Validation of Spleen Stiffness Measurement for Screening of High-risk Esophageal Varices Among Cirrhotic Patients in Indonesia: A Single-Center Cross-sectional Study

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ABSTRACT

Background: *Spleen stiffness measurement (SSM) is a recently developed non-invasive method for predicting clinically significant portal hypertension and esophageal varices in compensated advanced liver disease or cirrhosis. This study aims to validate the accuracy of SSM for screening high-risk esophageal varices among cirrhotic patients in Indonesia* ***Methods:*** *This is a single-center, cross-sectional study. Patients with liver cirrhosis who underwent endoscopy at Cipto Mangunkusumo Hospital, Jakarta were included. Clinical data and data from laboratory tests, endoscopy, liver, and spleen stiffness measurement by transient elastography (TE) were collected. A 100 Hz spleen-dedicated TE probe was used for SSM.* ***Results****: Of 86 patients, 52 had high-risk esophageal varices. The median (IQR) value of SSM were significantly higher in patients with high-risk varices [36.1 kPa (IQR 21.5-59.1) vs. 70.3 kPa (IQR (52.2-86.0); p<0.001). SSM with a low cutoff value of 20 kPa had sensitivity and negative predictive value of 98.1% and 87.5%, respectively. The high cutoff value of 70 kPa had specificity and positive predictive value of 82.4% and 81.3%, respectively.* ***Conclusions:*** *SSM is useful for screening high-risk esophageal varices. Furthermore, the new dual cutoff value can help rule-in and rule-out high-risk esophageal varices among cirrhotic patients in Indonesia.*

Keywords**:** *spleen stiffness, esophageal varices, cirrhosis, Indonesia, validation.*

INTRODUCTION

Liver cirrhosis is the most common representation of the advanced stage of chronic liver disease. According to the Indonesian national health insurance program, liver cirrhosis is one of the diseases with a catastrophic cost expenditure.[1] Hepatitis B virus is the most common etiology of liver cirrhosis in Southeast Asia region, including Indonesia. Based on a study conducted at the Hepatobiliary Division of Cipto Mangunkusumo National General Hospital (RSCM) Jakarta Indonesia, the prevalence of hepatitis B cirrhosis is around 51.8%.[2] In the United States, hepatitis C virus, alcohol-related liver disease, and non-alcoholic fatty liver are the most common etiology of cirrhosis.[3]

The progressive course of cirrhosis leads to increased portal pressure and worsening of hepatocellular function. The clinical spectrum of cirrhosis ranges from the asymptomatic or

compensated stage to the decompensated stage which includes ascites, spontaneous bacterial peritonitis, variceal bleeding, encephalopathy, and hepatorenal syndrome. Gastroesophageal variceal bleeding is one of the most common complications found in cirrhotic patients with portal hypertension.[4] Clinically significant portal hypertension (CSPH) characterized by a hepatic venous pressure gradient (HVPG) value of ≥ 10 mmHg is a predictive factor for the decompensated stage and death in patients with liver cirrhosis.[5] Gastroesophageal variceal bleeding is associated with a mortality rate of 10-20% within six weeks. Cirrhosis patients with a history of bleeding still have a risk of recurrent bleeding of approximately 60% in the first year with a mortality rate of up to 33%.[4]

Early diagnosis of portal hypertension in cirrhosis is important to prevent gastroesophageal variceal bleeding. HVPG measurement is the gold standard for diagnosing portal hypertension, but it is invasive and also not suitable for screening.[5] The gold standard for diagnosing gastroesophageal varices is endoscopy. However, performing endoscopic examination periodically is costly and it causes low compliance of the patients. Considering these reasons, a non-invasive approach is needed to select patients who really need invasive examinations, such as patients with high-risk gastroesophageal varices.

As cirrhosis-related portal hypertension progresses, there is a progressive increase in spleen size and stiffness due to increased venous return, cell hyperplasia, angiogenesis, and fibrogenesis.[6] Spleen stiffness can be measured non-invasively using different techniques such as transient elastography (TE), point and 2D shear wave elastography or magnetic resonance elastography (MRE). Previous meta-analysis study showed that in chronic liver disease patients, spleen stiffness measurement (SSM) using ultrasound elastography and MRE had a pooled sensitivity of 87% for detecting high-risk varices, but with lower specificity (66%).[7] Accordingly, the Baveno VII consensus recommend SSM using TE for identifying CSPH or rule out high-risk varices.[5] However further study is suggested to validate the optimal cutoff for ultrasound elastography, including using the new100 Hz spleen-dedicated TE probe. SSM using 100Hz TE probe showed higher applicability with less failure rate compared to standard 50 Hz TE probe.[8] Clinical data related to SSM using 100 Hz TE probe for identifying high-risk varices among cirrhotic patients in Indonesia is still limited. The aim of our study is to assess diagnostic performance of SSM using 100 Hz TE probe to detect high-risk esophageal varices among cirrhotic patients in Indonesia. The ability of SSM was compared at different cutoff values and with Baveno VII criteria.

METHODS

Study Design

This is a cross-sectional study conducted at Cipto Mangunkusomo National General Hospital, a tertiary referral hospital in Jakarta Indonesia. This study was approved by the Ethics Committees of the Faculty of Medicine, Universitas Indonesia (approval no. KET-375/UN2.F1/ETIK/PPM.00.02/2022) and conducted in compliance with the Declaration of Helsinki.

Patient Population

The inclusion criteria were adult patients with liver cirrhosis and available for esophagogastroduodenoscopy (EGD), liver stiffness measurement (LSM), and SSM examination within one day at the endoscopy unit of the Hepatobiliary Division from February until June 2022. The exclusion criteria were refusal to provide informed consent, under 18 years of age, intra or extrahepatic malignancy, portal or splenic vein thrombosis, and previous splenectomy or embolization.

Data Collection

We collected clinical data and results of laboratory tests, EGD, LSM, and SSM. The diagnosis of cirrhosis was based on a combination of typical clinical findings (stigmata of cirrhosis), radiology (morphological changes of the liver, ascites, and splenomegaly), and laboratory tests. The clinical data included age, sex, and the etiology of cirrhosis. The laboratory data included hemoglobin, platelet count, aspartate and alanine aminotransferase (AST and ALT), albumin, total bilirubin, and INR.

Endoscopy, LSM, and SSM

All esophagogastroduodenoscopies were performed with the same unit of endoscopy equipment that used a video gastroscope (Pentax EG29-i10) by endoscopists at the Hepatobiliary Division. High-risk esophageal varices were defined as medium or large varices, small varices with red signs, or in Child-Pugh C. Liver and spleen stiffness measurements were performed on the same day using transient elastography (TE) (Fibroscan Touch 630, Echosens, Paris, France) using liver (50 Hz) and spleen (100 Hz) dedicated probe. The patients fasted for three hours before measurement. The results were expressed in kilopascals (kPa). A success rate of < 60% or an interquartile range/median value > 30% was considered to be unreliable.[9] Baveno VII criteria were defined as conforming to Baveno VI criteria (LSM < 20 kPa + platelet count > 150 x10^9/L) or not conforming but with SSM ≤ 40 kPa.[5]

Statistical Analysis

A minimum sample size of 70 patients was calculated to diagnose high-risk esophageal varices, using a significance level of 0.05, with 90% sensitivity, a precision of 0.1, and a prevalence of high-risk esophageal varices of 50%. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean and standard deviation if it was normally distributed, or median and interquartile range if it was not normally distributed. Categorical data were expressed as numbers and percentages. Continuous data were compared using the Student's t-test, Mann–Whitney U test, or Chi-square test for proportions of categorical data between two groups (low-risk vs. high-risk). The diagnostic estimates for predicting high-risk esophageal varices were evaluated by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and corresponding positive and negative likelihood ratio. A p-value <0.05 was considered to be statistically significant.

RESULTS

Baseline Characteristics

Table 1 shows the basic characteristics of our patients. A total of 86 patients with cirrhosis were analyzed in this study (**Figure 1**). Sixty percent of them (52 patients) were in the high-risk group. The most common etiology was hepatitis B virus (60.5%). The majority of patients were male (75.6%) and the mean age was 52±11.4 years old. There were no significant differences in age and sex between the low-risk and the high-risk groups. Child-Pugh grade, LSM, and SSM were significantly higher in high-risk patients.

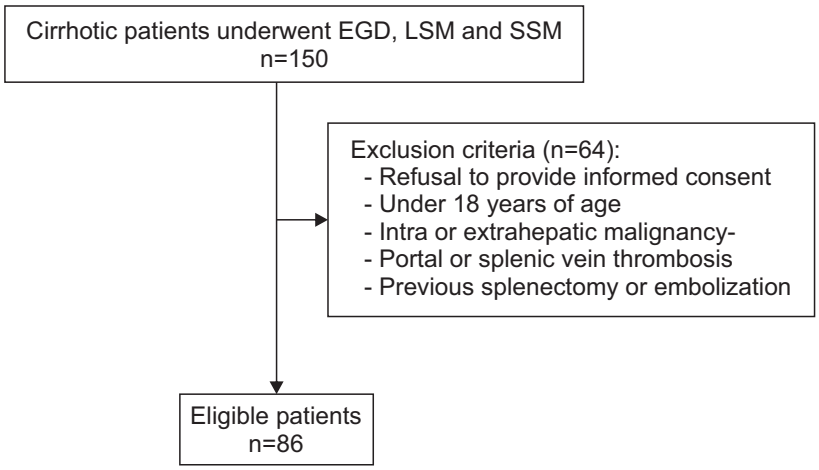

Figure 1. Flow chart of the study

Table 1. Baseline Characteristics of the Patients.

	Total N=86	Low Risk N=34	High Risk N=52
Demographic			
Sex, n (%)			
Female	21 (24.2)	11 (32.4)	10 (19.2)
Male	65 (75.6)	23 (67.6)	42 (80.8)
Age (years), mean ± SD	52±11.4	52±12.2	52±11.3
Etiology, n (%)			
NAFLD	3 (3.5)	1 (2.9)	2 (3.8)
HBV	52 (60.5)	25 (73.5)	27 (51.9)
HCV	22 (25.6)	5 (14.7)	17 (32.7)
Others	9 (10.5)	3 (8.8)	6 (11.5)
BMI (kg/m^2), median (IQR)	23.9 (21.1-27.1)	24.4 (22.5-28.2)	23.5 (20.5-25.7)
Laboratory			
Hemoglobin (g/dL), mean ± SD	12.51 ± 9.37	12.24 ± 2.20	12.69 ± 11.94
Platelet(x10^3/μL), median (IQR)	123 (84-186)	130 (106-130)	105 (74-109)
AST (U/L), median (IQR)	31 (25-41)	30 (23-39)	32.5 (26 -49)
ALT (U/L), median (IQR)	26 (18-37)	24 (28-37)	27 (18-36)
Albumin (g/dL), median (IQR)	3.60 (3.1-4.1)	4.00 (3.6-4.4)	3.50 (2.8-4.0)
Bilirubin(mg/dL), median (IQR)	0.92 (0.7-1.6)	0.75 (0.6-1.1)	1.08 (0.7-1.9)
INR(s), median (IQR)	1.10 (1.1-1.2)	1.05 (0.9-1.1)	1.16 (1.1-1.2)
Child-Pugh, n (%)			
A	53 (61.6)	32 (94.1)	21 (40.4)
B	27 (31.4)	1 (2.9)	26 (50.0)
C	6 (7.0)	1 (2.9)	5 (9.6)
Liver Stiffness Measurement (kPa), median (IQR)	20 (12.6-48.0)	15.5 (10.2-42.3)	23.2 (16.2-52.1)
Spleen Stiffness Measurement (kPa), median (IQR)	56.8 (36.1-83.2)	36.1 (21.5-59.1)	70.3 (52.2-86.0)

NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Diagnostic Accuracy of Spleen Stiffness Measurement

We compared the diagnostic accuracy of SSM using different cutoff values with Baveno VII criteria to diagnose high-risk esophageal varices (Table 2). Using a cutoff value of 40 kPa, SSM had a sensitivity of 86.5%, specificity of 55.9%, PPV of 75%, and NPV of 73.1%. These results were comparable with Baveno VII criteria with sensitivity, specificity, PPV, NPV 88.2%, 54.5%, 75%, and 75%, respectively. Using dual cutoff values, SSM with a cutoff value of 20 kPa had higher sensitivity (98.1%) with a negative predictive value of 87.5%, while a cut-off value of 70 kPa had a higher specificity (82.4%) with a positive predictive value of 81.3%.

Table 2. Diagnostic Accuracy of SSM for High-risk Esophageal Varices.

Cutoff	SSM 20 kPa	SSM 40 kPa	SSM 70 kPa	Baveno VII[#]
Sensitivity	98.1 (89.7 – 99.9%)	86.5% (74.2 – 94.4%)	50% (35.8 – 64.2%)	88.2 (76.1 – 95.6%)
Specificity	20.6 (8.7 – 37.9%)	55.9% (37.9 – 72.8%)	82.4% (65.5 – 93.2%)	54.5 (36.4 – 71.9%)
PPV	65.4 (53.8 – 75.8%)	75% (62.1 – 85.3%)	81.3% (63.6 – 92.8%)	75 (62.1 – 85.3%)
NPV	87.5 (47.4 – 99.7%)	73.1% (52.2 – 88.4%)	51.9% (37.8 – 65.7%)	75 (53.3 – 90.2%)
LR+	1.24 (1.04 – 1.47)	1.96 (1.32 – 2.91)	2.83 (1.30 – 6.15)	1.94 (1.32 – 2.86)
LR-	0.09 (0.01 – 0.73)	0.24 (0.11 – 0.51)	0.61 (0.44 – 0.83)	0.22 (0.10 – 0.49)

SSM, spleen stiffness measurement; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio
[#]Baveno VII: LSM < 20 kPa + platelet count > 150 x10^9/L or not conforming but with SSM ≤ 40 kPa.

DISCUSSION

The gold standard of esophageal varices evaluation in cirrhosis is endoscopy, but it is still considered as an invasive procedure and costly, especially in developing country such as Indonesia. As an alternative, a non-invasive tool, such as LSM using TE, has been evaluated to detect portal hypertension including the presence of esophageal varices.[10] In the development of cirrhotic portal hypertension, LSM only reflects the intrahepatic resistance, while spleen stiffness reflects the splenic congestion, angiogenesis, fibrogenesis, and hyperactivation of splenic lymphoid tissue due to hyperdynamic splanchnic circulation.[6] A randomized trial by Wong et al showed that the variceal screening approach using liver and spleen stiffness measurement had a similarly low incident rate of variceal bleeding within three years compared to the endoscopy approach.[11] According to Baveno VI criteria, the combination of LSM < 20 kPa and platelet count > 150 x10^9/L can identify patients with a low probability of high-risk varices with an NPV of 99%.[12] In patients who do not fulfill those criteria, an SSM ≤ 40 kPa by TE can significantly improve stratification of the low-risk patients.[5]

In this study, using a 100 Hz spleen dedicated TE probe, we validated the accuracy of SSM to screen high-risk esophageal varices among liver cirrhotic patients in Indonesia. Previous studies showed that SSM could reliably rule out high-risk esophageal varices in patients with cirrhosis. A meta-analysis of 17 studies has shown that SSM could help rule out high-risk esophageal varices with pooled sensitivity, specificity, PPV, and NPV of 87%, 66%, 54%, and 88%, respectively. With a pooled sensitivity and NPV more than 85%, it was suggested that SSM could help in ruling out high-risk varices, and therefore, could avoid unnecessary endoscopy.[7] However, most studies included in that meta-analysis did not use spleen-dedicated TE probe. In our study, using a SSM cutoff of 40 kPa, we found that SSM alone had a sensitivity of 86.5% and a specificity of 55.9%. These results were also comparable when using Baveno VII criteria. However, in our study, SSM had lower NPV (73,1%), and when using Baveno VII criteria, the NPV was 75%. This lower NPV could be due to the high prevalence of high-risk varices in our cohort (60%).

According to Baveno VII consensus, dual cutoff values (SSM < 21 and > 50 kPa) can be used to rule out or rule in clinically significant portal hypertension in compensated advanced liver disease due to viral hepatitis.[5] Previous study by Siahaan BS et al. proposed only a single cutoff of SSM to detect esophageal varices among Hepatitis B-related cirrhosis and there was no evaluation for detection of high-risk varices.[13] Therefore, to improve its predictive value, we also evaluated the performance of SSM based on dual cutoff. Applying the 20 kPa cutoff, there was an improvement in sensitivity and NPV (98.1% and 87.5%). Applying the 70 kPa cutoff, the specificity was improved (82.4%) with PPV 81.3%. Based on these results, we can rule-out (SSM < 20 kPa) or rule-in (SSM > 70 kPa) the presence of high-risk varices in cirrhotic patients.

A strength of our study is the validation of dual cutoff SSM using a spleen-dedicated TE probe. Such dual cutoff showed better sensitivity and specificity for ruling out and ruling in high-risk varices compared to Baveno VII criteria. Our study has some limitations. First, this is a single-center study with a high prevalence of high-risk esophageal varices. The prevalence of high-risk esophageal varices might be different across different regions in Indonesia. Therefore, a national multicenter study with a larger sample size involving different regions in Indonesia is needed to validate our findings. Second, the most common etiology of cirrhosis in our cohort was hepatitis B and C virus. As the prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing,[14] future validation study in NAFLD patient population is needed.

CONCLUSION

In conclusion, this study validated the performance of SSM as a non-invasive screening tool for high-risk esophageal varices among cirrhotic patients in Indonesia. In addition, we propose a dual cutoff value of SSM to help rule out and rule in high-risk esophageal varices using a 100 Hz spleen dedicated TE probe.

AUTHOR'S CONTRIBUTION

Saut Horas H. Nababan and Rino Alvani Gani proposed the study. Pitt Akbar, Kemal Fariz Kalista, Chyntia Olivia Maurine Jasirwan, Juferdy Kurniawan, Cosmas Rinaldi A. Lesmana, Andri Sanityoso Sulaiman, Irsan Hasan conducted the study. Gita Aprilicia analyzed the data. All authors contributed to the design of the study, interpreted the results, and write the final manuscript. Saut Horas H. Nababan is the guarantor.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

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CONFLICT OF INTEREST

There is no conflict of interest.

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