Original Article

Spleen Stiffness as A Predictor of Esophageal Varices in Patients with Cirrhosis of Liver

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Abstract

Background: Current guidelines recommend upper GI endoscopy for detection of esophageal varices (EV) in patients with cirrhosis. Upper GI endoscopy is invasive, so several non-invasive methods for detecting varices were proposed. This study evaluates if spleen stiffness measurement (SSM) by vibration controlled transient elastography (VCTE) using FibroScan can be used as a viable predictor of EV.

Materials and Methods: This study was carried out to evaluate the utility of spleen stiffness measurement in detecting the presence of esophageal varices. Study included 100 patients with cirrhosis attending the inpatient and outpatient department of Gastroenterology of Dhaka Medical College Hospital. All patients underwent liver stiffness and spleen stiffness measurements by VCTE and upper GI endoscopy. According to the endoscopic findings, they were divided into no varix, low-risk varices, and high-risk varices groups. Diagnostic performance of the spleen stiffness cutoff for the cirrhotic population obtained from the ROC curve was evaluated in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy in detecting high-risk EV.

Results: Of the 100 cirrhosis patients, 76 (76%) had EV (low risk varices=34, high risk varices=42). There was a significant difference ($p < 0.05$) in mean spleen diameter, spleen stiffness measurement, and liver stiffness measurement among the no varix, low-risk varices, and high-risk varices groups. A tendency towards increasing spleen stiffness levels was observed with increasing severity of varices (25.87±10.48 kPa in no varix, 46.58±14.03 kPa in low-risk varices, and 77.29±17.59 kPa in high-risk varices). Spleen stiffness cutoff 46.7 kPa has 95.2% sentivety, Sp 81% specificty, 87% accuracy, 78.4% PPV and 95.91% NPV in predicting high-risk varices.

Conclusion: The study result suggests that spleen stiffness is significantly correlated with the presence and severity of esophageal varices. Spleen stiffness measured using VCTE can be useful in diagnosing high-risk varices in patients with cirrhosis.

Keywords: Vibration-controlled transient elastography, Cirrhosis of the liver, Esophageal varices, Spleen stiffness, Liver stiffness.

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Introduction:

Liver cirrhosis, the advanced stage of most chronic liver diseases, affects nearly a billion people worldwide and results in approximately 2 million deaths annually, accounting for 3.5% of all global deaths.[1] Portal hypertension and esophageal varices, which occur in about 40–60% of cases, are two major consequences of the disease course of cirrhosis.[2] Once esophageal varices have developed, the incidence of variceal bleeding is 35%, and mortality is as high as 10-20%.[3]

According to current guidelines, screening endoscopy should be performed on all cirrhotic patients at the time of diagnosis in order to identify those who have varices.[3] After that, patients should have screening endoscopies every two to three years if they have compensated disease and no varices, every 1-2 years if they have small varices, and every year if they have decompensated disease, with or without varices. Upper GI endoscopy is considered the gold standard against which all other tests are compared.[4] Studies have shown that the annual incidence of EV is only 7%, EV incidence is 21% over a 5-year period, and 50% of patients do not acquire esophageal varices 10 years following diagnosis of cirrhosis.[5,6] So, repetitive negative endoscopies would increase the costs of care of newly diagnosed cirrhotic patients. Though endoscopy is generally a safe procedure, it can be unpleasant for patients; there are risks related to conscious sedation, and it is relatively resource-intensive. It might not be economical or convenient to have screening endoscopies on every cirrhosis patient. Instead, identifying high-risk individuals using easily obtainable clinical factors could allow for more cost-effective screening.

Splenomegaly is 60–65% prevalent in patients with liver cirrhosis and portal hypertension.[7] It is typically caused by blood congestion, elevated portal pressure, increased resistance to splenic vein outflow, and increased angiogenesis and fibrogenesis.[8] Using transient elastography (TE), these alterations in fibrogenesis or spleen stiffness can be measured. Non-invasive methods that quantify SSM to detect EVs and their risk of bleeding are gaining more interest lately.[9] Fibroscan evaluates tissue stiffness using the vibration-controlled transient elastography

(VBTE) principle. According to several studies, TE was also connected with the severity of PH and the existence of esophageal varices.[10] It was utilized in chronic liver disorders and demonstrated to accurately predict liver fibrosis in a range of clinical circumstances.[11] Recently, FibroScan started to be used for the assessment of spleen stiffness in cirrhotic patients. Because spleen stiffness better represents splanchnic flow than liver stiffness, previous investigations using transient elastography have revealed that spleen stiffness has good diagnostic accuracy in predicting portal hypertension and esophageal varices. This study was designed to investigate the efficacy of spleen stiffness, as determined by TE, in predicting the presence and size of esophageal varices in patients with cirrhosis of the liver.

Materials and Methods:

This descriptive cross-sectional study included a total of 150 patients (aged >18 years) with cirrhosis from the Gastroenterology department of Dhaka Medical College Hospital between November 2022 to March 2024. The diagnosis of cirrhosis was made based on clinical, biochemical, and imaging (ultrasound) evidence. Patients were excluded from the study if they have moderate to severe ascites, history of treatments for portal hypertension (β-blocker therapy, or endoscopic therapies, splenectomy, partial splenic embolization, trans-jugular intrahepatic portosystemic shunt, balloon-occluded retrograde transvenous obliteration), acute/ chronic liver failure, HCC/SOL in liver, active gastrointestinal bleeding, portal vein thrombosis, biliary obstruction and acute cholangitis, other end organ failure i.e., renal, cardiac or respiratory failure or not willing to be included in the study. Among the 150 patients, 50 were excluded. All patients underwent TE for measurement of liver stiffness and spleen stiffness, and upper GI endoscopy for evaluation of esophageal varices. Routine biochemical parameters were also recorded for every patient, which included hemoglobin, platelet count, INR, ALT, albumin, bilirubin, serum creatinine, and relevant workup for evaluation of the cause of CLD. All patients also underwent an ultrasonogram, and spleen and liver sizes were recorded. Informed written consent was taken from all patients. The study was approved by the ethical review committee of Dhaka Medical College.

Vibration-controlled transient elastography (VCTE) was performed on each patient, after at least 3 hours of fasting, using FibroScan 630 Xpert. After the liver was localized in each patient and the probe positioned correctly, at least 10 valid measurements on the same spot were taken. LSM>12.5 kPa was marked as cirrhosis. After the spleen was localized in each patient and the probe positioned correctly, at least 10 valid measurements on the same spot were taken for spleen stiffness measurement.

Esophageal varices were evaluated for each patient, using upper gastrointestinal endoscopy, and were classified into three groups, according to the expanded Baveno VI criteria.[12] Group 1 included patients with no esophageal varices, Group 2 patients with low risk esophageal varices (varices that had a thickness of less than 5 mm) and Group 3 patients with high risk varices needing treatment (VNT- either large esophageal varices that had a thickness of more than 5 mm or varices displaying any signs of a high risk of bleeding: red wales, cherry red spots).

All the data collected were analyzed and correlated. Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS, version 25). Descriptive analysis was performed on participants' socio-demographic characteristics. The Kruskal-Wallis test was used to analyze the clinical characteristics of the study population with cirrhosis. The correlation between endoscopic findings and SSM values were obtained using Kruskal Wallis test. Variables were considered statistically significant if $p < 0.05$. To evaluate the diagnostic efficiency SSM for the detection of EV, an analysis of the area under the ROC curve (AUROC) was performed. The value of the highest point of the Youden index was taken as the cut-off point. The diagnostic efficiency of this cut-off value of SSM for the detection of large EV was calculated using the comparative analysis and ROC curve.

Results:

This study included a total of 100 patients, out of which 67 were male and 33 were female. Mean BMI was 20.55 ±3.34 kg/m2. Most of the people (n=46) are middle-aged (40- 59 years) (Table 1).

Table 1. Distribution of patients according to socio-demographic characteristics (n=100)

Variables	Number of Patients (Percentage)
Sex	
Male	67 (67)
Female	33 (33)
Age (years) Mean±SD:	48.22±12.23
18-39	32 (32)
40-59	46 (46)
>60	22 (22)
BMI (kg/m ^{2}) Mean±SD:	**20.55±3.34**
<18.1	4 (4)
18.5 -23	54 (54)
23-27.5	38 (38)
>27.5	4 (4)
Place of living	
Rural	54 (54)
Urban	46 (46)

The etiologies of cirrhosis were hepatitis B (59 patients), NAFLD (11patients), hepatitis C (10 patients), autoimmune (1 patient), alcohol (1 patient) and cryptogenic (18 patients) (Figure 1).

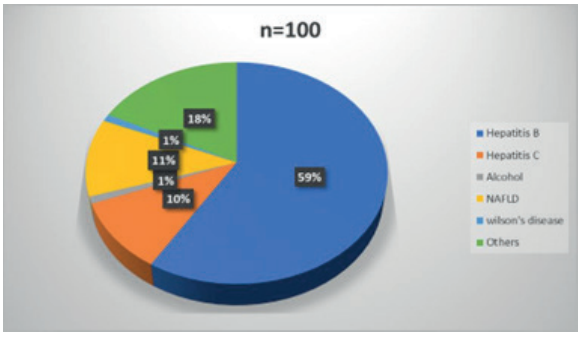

Figure 1: Distribution of patients according to etiology of cirrhosis (n=100)

Univariate analysis identified several factors that were associated with the size of varices, including hemoglobin, platelet count, SGPT, serum albumin, INR, Spleen size, liver stiffness, and spleen stiffness ($p<0.05$). Higher values of spleen stiffness, spleen size, and lower values of serum albumin and platelet counts were observed in the high-risk varices group, as listed in Table 2.

Table 2: Distribution of patients according to clinical and biochemical characteristics (n=100)

Variable	Esophageal varices			*p* value
	No varix (n=24)	Low risk varices (n=34)	High risk varices (n=42)	
Hemoglobin (g/dl)	11.75±2.07	11.37±1.99	10.23±1.86	.008[s]
Platelet($\times10^3$/mm^3)	207.71±87.96	151.03±75.12	109.51±65.52	.000[s]
SGPT(IU/ml)	73.11±46.20	57.63±36.55	50.57±36.22	.048[s]
Bilirubin (mg/dl)	1.35±1.36	1.28±0.93	1.93±3.41	.392
Albumin (g/dl)	3.68±0.78	3.20±0.64	3.10±0.56	.003[s]
INR	1.09±0.13	1.34±0.31	1.31±0.31	.000[s]
Creatinine (mg/dl)	1.00±0.26	1.07±0.35	0.95±0.21	.611
Spleen size (cm)	10.37±2.26	12.52±2.13	13.54±2.41	.000[s]
Liver Stiffness	26.23±18.20	44.93±20.34	41.362±21.17	.001[s]
Spleen Stiffness	25.87±10.48	46.58±14.03	77.29±17.59	.000[s]

There was a stepwise increase in spleen stiffness values with increased risk of varices among the study population with cirrhosis. The population with low-risk varices had higher SSM than those with no varices (46.58±14.034 vs 25.87±10.48), while those with high-risk varices had an even higher SSM than those with low-risk varices (77.29±17.59 vs 46.58±14.034) (Figure 2). This difference of SSM among the no varices, low risk varices, and high risk varices groups was significant ($p<.05$) (Table 2).

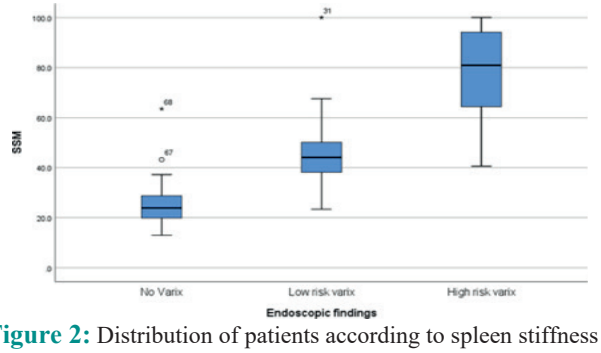

Figure 2: Distribution of patients according to spleen stiffness esophageal variceal status (n=100).

Our study showed that SS measured using VCTE is a good method of predicting high-risk esophageal varices (AUROC = 0.942, CI 95%:.898-.987). A spleen stiffness cut-off value of 46.7 kPa using the highest Youden index could exclude EV with 95.2% sensitivity and 81% specificity. Positive predictive value was 78.4% and negative predictive value was 95.91% with an accuracy of 81% (Figure 3 and Table 3).

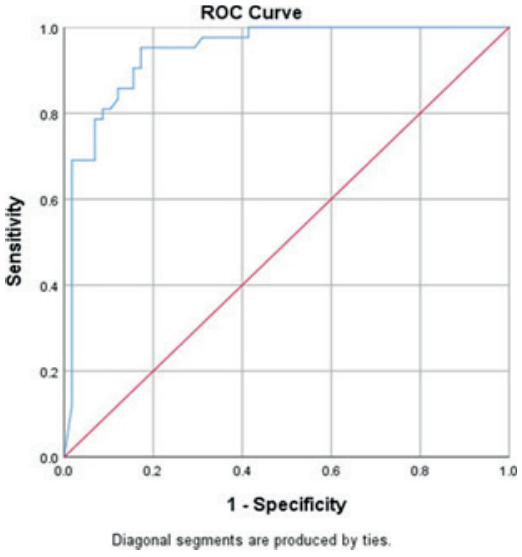

Figure 3: Area under the receiver operating curve (AUROC) analyses spleen stiffness in predicting the presence of high-risk esophageal varices.

Table 3: Cut of value, Sensitivity, specificity, and AUC from ROC curve by spleen stiffness for predicting high-risk varices in the study population with cirrhosis

	AUC	Cutoff value (kPa)	Sensitivity (%)	Specificity (%)	*p* value	95% CI
Spleen stiffness	.942	46.7	95.2	82.8	.000[s]	.898-.987

Discussion:

Multiple observations of our study were significant, and many of them matched with the previous studies published in the literature. One hundred patients with cirrhosis of the liver underwent transient elastography for measurement of liver and spleen stiffness. The study populations with cirrhosis were further divided into three groups according to their upper GI endoscopy findings: No varix group (n=24), low risk varix group (n=34), and high risk varix (n=42) group. Among the study population, 67 (67%) were male and 33 (33%) were female. Most of the people (n=46) were middle-aged (40-59 years). Most of the patient (54%) had a BMI within 18.5-23 kg/m2. Mean BMI was 20.55 ±3.34 kg/m2. Gomes and Ali., conducted a study on the Bangladeshi population where 100 patients with cirrhosis were included.[13] Socio-demographical characteristics of cirrhotic patients were consistent with this study. Most of the study population in this study suffered from Hepatitis B (59%), 11% of participants suffered from NAFLD, and 10% suffered from Hepatitis C. Total 18% of participants did not have hepatitis B, hepatitis C, NAFLD, or alcoholic related liver cirrhosis. Al Mahtab et al., also found that Hepatitis B virus was the most common cause (53.2%) of cirrhosis, followed by NASH in 18.8% and cryptogenic (16.7%) patients in their study.[14] Most of the study population with cirrhosis were CTP class A (80%), and 20% were CTP class B, and none were CTP class C. This was due to the exclusion criteria of our study, which excluded all patients with

moderate to severe ascites. Regarding the clinical characteristics of the study population with cirrhosis, significant differences were observed in spleen size, liver stiffness, and spleen stiffness measurement values among the no varix, low-risk varices, and high-risk varices groups ($p< .05$). These findings align with a study conducted by Fierbinteanu-Braticevici in 2019.[15] Similarly, in a study by Wang et al., in LSM and SSM values differed significantly between the no varices, moderate esophageal varices, severe esophageal varices, and esophageal variceal bleeding groups.[16] Furthermore, Sharma et al., also found significant differences in spleen diameter, LSM, and SSM values between the no esophageal varices and esophageal varices groups.[17]

There was a stepwise increase in spleen stiffness values with increased risk of varices among the study population with cirrhosis. The population with low-risk varices had higher SSM than those with no varices (46.58±14.034 kPa vs 25.87±10.48 kPa), while those with high-risk varices had an even higher SSM than those with low-risk varices (77.29±17.59 kPa vs 46.58±14.034 kPa). This pattern of increasing SSM with increased risk of varices is also observed in studies conducted by Wang et al[16], Fierbinteanu-Braticevici et al[15] and Sharma et al[17] This difference of SSM among the no varices, low risk varices and high-risk varices group was significant ($p<.05$).

Several studies have evaluated SSM measured by transient elastography as a non-invasive method of predicting esophageal varices. Like our study, Sharma et al., 2013 found that a SSM cutoff of 40.8 kPa with AUROC 0.898 had 94% sensitivity and 76% specificity.[17] The study of Anta et al., 2018 had an AUROC curve of 0.8 for a cut-off value of 48 kPa, with 87% sensitivity and 69% specificity.[18]

Our study showed that SS measured using VCTE is a good method of predicting high-risk esophageal varices (AUROC = 0.942, CI 95%:.898-.987). A spleen stiffness cut-off value of 46.7 kPa using the highest Youden index could exclude EV with 95.2% sensitivity and 81% specificity. In this study, the diagnostic performance of SSM was evaluated, revealing a sensitivity of 95.2%, specificity of 81%, and accuracy of 87%. These findings suggest that SSM has high sensitivity (95.2%) in correctly identifying positive cases of high-risk varices. The specificity of 81% indicates that the SSM has a moderately high ability to correctly identify individuals without the high-risk varices. The overall accuracy of 87% suggests that SSM has a high level of accuracy in diagnosing high-risk varices. In this study, positive predictive value was 78.4% and negative predictive value was 95.91%. Overall, these results indicate that SSM has shown satisfactory results in diagnosing high-risk varices, with reasonably good sensitivity and negative predictive value. Our result was almost similar to previous studies conducted to find the diagnostic efficacy of SSM in detecting varices. Rizzo et al. reported sensitivity of SSM in detecting high-risk varices to be 96.4%, specificity 88.5%, positive predictive value 90%, and negative predictive value to be 96%.[19]

Conclusion:

In conclusion, this study evaluated the role of SSM in predicting esophageal varices in cirrhotic patients. Here SSM has shown satisfactory result in predicting presence of esophageal varices, demonstrating reasonably acceptable sensitivity (95.2%), negative predictive value (95.91%) and accuracy (87%), along with moderate specificity (81%) and positive predictive value (78.4%) in detecting high risk varices. However, this study was a single-center study with a small sample size, which may limit the generalizability of the findings to other populations or different healthcare settings. Further study with a large sample size from multiple centers is recommended.

Conflicts of Interest: There is no conflict of interest.

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