of the median values of the EV group were significantly higher than that of the no EV group. The median values of LS, SS, LSPS, and SSPS of the no EV group versus the EV group were 9.9 kPa versus 13.4 kPa, 27.5 kPa versus 34.9 kPa, 0.73 versus 1.89, and 1.89 versus 5.20, respectively. The SS and SSPS values for the high-risk EV group were significantly higher than that for the no high-risk EV group. The median values for SS and SSPS in the no high-risk EV group and the high-risk EV group were 29.9 kPa versus 40.2 kPa and 2.62 versus 5.87, respectively. However, the LS and LSPS values between the no high-risk EV and high-risk EV groups were not statistically different. The median values of LS and LSPS of the no high-risk EV group and high-risk EV group were 12.2 kPa versus 13.9 kPa and 1.15 versus 1.89, respectively. Box-and-whisker plots (Fig. 2a–d) show comparison of LS, SS, LSPS, and

Table 2

Median values of each parameter of the patients with no esophageal varix, esophageal varix, and high-risk esophageal varix.

	No EV (N = 26)	EV (N = 39)	*P* value	No HREV (N = 53)	HREV (N = 12)	*P* value
LS (kPa)	9.9 (6.5–12.9)	13.4 (10.6–18.4)	<.001	12.2 (8.4–17.4_	13.9 (9.0–19.4)	.589
SS (kPa)	27.5 (21.9–29.9)	34.9 (30.2–40.1)	<.001	29.9 (23.2–35.2)	40.2 (34.1–45.0)	.003
LSPS	0.73 (0.40–1.55)	1.89 (1.10–3.40)	<.001	1.15 (0.59–2.16)	1.89 (1.38–3.35)	.063
SSPS	1.89 (1.56–2.78)	5.20 (2.69–6.88)	<.001	2.62 (1.72–4.84)	5.87 (4.84–7.15)	.002

Data are medians, with first-third quartile values in parentheses. EV = esophageal varices, HREV = high-risk esophageal varices, LS = liver stiffness, LSPS = liver stiffness-spleen size-to-platelet ratio risk score, SS = spleen stiffness, SSPS = spleen stiffness-spleen size-to-platelet ratio risk score.

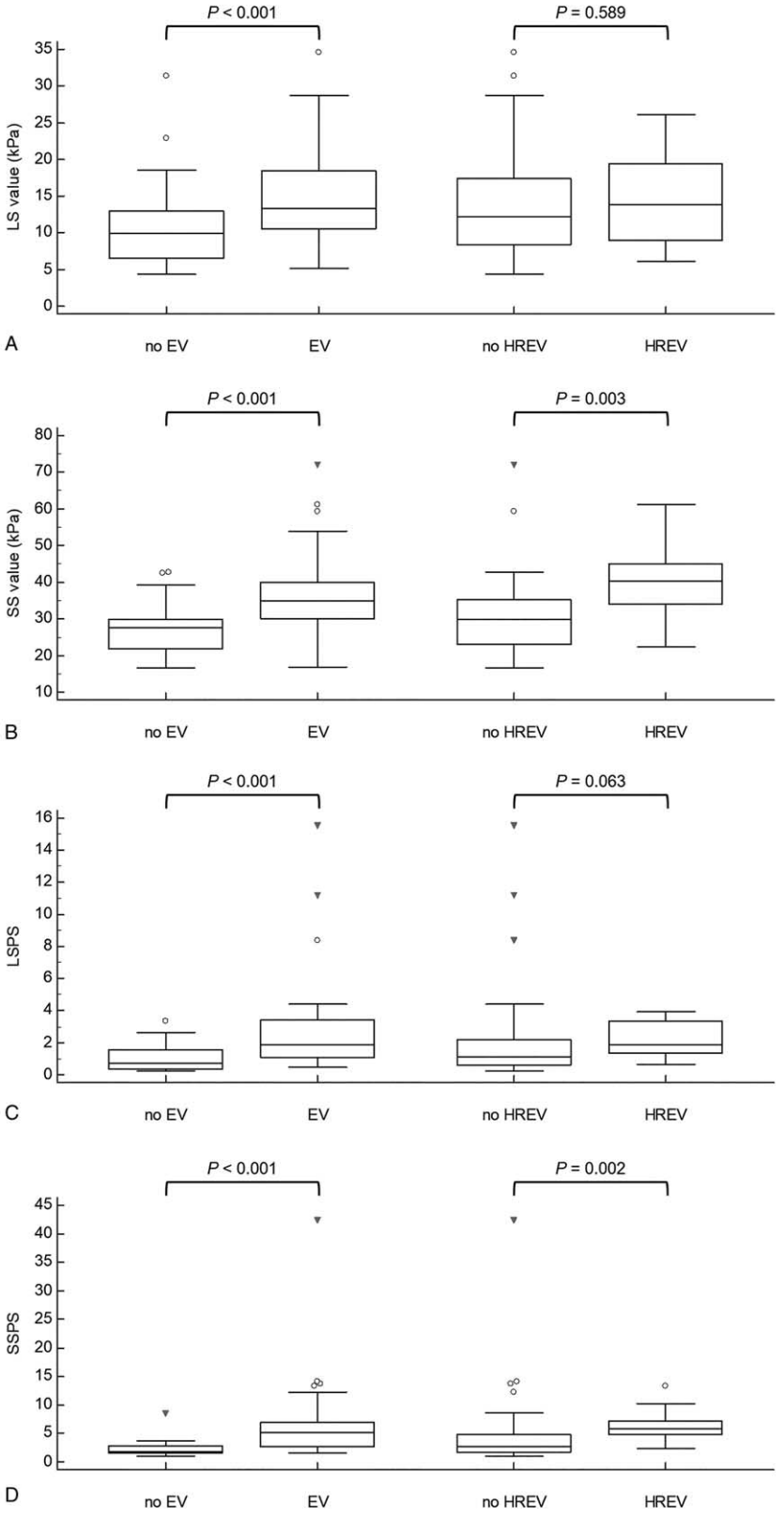

Figure 2. Liver stiffness (LS), spleen stiffness (SS), liver stiffness-spleen size-to-platelet ratio risk score (LSPS), and spleen stiffness-spleen size-to-platelet ratio risk score (SSPS) values in no esophageal varix (EV) versus EV groups, and no high-risk esophageal varix (HREV) versus HREV groups. Box-and-whisker plots show comparison of LS (A), SS (B), LSPS (C), and SSPS (D) values among the groups by presence of EV and HREV.

Table 3

Predicting performance and cutoff values of each parameter for presence of esophageal varix: receiver operating characteristic analysis.

Parameter	Cutoff	AUROC	95% CI	*P* value	Sensitivity, %	Specificity, %
LS (kPa)	> 9.9	0.723	0.598–0.827	.001	82.05	57.69
SS (kPa)	> 29.9	0.767	0.646–0.863	<.001	76.92	76.92
LSPS	> 0.8279	0.803	0.685–0.891	<.001	84.62	69.23
SSPS	> 3.6971	0.845	0.734–0.923	<.001	64.10	96.15

AUROC = area under the receiver operating characteristic curve, CI = confidence interval, LS = liver stiffness, LSPS = liver stiffness-spleen size-to-platelet ratio risk score, SS = spleen stiffness, SSPS = spleen stiffness-spleen size-to-platelet ratio risk score.

SSPS values among the groups by presence of EV and high-risk EV.

2.7. ROC curve analyses for predicting EVs and high-risk EVs

The AUCs of LS, SS, LSPS, and SSPS for predicting EVs were 0.72, 0.77, 0.80, and 0.85, respectively (Table 3) (Fig. 3a). None of them showed statistical differences. The optimal cutoff value of LS for predicting EVs was 9.9 kPa with 82.05% sensitivity and 57.69% specificity. The optimal cutoff value of SS for predicting EVs was 29.9 kPa with 76.92% sensitivity and 76.92% specificity. The optimal cutoff value of LSPS for predicting EVs was 0.83 with 84.62% sensitivity and 69.23% specificity. The optimal cutoff value of SSPS for predicting EVs was 3.70 with 64.10% sensitivity and 96.15% specificity.

The AUCs of LS, SS, LSPS, and SSPS for predicting high-risk EVs were 0.55, 0.78, 0.67, and 0.80, respectively (Table 4) (Fig. 3b). Pairwise comparison of ROC curves showed that the AUC of LS was significantly lower than the AUCs of SS, LSPS, and SSPS ($P = .012$,.028, and.005, respectively). The AUC of SSPS was significantly higher than that of LSPS ($P = .009$). There was no statistical difference between SS and either LSPS or SSPS. The optimal cutoff value of LS for predicting high-risk EVs was 15.4 kPa with 50.00% sensitivity and 67.92% specificity. The optimal cutoff value of SS for predicting high-risk EVs was 34.9 kPa with 75.00% sensitivity and 75.47% specificity. The optimal cutoff value of LSPS for predicting high-risk EVs was 1.28 with 83.33% sensitivity and 54.72% specificity. The optimal cutoff value of SSPS for predicting high-risk EVs was 4.42 with 83.33% sensitivity and 73.58% specificity.

4. Discussion

There have been many studies looking for noninvasive predictors for progression of liver fibrosis, which is represented by the presence of significant portal hypertension, varices, variceal bleeding, and hepatic decompensation. Among them, LS, SS, and LSPS are well known as noninvasive parameters for detection of EVs.[16] From the meta-analysis study by Manatsathit et al,[16] SS and LSPS were superior to LS for detection of EVs with higher sensitivity, specificity, AUC, and log diagnostic odds ratio. However, for detection of high-risk EV, LS, SS, and LSPS showed moderate sensitivity and specificity, not enough to be recommended as noninvasive predictors. In the current study, LS showed the lowest AUC value among 4 predictors for predicting both EVs and high-risk EVs, consistent with the study by Manatsathit et al.

In our study, SS and SSPS showed higher AUCs to detect EVs and high-risk EVs compared with LS and LSPS, because SS is directly related to portal hypertension and results in EVs. LS value is not only affected by liver fibrosis, but also by other factors including inflammation, infiltrative diseases, cholestasis, and venous congestion.[17] Thus, an increasing LS indirectly reflects the severity of portal hypertension.[18] Increasing SS by passive congestion and tissue hyperplasia of the spleen directly reflects the severity of portal hypertension in patients with liver cirrhosis.[18,19] The better performance of SS and its derivative

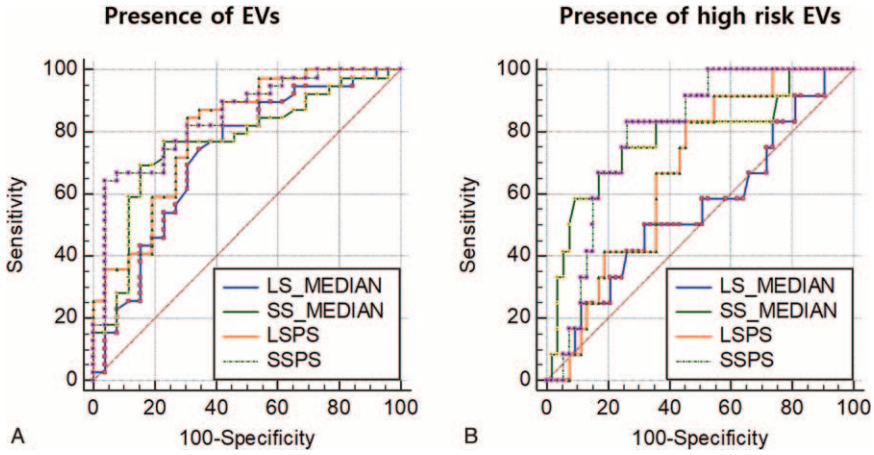

Figure 3. Comparison of receiver operating characteristic curves of liver stiffness (LS), spleen stiffness (SS), liver stiffness-spleen size-to-platelet ratio risk score (LSPS), and spleen stiffness-spleen size-to-platelet ratio risk score (SSPS) for predicting (A) esophageal varix (EV) and (B) high-risk esophageal varix (HREV).

Table 4

Predicting performance and cutoff values of each parameter for presence of high-risk esophageal varix: receiver operating characteristic analysis.

Parameter	Cutoff	AUROC	95% CI	*P* value	Sensitivity, %	Specificity, %
LS (kPa)	> 15.4	0.550	0.422–0.674	.603	50.00	67.92
SS (kPa)	> 34.9	0.778	0.658–0.872	.001	75.00	75.47
LSPS	> 1.2773	0.673	0.545–0.784	.020	83.33	54.72
SSPS	> 4.4234	0.796	0.677–0.886	<.001	83.33	73.58

AUROC = area under the receiver operating characteristic curve, CI = confidence interval, LS = liver stiffness, LSPS = liver stiffness-spleen size-to-platelet ratio risk score, SS = spleen stiffness, SSPS = spleen stiffness-spleen size-to-platelet ratio risk score.

SSPS compared with LS and LSPS is in line with the previous study.[20]

The main strength of our study is the first utilization of SSPS as a predicting factor for EVs and high-risk EVs in cirrhotic patients. Importantly, we report that SSPS, when using the cutoff value of 3.70, showed the highest AUC (0.85) and specificity (96.15% [24/26]) for predicting EVs with 64.1% (25/39) sensitivity. This finding reveals the possibility of using SSPS as a noninvasive screening tool for EVs in patients with hepatitis B virus-related cirrhosis, although further large-scale prospective studies are needed.

There are several limitations in the present study. First, there might be selection bias from a single-center study, and our analysis was performed in a small number of patients with a retrospective design. The small number of patients was included because strict criteria were applied, such as the exclusion of patients who were treated or received prophylactic treatment for esophageal varix. Second, 2D-SWE measurements were obtained by three observers. Measurement variance from 3 different operators might have neglectable effects on the results, despite the fact that the operators were all highly experienced and used the same protocol for the LS and SS measurements.

In conclusion, LS, SS, LSPS, and SSPS were defined as noninvasive, useful methods to predict EVs in patients with hepatitis B virus-related cirrhosis. Among them, SSPS may be beneficial to exclude from having EVs and it is expected that the frequency of performing endoscopies for screening EVs can be reduced.

Author contributions

Conceptualization: Sanghyeok Lim, Yongsoo Kim, Young Seo Cho.
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Writing – review & editing: Ji Eun Lee, Min Hee Lee, Sanghyeok Lim, Seo-Youn Choi, Yongsoo Kim, Young Seo Cho.

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