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Original Article

Age, Sex, and Body Mass Index Should Be Considered When Assessing Spleen Length in Patients with Compensated Advanced Chronic Liver Disease

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Background/Aims: We investigated the factors related to spleen length and the diagnostic accuracy of a model using spleen length corrected by related factors, for the prediction of varices needing treatment (VNT).

Methods: Various prediction models for VNT including spleen length were analyzed in the cohort of compensated advanced chronic liver disease (cACLD), defined as liver stiffness (LS) ≥10 kPa in a recent study. The associated factors for spleen length were identified in healthy subjects to improve the prediction of VNT.

Results: Among 1,218 cACLD patients, VNT was noted in 249 patients (20.4%). On multivariate analysis, longer spleen length, lower platelet count, and higher LS value were independent predictors for VNT (all $p<0.001$). In multivariate analysis of 1,041 healthy subjects, age (β=–0.027), sex (β=0.762), and body mass index (β=0.097) were found to be significant factors for spleen length (all $p<0.001$). Using the β values, the estimated spleen length was calculated. To improve the prediction of VNT, the ratio of measured and estimated spleen length was calculated. Based on binary regression analysis results, the LS value-spleen ratio to platelet score (LSRPS) was calculated as follows: 0.027×LS value (kPa)+2.690×measured/estimated spleen ratio–0.011×platelet count (cells×10^9/L)–4.215. The area under the receiver operating characteristic of the LSRPS for VNT was 0.820, which was significantly higher than 0.797 of LS value-spleen diameter to platelet ratio score (LSPS) ($p=0.006$).

Conclusions: Spleen length is influenced by age, sex, and body mass index in the Asian population. The LSRPS using the measured/estimated spleen ratio had higher diagnostic accuracy than LSPS in predicting VNT in patients with cACLD. **(Gut Liver 2023;17:299-307)**

Key Words: Splenomegaly; Platelet; Liver stiffness; Body mass index

INTRODUCTION

Splenomegaly plays an important role in the pathophysiology of portal hypertension by increasing splanchnic flow.[1,2] Generally, upper limit of normal in spleen length is defined as 12 cm.[3,4] According to that, the prevalence of splenomegaly in patients with liver cirrhosis was reported as 60% to 65%.[5] However, a study of a healthy Western population showed that the median spleen length was 10.9 cm, and 26% of men and 6% of women had spleen lengths that exceed 12 cm, suggesting the concern about using 12 cm as the definition of splenomegaly.[6] There are no sufficient data in the Eastern population, because only few studies with small number of healthy subjects have investigated the normal spleen length.[7,8] In addition, previous studies suggested that the spleen length is significantly

influenced by age, height, and sex, suggesting that using uniform standard of 12 cm in defining splenomegaly is not acceptable.

Recently, parameters of spleen have been proposed as an important variable in predicting the presence of varices needing treatment (VNT).[9,10] Although esophagogastroduodenoscopy (EGD) is a standard screening modality for VNT, its invasiveness and risk of complication should be considered.[11-13] Furthermore, because of lower prevalence of VNT in patients with compensated advanced chronic liver disease (cACLD), endoscopic surveillance are not recommended in all cACLD patients due to the increased medical costs raised by unnecessary tests.[14-16]

Therefore, various noninvasive tests for predicting VNTs have been developed to reduce needless endoscopic surveillance. Several prediction models including Baveno VI criteria were based on liver stiffness (LS) value and platelet count.[14,17] A previous study developed LS value-spleen diameter to platelet ratio score (LSPS), a useful prediction model for high-risk esophageal varices.[9] In the ANTICIPATE study, the LSPS had highest discriminative value for the presence of VNT while LS and platelet count model was the second best model.[10] However, using measured spleen length as it is without consideration of related factors could interference the accuracy of prediction models based on spleen parameters.[6,18-20] Consideration of associated factors of spleen lengths and correction of measured spleen length with those factors would improve the diagnostic accuracy of previous prediction models.

Therefore, in this large, retrospective study, we investigated the normal value and the factors related to spleen length in healthy subjects who had undergone health checkups. Second, the diagnostic accuracy of spleen length corrected by related factors and prediction models based on corrected spleen length for predicting VNT in patients with cACLD were evaluated.

MATERIALS AND METHODS

1. Patients

Patients with cACLD, defined with LS ≥10 kPa, and who had undergone EGD, laboratory tests, and abdominal computed tomography (CT) within 6 months of transient elastography from January 2014 and December 2017 in five academic teaching hospitals were screened for eligibility (Supplementary Fig. 1). The cohort of this study was derived from a recent study performed in South Korea.[21] The exclusion criteria were as follows: (1) age <18 years; (2) insufficient clinical or laboratory information; (3) liver function of Child-Pugh score ≥7; (4) previous history or present hepatic decompensation defined by the presence of ascites, variceal bleeding or hepatic encephalopathy; (5) presence of portal vein thrombosis; and (6) history of hepatocellular carcinoma or organ transplant.

The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the human ethic committee of each hospital including Korea University Anam Hospital (IRB number: 2018AN0020). The requirement for informed consent was waived in this study due to its retrospective design.

2. Healthy controls

Healthy subjects who had undergone health checkups in Korea University Anam Hospital and Sanggye Paik Hospital between January 2014 and December 2017 were included. Subjects provided a complete medical history and had undergone physical examination, blood pressure measurement, 12-lead electrocardiography, abdominal CT scan, and laboratory tests. Patients with liver disease including chronic liver disease and hepatitis and patients having abnormality in liver function tests were excluded. Finally, only subjects with normal physical examination, non-pathologic laboratory values and no significant medical illness including hypertension, diabetes, malignancies, and cardiovascular and lung diseases were considered for analysis.

3. Measurement of spleen length

The coronal CT images were evaluated using commercially available CT software (Rapidia 2.8; Infinitt Healthcare, Seoul, Korea) to measure the craniocaudal length of the spleen. Maximum craniocaudal length was measured from the most superior margin to the most inferior one. LSPS was calculated according to the following equation: LSPS=LS (kPa)×spleen length (cm)/platelet count ($\times 10^9$ cells/L).[9]

4. Transient elastography

Transient elastography was performed with the FibroScan® (Echosens, Paris, France). Experienced operators measured the LS value on the right lobe of the liver through intercostal spaces of patients lying on their back with the maximal abduction of the right arm. The median LS value was considered reliable when 10 valid measurements were obtained with a success rate ≥60% and the interquartile range (IQR) to median ratio ≤30%.

5. Esophagogastroduodenoscopy

Experienced endoscopy operators in each hospital (>500 examinations) performed EGD. The size of the esophageal varix was classified into three groups as follows: F1,

straight and small varices; F2, moderately enlarged and beaded varices; and F3, markedly enlarged, nodular or tumor-shaped varices.[22] VNT was defined as varices larger than F2 or varices with red color signs.

6. Statistical analysis

Demographic and laboratory data are summarized as median (IQR) for continuous variables and number with percentages for categorical variables. Categorical and quantitative variables of groups were compared using the chi-square test and the Student t-test, respectively. The primary outcome was the presence of VNT. Binary regression analyses were performed to analyze the factors associated with the presence of VNT. Logistic binary regression analyses were performed to determine the predictors of the variability of spleen length. Using the beta values of multivariate linear regression analysis for spleen length, formula for estimated spleen length was developed.

Prediction models for VNT were developed using its related factors. The predictive accuracies of the noninvasive models were assessed and compared using area under the receiver operating characteristic (AUROC) curve analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences version 25.0 software (IBM Corp., Armonk, NY, USA). p-values <0.05 were considered statistically significant.

RESULTS

1. Patient with cACLD

Among 20,689 patients who had undergone transient elastography between January 2014 and December 2017, 19,471 patients were excluded according to the established exclusion criteria. A total of 1,218 patients were selected for statistical analysis (Supplementary Fig. 1). The baseline characteristics of the patients with cACLD are shown in Table 1. The median age was 55.9 years (IQR 48.1 to 63.5 years). Chronic hepatitis B was the most prevalent etiology of liver disease (483 patients, 39.7%), followed by alcoholic etiology (356 patients, 29.2%). The median Model for End-Stage Liver Disease score was 6.5 (IQR, 6.0 to 7.1). The median platelet count was 128.0×10^9 cells/L (IQR, 90.0×10^9 to 173.0×10^9 cells/L). The median LS and spleen size were 18.0 kPa (IQR, 12.3 to 29.9 kPa) and 11.0 cm (IQR, 9.6 to 12.8 cm), respectively.

2. Varices needing treatment

VNT was noted in 249 patients (20.4%) in EGD. The median age and proportion of male were similar between patients with and without VNT. The median platelet count was significantly lower in patients with VNT (89.0×10^9 cells/L vs 139.0×10^9 cells/L, p<0.001). Patients with VNT had a significantly higher LS value (27.0 kPa vs 16.9 kPa, p<0.001) and longer spleen length (13.0 cm vs 10.6 cm, p<0.001), when compared to those without VNT (Table 1).

On multivariate logistic regression analysis, longer

Table 1. Characteristics of Patients with Compensated Advanced Chronic Liver Disease According to the Presence of VNT

Variable	All patients (n=1,218)	Patients without VNT (n=969)	Patients with VNT (n=249)	p-value
Age	55.9 (48.1–63.5)	55.7 (47.6–63.5)	56.5 (48.7–63.5)	0.227
Male sex	778 (63.9)	611 (63.1)	167 (67.1)	0.240
Etiology				0.050
HBV	483 (39.7)	387 (39.9)	96 (38.6)	
HCV	147 (12.1)	126 (13.0)	21 (8.4)	
Alcohol	356 (29.2)	268 (27.7)	88 (35.3)	
Other	232 (19.0)	188 (19.4)	44 (17.7)	
Diabetes	377 (31.0)	292 (30.1)	85 (34.1)	0.223
Platelet count, $\times10^9$/L	128.0 (90.0–173.0)	139.0 (99.3–184.0)	89.0 (63.8–120.0)	<0.001
INR	1.03 (1.00–1.12)	1.02 (1.00–1.11)	1.08 (1.00–1.15)	<0.001
ALT, IU/L	38.0 (25.0–65.0)	37.0 (23.0–68.0)	40.5 (30.0–57.0)	<0.001
Total bilirubin, mg/dL	1.0 (0.8–1.2)	1.0 (0.7–1.2)	1.0 (1.0–1.5)	<0.001
Serum albumin, g/dL	4.0 (3.6–4.1)	4.0 (3.7–4.1)	4.0 (3.4–4.0)	<0.001
MELD score	6.5 (6.0–7.1)	6.4 (6.0–7.1)	6.7 (6.0–7.4)	0.089
Child-Pugh score				0.002
5	933 (76.6)	761 (78.5)	172 (69.1)	
6	285 (23.4)	208 (21.5)	77 (30.9)	
Liver stiffness, kPa	18.0 (12.3–29.9)	16.9 (12.0–27.0)	27.0 (17.5–44.1)	<0.001
Spleen diameter, cm	11.0 (9.6–12.8)	10.6 (9.3–12.0)	13.0 (11.5–15.0)	<0.001

Data are presented as median (interquartile range) or number (%).
VNT, varices needing treatment; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; ALT, alanine aminotransferase; MELD, Model for End-Stage Liver Disease.

spleen length (odds ratio, 1.319; 95% confidence interval [CI], 1.229 to 1.417), lower platelet count (odds ratio, 0.998; 95% CI, 0.985 to 0.992), and higher LS value (odds ratio, 1.026; 95% CI, 1.017 to 1.035) were independent predictors for VNT (all p<0.001) (Table 2).

3. Noninvasive prediction models for VNT

The AUROC of the LS value for the prediction of VNT was 0.681 (95% CI, 0.654 to 0.707), and that of platelet count was 0.745 (95% CI, 0.712 to 0.778). The LSPS had an AUROC of 0.797 (95% CI, 0.774 to 0.820), and it was significantly higher than those of LS value (p<0.001), platelet count (p<0.001), and spleen length (p=0.006). With the optimal cutoff value of LSPS for predicting VNT, 1.47, screening EGD could have been avoided in 536 patients (44.0%) with a low VNT miss rate (23 patients, 4.3%).

4. Spleen length in healthy subjects

To improve the prediction models of VNT, we investigated the associated factors of spleen size in 1,041 healthy subjects. Of the healthy subjects, 518 (49.8%) were women and 523 (50.2%) were men (Supplementary Table 1). The median age was 53.0 years (range, 18 to 82 years). The median height was 157.7 cm (range, 140.1 to 175.1 cm) in

Table 2. Binary Regression Analysis for Varices Needing Treatment

Variable	Rating	Univariate analysis	Multivariate analysis			Multivariate analysis		
		p-value	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value
Age	yr	0.196						
Sex	0=female; 1=male	0.245						
Body mass index	kg/m^2	0.992						
Spleen length	cm	<0.001				0.277	1.319 (1.229–1.417)	<0.001
Measured/estimated spleen ratio		<0.001	2.690	14.735 (7.533–28.820)	<0.001			
Platelet count	×10^9/L	<0.001	–0.011	0.989 (0.985–0.992)	<0.001	–0.012	0.998 (0.985–0.992)	<0.001
Liver stiffness	kPa	<0.001	0.027	1.028 (1.019–1.037)	<0.001	0.026	1.026 (1.017–1.035)	<0.001

OR, odds ratio; CI, confidence interval.

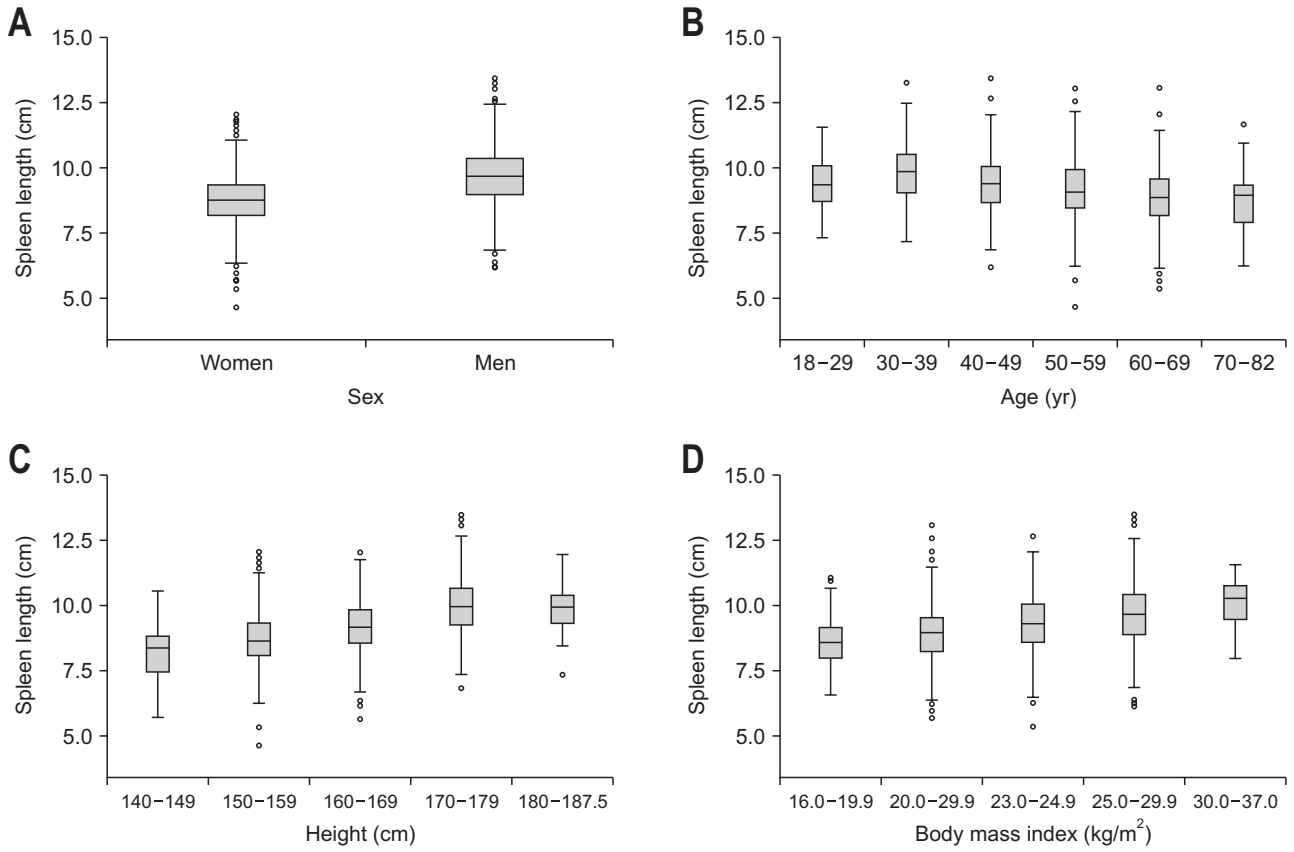

Fig. 1. Spleen length in healthy subjects according to sex (A), age (B), height (C), and body mass index (D).

women, and 170.7 cm (range, 151.6 to 187.5 cm) in men. The median body mass index (BMI) of women was 22.7 kg/m^2 (range, 16.0 to 31.1 kg/m^2), and that of men was 24.3 kg/m^2 (range, 17.9 to 37.0 kg/m^2).

The median spleen length was 9.1 cm (5th to 95th interpercentile range [IPR], 7.4 to 11.1 cm) in all healthy subjects. The median spleen length of men was 9.6 cm (5th to 95th IPR, 7.8 to 11.7 cm), which was significantly longer than 8.7 cm (5th to 95th IPR, 7.2 to 10.5 cm) of women (p<0.001) (Fig. 1A). The spleen length in 21 of men (4.0%) and four of women (0.8%) exceeded the 12 cm, which is generally suggested as a definition of splenomegaly. The spleen length decreased with age (r=–0.224, p<0.001), and increases with height (r=0.285, p<0.001) and BMI (r=0.265, p<0.001) (Fig. 1B-D).

Table 3. Spleen Length of Healthy Subjects

Variable	Spleen length, cm	
	Women (n=518)	Men (n=526)
Age, yr		
18–29	8.9 (7.4–11.2)	10.1 (7.3– NA)
30–39	9.3 (7.6–11.0)	10.2 (8.6–12.0)
40–49	8.9 (7.5–10.5)	9.7 (8.4–11.8)
50–59	8.7 (7.2–10.6)	9.6 (7.7–11.9)
60–69	8.3 (6.4–9.9)	9.2 (7.6–11.4)
70–82	8.3 (6.2–10.8)	9.2 (7.4–10.8)
Height, cm		
140–149	8.3 (6.0–9.8)	-
150–159	8.6 (7.2–10.6)	9.0 (7.8–10.3)
160–169	9.0 (7.3–10.5)	9.3 (7.5–11.0)
170–179	9.5 (8.6–NA)	9.9 (8.0–12.1)
180–187.5	-	9.9 (8.4–11.8)
Body mass index, kg/m^2		
16.0–19.9	8.4 (6.8–10.2)	9.0 (6.7–10.9)
20.0–22.9	8.7 (7.2–10.2)	9.2 (7.5–11.2)
23.0–24.9	8.8 (7.3–10.5)	9.6 (8.0–11.4)
25.0–29.9	8.8 (7.1–11.0)	9.9 (8.1–12.0)
≥30.0	9.4 (7.9–NA)	10.5 (9.0–NA)

Data are presented as median (5th–95th interpercentile range).
NA, not available.

5. Spleen length according to sex, age, height, and BMI in healthy subjects

The median values and 5th to 95th IPRs of spleen length stratified according to sex, age, height, and BMI are presented in Table 3. When patients were classified by sex, the spleen length decreased with age (median 8.9, 9.3, 8.9, 8.7, 8.3, and 8.3 cm in 18–29, 30–39, 40–49, 50–59, 60–69, and 70–82 years in women; median 10.1, 10.2, 9.7, 9.6, 9.2, and 9.2 cm in corresponding age in men, respectively), and had significant correlation with age in both women (r=–0.271, p<0.001) and men (r=–0.229, p<0.001) (Table 3).

The spleen length increased with height (median 8.3, 8.6, 9.0, and 9.5 cm in 140–149, 150–159, 160–169, and 170–179 cm in women; median 9.0, 9.3, 9.9, and 9.9 cm in 150–159, 160–169, 170–179, and 180–187.5 cm in men, respectively), and had significant correlation with height in both women (r=0.303, p<0.001) and men (r=0.253, p<0.001) (Table 3, Fig. 2A).

Finally, the spleen length increased with BMI (median 8.4, 8.7, 8.8, 8.8, and 9.4 cm in 16.0–19.9, 20.0–22.9, 23.0–24.9, 25.0–29.9, and ≥30.0 kg/m^2 in women; median 9.0, 9.2, 9.6, 9.9, and 10.5 cm in corresponding BMI in men, respectively), and had significant correlation with BMI in both women (r=0.145, p=0.001) and men (r=0.288, p<0.001) (Table 3, Fig. 2B).

6. Associated factors for spleen length

We performed linear regression analyses to evaluate the factors associated with spleen size (Table 4). On univariate analysis, age, sex, height, body weight, and BMI were significantly associated with spleen length (all p<0.001). Multivariate analysis showed that age (β=–0.027; 95% CI,

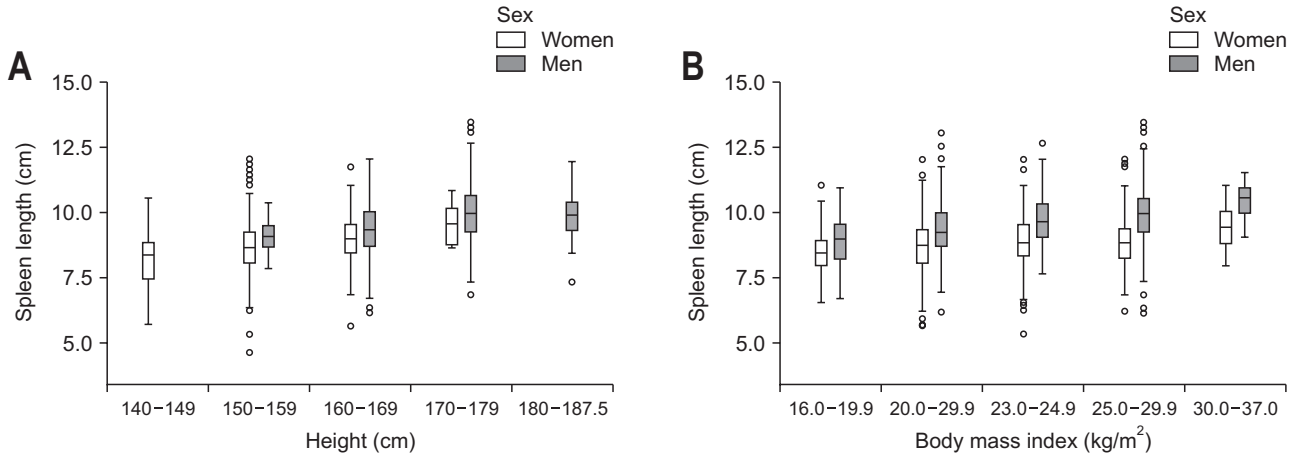

Fig. 2. Spleen length in healthy subjects according to sex and height (A), and sex and body mass index (B).

Table 4. Associated Factors for Spleen Length

Variable	Rating	Univariate analysis		Multivariate analysis	
		β (95% CI)	p-value	β (95% CI)	p-value
Age	yr	−0.026 (−0.032 to −0.020)	<0.001	−0.027 (−0.032 to −0.021)	<0.001
Sex	0=female; 1=male	0.933 (0.799 to 1.067)	<0.001	0.762 (0.630 to 0.894)	<0.001
Height	cm	0.062 (0.055 to 0.070)	<0.001		
Body weight	kg	0.053 (0.047 to 0.058)	<0.001		
Body mass index	kg/m^2	0.133 (0.108 to 0.157)	<0.001	0.097 (0.073 to 0.120)	<0.001

CI, confidence interval.

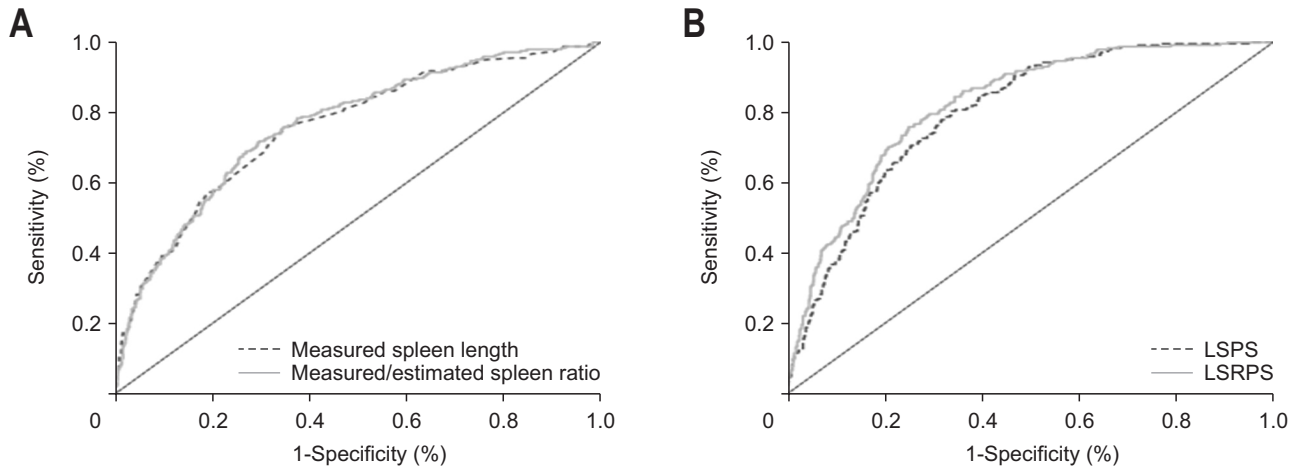

Fig. 3. The area under the receiver operating characteristic curve of the measured spleen length and measured/estimated spleen ratio (A), and LSPS and LSRPS (B).
LSPS, liver stiffness value-spleen diameter to platelet ratio score; LSRPS, liver stiffness value-spleen ratio to platelet score.

–0.032 to –0.021), sex (β=0.762; 95% CI, 0.630 to 0.894), and BMI (β=0.097; 95% CI, 0.073 to 0.120) were related factors for spleen length (all p<0.001).

Using the beta values of age, sex, and BMI from the results of multivariate linear regression analysis for spleen length, formula for estimated spleen size was developed as follows: estimated spleen length (cm)=–0.027×age (yr)+0.762×sex (women, 0; men, 1)+0.097×BMI (kg/m^2)+7.926.

7. The role of age, sex, and BMI in the evaluation of spleen length in patients with cACLD

Estimated and measured spleen lengths were comparable in patients without VNT (10.4 cm [IQR, 10.1 to 10.6 cm] vs 10.6 cm [IQR, 10.1 to 10.6 cm], p=0.134), while measured spleen length was significantly greater than estimated spleen length in patients with VNT (13.0 cm [IQR, 11.5 to 15.0 cm] vs 10.4 [IQR 10.3 to 10.7 cm], p<0.001). The median value of measured spleen length was significantly higher in men than in women (11.2 cm [IQR, 9.8 to 13.0 cm] vs 10.7 cm [IQR, 9.1 to 12.3 cm], p=0.001). Measured spleen length was significantly correlated with age (r=–0.122, p<0.001), BMI (r=0.145, p<0.001), Model for End-Stage Liver Disease score (r=0.166, p<0.001), and LS value (r=0.212, p<0.001) (Supplementary Fig. 2).

Considering the difference in measured spleen length between patients with and without VNT, we calculated the ratio of measured and estimated spleen length to improve the prediction of VNT as follows: measured/estimated spleen ratio=measured spleen length (cm)/estimated spleen length (cm). The AUROC of measured/estimated spleen ratio for the prediction of VNT were 0.762 (95% CI, 0.728 to 0.795), which was comparable with 0.754 of measured spleen length (95% CI, 0.722 to 0.790; p=0.369, z statistics=0.898) (Fig. 3A). Optimal cutoff value of measured spleen length for VNT was 11.5 cm (sensitivity 76.0%, specificity 64.3%, positive predictive value 35.4%, and negative predictive value 91.2%), and that of measured/estimated spleen ratio was 1.3 (sensitivity 69.1%, specificity 72.7%, positive predictive value 39.4%, and negative predictive value 90.1%).

8. LS value-spleen ratio to platelet ratio score

When the spleen length in LSPS was replaced with measured/estimated spleen ratio, the AUROC for VNT was 0.8, which was similar with that of LSPS (AUROC=0.797,

p=0.194, z statistics=–1.3). Then, we developed the new prediction score, LS value-spleen ratio to platelet score (LSRPS) based on the results from binary regression analysis for the prediction of VNT (Table 4) as follows: LSRPS=0.027×LS value (kPa)+2.690×measured/estimated spleen ratio–0.011×platelet count ($\times 10^9$/L)–4.215.

The median LSRPS was significantly higher in patients with VNT than those without (4.29 vs 2.91, p<0.001). The AUROC of LSRPS for the presence of VNT was 0.820 (95% CI, 0.793 to 0.847), which was significantly higher than that of LSPS (p=0.006, z statistics=–2.765). The optimal cutoff value of LSRPS was 3.75, with sensitivity of 76.0%, specificity of 74.8%, positive predictive value of 43.7%, and NPV of 92.4%, respectively (Fig. 3B). With the LSRPS of 3.75, larger number of patients (710 [59.1%] patients vs 536 [44.0%] patients with LSPS of 1.47) could avoid unnecessary EGD, and VNT miss rate was safe (59 [4.9%] patients vs 23 [4.3%] patients with LSPS of 1.47).

DISCUSSION

Spleen length has been suggested as one of the major variables in prediction of portal hypertension. However, normal range of spleen length in Asian population and its related factors have not been fully evaluated. In this large retrospective study, the median spleen length of healthy population was 9.6 cm in men and 8.7cm in women. Younger age, male sex, and higher BMI were significant predictors for increased spleen length. The new prediction model, LSRPS, based on the ratio of measured spleen length and spleen length corrected with related factors had superior diagnostic accuracy than LSPS for the prediction of VNT in patients with cACLD.

Our study has several clinical implications. Age, sex, and BMI corrected spleen length improved the prediction of VNT, which is the representative sign of portal hypertension. In our study, the LSRPS, which includes LS value, measured/estimated spleen ratio, and platelet count, had significantly higher diagnostic accuracy than LSPS (AUROC 0.820 vs 0.797, p=0.006). With the optimal cutoff value of LSRPS, 92.4% NPV was provided, and screening EGD could be saved in larger proportion of patients (59.1% with LSRPS 3.75 vs 44.0% with LSPS 1.47) with acceptable VNT miss rate less than 5.0%. This result is even better than reported spared EGD rate of 40.0% with expanded Baveno VI criteria.[17] This superiority was derived using measured/estimated spleen ratio, which is better to reflect the severity of portal hypertension compared to the directly measured spleen size, because spleen size is associated with various factors including age, sex, and BMI.

In 1,041 healthy Korean subjects, the median spleen length was 9.1 cm (5th to 95th IPR, 7.4 to 11.1 cm). A study of German healthy volunteers showed the median spleen length of 10.9 cm (5th to 95th IPR, 8.7 to 13.3 cm).[6] In the present study, only 4.0% of men and 0.8% of women had a generally defined splenomegaly (>12 cm), which is quite different from the result of a German study that 26% of men and 6% of women had spleen lengths that exceed 12 cm.[6] The difference between the two studies might be caused by the different clinical characteristics of enrolled subjects; the median age and BMI of the German study were 31 years and 25.0 kg/m^2, contrastively, those of the present study were 53.0 years, and 23.30 kg/m^2.

In the present study, women had markedly shorter spleen length (9.6 cm vs 8.7 cm, p<0.001) even after adjustment for age and BMI (β=0.762, p<0.001), which was consistent with previous data.[6,7,20,23] Lower total red cell mass in women might explain this observation.[6] In addition, we found that the relationship between age and spleen size was independent of other variables (β=–0.027, p<0.001). An association of age and spleen size have been previously investigated. Studies from Japan and China reported the decrease in spleen volume and length with age.[7,24] Another study suggested that age-related shortening, thickening, and loss of elastic fibers within the splenic capsule may contribute to a decrease in spleen size with age.[25] Although other studies only reported marginal or no correlation between age and spleen size, the result from the present study which analyzed patients with wider range of age (18 to 82 years) seems valuable.[24,26,27]

Lastly, BMI was another related factor of spleen length (β=0.097, p<0.001). In univariate analysis, both weight and height were associated with spleen length. However, only weight had significant correlation with spleen length in multivariate regression analysis; the correlation of weight with spleen length was weaker than that of BMI (β=0.036, p<0.001). In addition, in the present study, correlation of height and spleen length was only shown in women, not in men, leading to the use of BMI as a variable in formula for estimated spleen length. In contrast, a study of German healthy volunteers reported that the both height and weight were correlated with spleen size, and height was the strongest factor.[6] However, they only included healthy subjects with age of 18 to 55 years, therefore, the effect of age might not be well adjusted. In another study of German hospital and general population, spleen length was influenced by height, weight, and BMI (all p<0.0001).[28]

In clinical practice, spleen length of 12 cm remains the upper limit of normal, irrespective of clinical characteristics of each patient. In addition, spleen length itself was investigated as a variable for the prediction of varices.

However, factors related with spleen length should be considered in assessing spleen length. Therefore, we developed the formula for estimated spleen length, and calculated the ratio of measured/estimated spleen length ratio. With the classical upper limit of 12 cm, 570 patients (47.4%) with cACLD were defined to have splenomegaly. However, with the optimal cutoff value of measured/estimated spleen ratio, 431 patients (35.9%) with cACLD had higher ratio than 1.3.

This study has several limitations. First, due to the retrospective design, a selection bias might exist. Second, because hepatic venous pressure gradient, the gold standard in diagnosis of portal hypertension, was not measured, we defined the presence of VNT as the primary outcome of this study. Therefore, we could not fully evaluated the clinical significance of age, sex, and BMI-corrected spleen size and its ratio in assessing the severity of portal hypertension in patients with cACLD. Third, we measured spleen length with CT scan, which is not a simple method for practical use, because we tried to measure spleen length as accurately as possible. Finally, although the largest number of Asian healthy subjects were enrolled, the normal range of spleen size should be further investigated in wider and larger population.

In conclusion, we provided reference range of normal spleen length in the Korean population, and showed that spleen length correlated independently with age, sex, and BMI. New prediction model based on the corrected spleen length had superior diagnostic accuracy for VNT in patients with cACLD. Rather than defining splenomegaly with uniform standard of 12 cm, considering related factors would be useful in assessing spleen length in patients with cACLD.

CONFLICTS OF INTEREST

S.U.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Study concept and design: H.A.L., Y.S.S. Data acquisition: H.A.L., J.L., S.U.K., M.Y.K., S.G.K., K.T.S, J.Y.J., H.A., H.J.Y., Y.S.S. Data analysis and interpretation: H.A.L., J.L., S.U.K., M.Y.K., S.G.K., K.T.S, J.Y.J., H.A., H.J.Y., Y.S.S. Drafting of the manuscript: H.A.L., S.U.K. Critical revision of the manuscript for important intellectual content: H.A.L., S.U.K. Administrative, technical, or material support; study supervision: Y.S.S. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220032.

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