Spleen and Liver Stiffness as Noninvasive Predictors of Varices in HBV Cirrhosis

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ABSTRACT

Background: *Esophageal varices (EV) are the most frequent complication of portal hypertension in patients with liver cirrhosis. Due to many reasons, esophagogastroduodenoscopy remains impractical for routine surveillance in everyday practice. Hence, ongoing studies into reliable non-invasive test for predicting EV are still important.*

Methods: *A total of 71 patients with liver cirrhosis due to hepatitis B who underwent endoscopy, spleen stiffness measurement (SSM), and liver stiffness measurement (LSM) between January and April 2023 were enrolled in this study. Diagnostic applicability was assessed using the area under the receiver-operator curve (AUC) to measure and compare the performance of each measurement and combination for predicting EV, as well as to obtain the corresponding optimal prediction value.*

Results: *This study included 71 patients with liver cirrhosis. Among them, 74.6% (53 patients) were classified as Child-Pugh A, 22.5% (16 patients) as Child-Pugh B, and 2.8% (2 patients) as Child-Pugh C. The prevalence of esophageal varices (EV) within the cohort was 71.8%. This study showed that SSM with a cut-off of 38.8 kPa had AUC 0.867 (95% CI: 0.774–0.960) (sensitivity 78.4%, specificity 80%), and LSM with a cut-off of 10.55 kPa had AUC 0.822 (95% CI: 0.701–0.943) (sensitivity 88.2%, specificity 65%).*

Conclusion: *Spleen and liver stiffness measurements demonstrate good performance in predicting EV in patients with liver cirrhosis caused by hepatitis B.*

Keywords: *Esophageal varices, liver stiffness, spleen stiffness*

ABSTRAK

Latar belakang: *Varises esofagus (EV) adalah komplikasi hipertensi portal yang umum terjadi pada sirosis hati. Karena berbagai alasan, esofagogastroduodenoskopi (EGD) masih belum sepenuhnya sesuai untuk pengawasan rutin dalam praktek sehari-hari. Oleh karena itu, penelitian yang bekerja untuk mencari uji non-invasif terbaik dalam memprediksi EV masih penting dikerjakan*

Metode: *Sebanyak 71 pasien sirosis hati terkait hepatitis B yang telah menjalani endoskopi, pemeriksaan kekakuan limpa (SSM), dan pemeriksaan kekakuan hati (LSM), antara Januari–April 2023. Performa diagnostik dinilai oleh area di bawah kurva (AUC) untuk mengukur dan membandingkan performa setiap pemeriksaan dan kombinasinya untuk memprediksi EV dan untuk mendapatkan nilai prediksi optimal yang sesuai.*

Hasil: *Penelitian ini diikuti oleh 71 subyek dengan sirosis hati. Prevalensi Child-Pugh A adalah 74,6% (53 pasien), Child-Pugh B 22,5% (16 pasien), dan 2,8% (2 pasien) dengan Child-Pugh C. Di antara pasien ini, proporsi EV didapatkan 71,8%. Penelitian ini menunjukkan bahwa SSM dengan titik potong 38,8 kPa memiliki AUC 0,867 (95% CI: 0,774–0,960) (sensitivitas 78,4%, spesifisitas 80%) dan LSM dengan titik potong 10,55 kPa memiliki AUC 0,822 (95% CI: 0,701–0,943) (sensitivitas 88,2%, spesifisitas 65%).*

Kesimpulan: *Pengukuran kekakuan limpa dan hati memiliki performa yang baik dalam memprediksi EV pada pasien dengan sirosis hati yang disebabkan oleh hepatitis B.*

Kata kunci: *Varises esofagus, kekakuan hati, kekakuan limpa*

INTRODUCTION

Liver cirrhosis, the end stage of progressive liver disease, remains the most common cause of death related to liver disease worldwide. Global data indicate that the prevalence of decompensated liver cirrhosis cases has reportedly increased, from 5.2 million in 1990 to 10.6 million in 2017.[1] In Indonesia, data from 2020 reported over 1,500 liver cirrhosis patients a year in ten healthcare centers.[2] A study conducted by Kalista et al at Dr. Cipto Mangunkusumo Hospital in 2017 documented 313 patients with liver cirrhosis who underwent endoscopy in the integrated procedure room between January 2016 and December 2017.[3] Another study from the same hospital by Sulaiman et al in 2020 examined 148 patients with liver cirrhosis who underwent endoscopy, revealing that around 57.4% (85 patients) had esophageal varices (EV), with hepatitis B identified as the most common underlying cause, accounting for 52%.[4]

EV are a significant complication and require serious attention as a consequence of portal hypertension.[5] Among patients with liver cirrhosis, the incidence of EV increases nearly 5% annually and the rate of progression from small to large varices is estimated at 5–10%.[5] Currently, Baveno VII recommends endoscopic examination for screening in liver cirrhosis patients if value of liver stiffness measurements (LSM) ≥ 20 kPa or platelet count ≤ 150 x 109 L and spleen stiffness measurements (SSM) ≤ 40 kPa can be used to identify those at low risk for high-risk varices.[6] Despite these refined criteria, endoscopy remains costly and burdensome, particularly due to the need for repeated procedures, which many patients find uncomfortable. Moreover, data suggest that nearly 50% of cirrhotic patients do not develop EV even after 10 years.[7] Therefore, continued research into reliable non-invasive markers for predicting the presence of EV remains crucial.

Various serum and radiological parameters have been investigated for their potential to predict esophageal varices, including the alanine amino transaminase (AST) ratio index score to the platelet count/aspartate to platelet ratio index (APRI), liver stiffness, and spleen stiffness.[8–10] Among these, liver and spleen stiffness measurements have shown better accuracy in identifying EV compared to other non-invasive parameters. Given that hepatitis B remains the most prevalent cause of liver cirrhosis in Indonesia, this study aims to evaluate the diagnostic performance of spleen stiffness measurement (SSM), liver stiffness measurement (LSM), and their combination in detecting EV among affected patients.

METHODS

This was a cross-sectional study with sample groups of liver cirrhosis patients who underwent upper gastrointestinal endoscopy to assess EV, followed by SSM and LSM. Patients were patients diagnosed with liver cirrhosis with hepatitis B as etiology who came to Dr. Cipto Mangunkusumo General National Hospital between January and April 2023. Inclusion criteria were adults aged ≥ 18 years with confirmed liver

cirrhosis who provided informed consent. Exclusion criteria included the presence of hepatocellular carcinoma, recent use of beta-blockers for more than one year, portal vein thrombosis, and refusal to undergo upper gastrointestinal endoscopy.

Transient elastography (TE) measurement was done using FibroScan™ (Echosens 630 Paris, France), a spleen-dedicated fibroscan with a 100 Hz probe. The LSM and SSM were recorded in the supine position after 6–8 hours of fasting using the same fibroscan machine. All measurements were taken on the same day prior to endoscopy. Only procedures yielding at least 10 valid measurements, a success rate of ≥ 60%, and an IQR-to-median ratio < 30% were considered reliable. Liver and spleen stiffness assessments were performed by two certified examiners. To assess inter-observer variability, 25 patients selected at random were evaluated by both operators, each of whom was blinded to the results obtained by the other. The concordance coefficient between inter-observer evaluations was 0.082 for SSM ($p < 0.001$) and 0.796 for LSM ($p < 0.001$), reflecting strong and moderate agreement. In addition to stiffness measurements, basic demographic data (age, gender, medical history) and anthropometric parameters (body weight, height, and body mass index) were recorded. All patients who provided informed consent subsequently underwent upper gastrointestinal endoscopy, performed by experienced staff from the hepatology division. Endoscopic findings were classified based on the presence or absence of esophageal varices.

All statistical analyses were conducted using statistical package for the social sciences (SPSS) for Windows version 25 (SPSS Inc., Chicago, IL, USA). Data were presented as mean and standard deviation (SD), median and interquartile range, and proportions and 95% confidence interval (CI) as appropriate. A p-value of < 0.05 was considered statistically significant. To evaluate the diagnostic performance for predicting esophageal varices (EV), receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUROC) was calculated. Cut-off values were determined based on the point of highest sensitivity and specificity. Sensitivity, specificity, predictive values, and likelihood ratios were calculated for these cut-off points. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No. KET-39/UN2. F1/ETIK/PPM.00.02/20123).

RESULTS

The baseline characteristics of the study participants are presented in **Table 1.** A total of 71 patients with hepatitis B-related liver cirrhosis who met the inclusion and exclusion criteria were enrolled. The mean SSM was 52.5 ± 24.6 kPa, while the median LSM was 21.2 kPa (IQR: 10.4-25.9). Among the participants, 53 patients were classified as Child-Pugh A, 16 as Child-Pugh B, and 2 as Child-Pugh C. The overall prevalence of esophageal varices (EV) in this cohort was 71.8%.

This study showed that SSM has a better performance to predict EV with a cut-off of 38.8 kPa had AUC 0.867 (95% CI: 0.774–0.960) (sensitivity 78.4%, specificity 80%) compared to LSM with a cut-off of 10.55 kPa had AUC 0.822 (95% CI: 0.701–0.943) (sensitivity 88.2%, specificity 65%). The positive predictive value (PPV) for SSM was 90.91, while the negative predictive value (NPV) was 59.26. For LSM, the PPV was 86.54 and the NPV was 68.42. Interestingly, combining SSM and LSM did not improve diagnostic performance beyond SSM alone, with the combined AUC reaching 0.853 (95% CI: 0.741-0.964). The complete results are shown in **Table 2** and **Table 3.**

Table 1. Baseline Characteristics of the Study Population

Characteristic	Result
Age (years), mean (SD)	51.2 (9.2)
Sex, n (%)	
Man	52 (73.2)
Woman	19 (26.8)
Body mass index, median (IQR)	23.12 (20.95–24.8)
Esophageal varices, n (%)	
Present	51 (71.8)
Absent	20 (28.2)
Liver stiffness, median (IQR)	21.2 (10.4–25.9)
Spleen stiffness, mean ± SD	52.5 ± 24.6
Child-Pugh, n (%)	
A	53 (74.6)
B	16 (22.5)
C	2 (2.8)

Table 2. Performance of spleen stiffness and liver stiffness for predicting esophageal varices in liver cirrhosis

	Hepatitis B (n = 71)	
	Spleen stiffness	Liver stiffness
Cut-Off	38.8	10.55
AUROC	0.867 (0.774–0.960)	0.822 (0.701–0.943)
P value	< 0.0001	< 0.0001
Sensitivity	78.4 (64.68–88.71)	88.24 (76.13–95.56)
Specificity	80 (56.34–94.27)	65 (40.78–84.61)
PPV	90.91 (80.44–96.05)	86.54 (77.82–92.17)
NPV	59.26 (45.20–71.95)	68.42 (48.89–83.07)
Accuration	78.87 (67.56–87.67)	81.69 (70.73–89.87)
LR (+)	3.92 (1.61–9.53)	2.52 (1.38–4.62)
LR (-)	0.27 (0.15–0.48)	0.18 (0.08–0.41)

AUROC: area under the ROC curve; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio

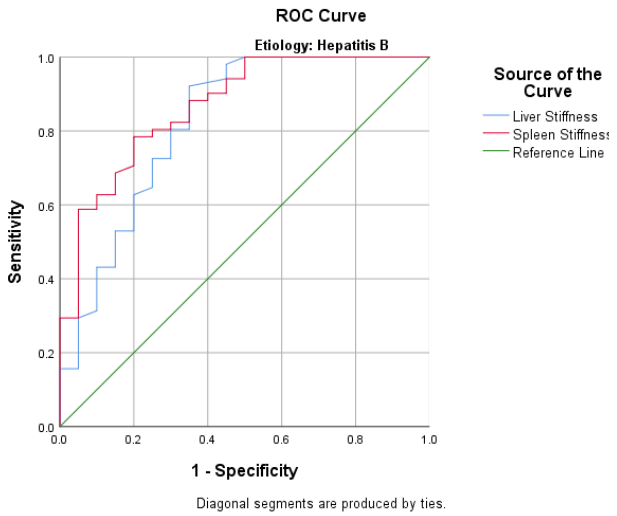

Figure 1. ROC curve spleen stiffness and liver stiffness for predicting esophageal varices in liver cirrhosis

Table 3. Performance combination of spleen stiffness and liver stiffness in predicting esophageal varices in liver cirrhosis

Variables	AUC (CI 95%)	*p* value
Spleen stiffness	0.867 (0.774–0.960)	< 0.0001
Liver stiffness	0.822 (0.701–0.943)	< 0.0001
Spleen stiffness + liver stifness	0.853 (0.741–0.964)	< 0.0001

AUC: area under the curve; CI: confidence interval

DISCUSSION

Liver biopsy remains the gold standard for assessing the severity of liver disease. However, in recent years, non-invasive methods have proven to be reliable measures. These include models for end-stage liver disease (MELD) and Child-Pugh class score (CPC).[11] Based on the CPC score, this study found that Class A was the most prevalent, accounting for 74.6% of the total subjects. This finding aligns with the study by Sulaiman et al, which reported that 49% of patients were classified as Child-Pugh A, followed by 27% in Class B and 24% in Class C.[4] We believe this trend may be attributed to the nature of our study population, which primarily consisted of outpatients undergoing elective endoscopic procedures. These patients were generally in stable condition and benefited from consistent management and surveillance, contributing to preserved liver function.

EV are a common consequence of portal hypertension, with a prevalence of approximately 50% among liver cirrhosis patients. The incidence increases by nearly 5% annually, and the progression rate from small to large varices is estimated at 5–10%.[5] Our study found that the prevalence of EV in patients with liver cirrhosis was 71.8%, which was higher that the 57.4% reported by Sulaiman et al, but closely aligns with the findings of Hong et al (2009), who observed a prevalence of 74.7%.[12] One plausible explanation for this similarity is the etiology of liver disease in our study population, which exclusively included patients with hepatitis B, matching the inclusion criteria of Hong et al's study. In contrast, Sulaiman's study involved a mixed etiology group (hepatitis B, hepatitis C, and non-viral causes). As we know until now hepatitis B viral clearance is hard to achieve because of the unique factor component of this viral. Unlike hepatitis C, which can now be effectively cured with current antiviral therapies, hepatitis B often leads to ongoing inflammation and fibrosis. This persistent disease activity may contribute to the progression of portal hypertension and a higher prevalence of EV.

Endoscopy is the gold standard for the evaluation of EVs; however, on the other hand, it has many side effects and cost burdens in a daily clinical setting. To reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices, several studies evaluated possible noninvasive markers of esophageal varices in patients with cirrhosis. However, the predictive accuracy of such noninvasive markers is still considered to be unsatisfactory, and none of them has been recommended for use in clinical practice so far.[5] One meta-analysis study in the recent year showed liver and spleen stiffness seems to have better accuracy than other non-invasive parameters.[13]

This study found that SSM has a better performance to predict EV, whereas with a cut-off of 38.8 kPa had AUC 0.867 (95% CI: 0.774–0.960) (sensitivity 78.4%, specificity 80%) compared to LS with a cut-off of 10.55 kPa had AUC 0.822 (95% CI: 0.701–0.943) (sensitivity 88.2%, specificity 65%). These findings align with a meta-analysis by Ma et al. (2016), which also highlighted the superiority of SSM over LSM in predicting EV among patients with chronic liver disease. That study reported an AUC of 0.88 (95% CI: 0.85–0.91) for spleen stiffness, compared to 0.81 (95% CI: 0.77-0.84) for liver stiffness. Notably, the 13 studies included in the meta-analysis used varying cut-off values, ranging from 30.3 kPa to 60.5 kPa.[13] Similarly, Shawky et al in 2019 reported consistent results, with spleen stiffness showing an AUC of 0.843 and liver stiffness an AUC of 0.748, although with different cut-off points, 61.25 kPa for spleen stiffness and 33.5 kPa for liver stiffness. One important takeaway from these findings is the diagnostic nuance between the two measurements. At the specified cut-off, spleen stiffness offers higher specificity, making it more reliable for confirming the presence of disease. Meanwhile, liver stiffness, with its slightly higher sensitivity, may be

better suited for screening purposes. Overall, SSM appears to be the more effective tool for diagnosing esophageal varices in patients with liver cirrhosis.

The optimal cut-off that in this study for spleen stiffness was 38.8 kPa. Interestingly, these findings were also different from many studies from several real-world studies. For instance, a meta-analysis revealed a range of cut-off values across different research: Grgurevic et al. reported 30.3 kPa, Sharma et al. 40.8 kPa, and Stefanescu et al. 46.4 kPa. [13] The novelty in our study was the use of Echosens expert 630 with spleen-dedicated probe. This advanced system offers greater accuracy than previous models than the last one with 100 Hz probe that provide measurement up to 100 kPa, which is more reliable because of the stiffness of the spleen is higher than liver. In contrast, studies conducted up to 2021 largely relied on older FibroScan models with 50 Hz probes, which are less precise. [14] When we observed in this study, the difference may correlate with the type of fibroscan (50 Hz or 100 Hz) and the etiology of liver cirrhosis.

In this study, the optimal cut-off for liver stiffness was found to be 10.55 kPa. This result was fairly consistent with the study conducted by Shibata et al in 2016 who obtained good accuracy LSM in predicting EV with an AUC of 0.896 (0.825–0.964) at an intersection of 7.9 kPa (sensitivity 86.4%, specificity 83.1%).[15] Other studies showed a difference cut-off. A study by Stefanescu et al in 2010 obtained an accuracy of liver stiffness for findings of EV at a higher cut point of 19.0 kPa with an unfavorable AUC of 0.656 (95% CI: 0.589–0.718).[16] The results from meta-analyses in different parts of the world also seem to have mixed results with different points of intersection of liver stiffness. A meta-analysis study by Cheng et al in 2018 involving 44 studies found the liver stiffness cut-off point in existing studies ranged from 6.1 kPa to 29.7 kPa in predicting EV in liver cirrhosis.[17] Several factors may explain these differences. First, our study utilized the Echosens 630 FibroScan device with a spleen-dedicated 100 Hz probe, which may yield different results compared to older models. Second, our patient population was relatively homogeneous, with hepatitis B as the predominant etiology. Most participants had been on long-term antiviral therapy, which likely reduced hepatic inflammation and, consequently, liver stiffness, particularly in patients with early-stage cirrhosis.

CONCLUSION

Both spleen stiffness and liver stiffness measurements have a good performance for predicting EV in patients with liver cirrhosis caused by hepatitis B. However, further research is needed regarding the performance of liver and spleen stiffness to predict esophageal varices with a high risk of bleeding, as well as their potential role in predicting recurrent bleeding episodes in cirrhotic patients.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contribution

All authors were involved in the conception, drafting, and approval of the final version of the manuscript.

Data Availability

The data that support the findings of this study are contained within the article.

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