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Original Article

Spleen Stiffness Measurement as Non-Invasive Surrogate for Esophageal Varices in Chronic Liver Disease

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Abstract

Background
In patients with chronic liver diseases, liver and spleen stiffness measurement by elastography is the most recent available noninvasive tool. However, the accuracy for prediction of esophageal varices has been inconsistent across various studies. So, this study was done to evaluate the diagnostic performance of spleen stiffness measurement for detecting esophageal varices.

Materials and Methods
This descriptive cross-sectional study was done from 19 March to 30 June 2019. Participants who met inclusion and exclusion criteria were consecutively enrolled for the study and underwent upper gastrointestinal endoscopic examination along with measurement of liver and spleen stiffness by fibroscan.

Results
A total of 78 patients were enrolled. Mean age (±SD) was 49.79 (±10.92) years. Out of 78 patients, 58 (74.4 %) had esophageal varices. Among patients with varices, Small esophageal varices were present in 44.8 % (26) and large esophageal varices were present in 55.2 % (32). Liver stiffness higher than 21.7 kPa was found to detect patients with large esophageal varices and the area under the receiver operating curve being 0.79 (95% confidence interval: 0.69 – 0.89); p<0.001. It had sensitivity of 100.0% and specificity of 63% in predicting the presence of large esophageal varices. While, spleen stiffness having a cutoff value of 40 kPa with the area under the receiver operating curve being 0.98 (95% confidence interval: 0.96 – 1.00); p<0.001, had sensitivity of 100.0 % and specificity of 87.0 % in predicting the presence of large esophageal varices.

Conclusion
Spleen stiffness measurements by transient elastography predict large esophageal varices better than liver stiffness measurements.

Keywords: *Elastography, Esophageal varices, Fibrosis, Liver diseases, Portal hypertension*

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Introduction

Chronic liver disease (CLD) refers to diffuse involvement of liver parenchyma due to various etiologies like chronic viral infections, metabolic, immunologic, toxic or genetic, lasting more than 6 months with a propensity to inflammation, followed by fibrosis and ultimately cirrhosis and portal hypertension (PH). Studies using transient elastography (TE) to measure liver stiffness (LS) have acceptable diagnostic performance in grading hepatic fibrosis and in detecting clinically significant portal hypertension (CSPH) [1,2].

According to Baveno consensus VI, screening esophagogastroduodenoscopy (EGD) can be avoided in patients with LS < 20kPa and platelet count >150,000 /ul [3]. Nevertheless, the role of LS alone in predicting esophageal varices (EV) is controversial due to unsatisfactory diagnostic accuracy and lack of consistent results [4]. In addition to formation of EV, PH leads to passive congestion and tissue hyperplasia of spleen that result in increased spleen stiffness (SS) [5].

So, the aim of the study is to evaluate whether the SS measured by TE/ Fibroscan would be a simpler, accurate and noninvasive method for detection of EV in CLD patients.

Materials and Methods

This was a hospital based descriptive, cross-sectional analytical study conducted at Hepatology Unit of Bir Hospital from 19 March to 30 June 2019. The study was started after acquiring approval from the Institutional Review Board of National Academy of Medical Sciences and written consent was taken from the enrolled patients.

All patients diagnosed as CLD after evaluation were included. The diagnosis of CLD was based on combination of history, physical, laboratory, imaging diagnosis and/or liver biopsy. Ultrasound (Sonosite) findings suggestive of CLD/ cirrhosis [6] were noted. Those included nodular surface or irregular margin of liver with dull edge, coarse echo texture and increase portal vein diameter ≥ 12 mm. Presence or absence of ascites was also recorded. Patients with active GI bleeding, hepatocellular carcinoma and with focal liver lesions were excluded. Patients with ascites of grade 2 &3, BMI > 30 kg/m^2, splenic parenchymal thickness of <4 cm at ultrasound, aminotransaminases flare, i.e., AT > 5 X ULN, age < 18 years old were also excluded. The minimum sample size was calculated to be 73, using the formula $N=Z^2 \times p \times q / e^2$ with 10 % margin of error and prevalence of varices of 75 %.

Venous blood sample was taken for measurement of complete blood profile including mean corpuscular volume, hemoglobin, platelet count, serum levels of alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin and Prothrombin Time/International Normalized ratio. Other relevant investigations were done as required. All patients underwent EGD (Fujinon EPX 2500) after overnight fasting. The presence and severity of EVs was recorded. Esophageal varices were graded as small esophageal varices (straight, <5 mm) and large esophageal varices (tortuous >5 mm) according to AASLD guideline [7].

Liver Stiffness measurement was done as per standard protocol. After 6 hours fasting, patients underwent TE using the FibroScan® Compact 530 (Echosens), which consists of an ultrasound transducer probe mounted on the axis of a vibrator. The tip of the transducer (M-probe) was covered with a drop of gel and placed perpendicularly in the intercostal space, with the patient lying in dorsal decubitus position with the right arm in maximal abduction. The median value of 10 successful measurements was kept as a representative of the LS, according to the manufacturer's recommendations and previous evidence: interquartile range (IQR) lower than 30% of the median value and success rate of at least 60% [8]. Spleen stiffness values was obtained using the FibroScan in the same setting, aided with USG. With the patient in a supine position with maximal abduction of the left arm, the transducer was placed in the left intercostal spaces, usually on the posterior axillary line or directly over the palpable spleen, just below the costal space, the measurement was taken after instructing the patient to hold their breath. To assess the reproducibility of SS measurement, a preliminary study on 34 healthy subjects were also performed to find the normal median value of SS.

A proforma was used to collect the data from the patients which was entered in the Microsoft excel spreadsheet. Continuous variables following normal distribution was summarized using mean and standard deviation whereas continuous variables not following the normal distribution (skewed data) was summarized using median and interquartile range (IQR). Categorical variable was summarized using number and percentage. A p-value of 0.05 was taken as statistically significant result. Receiver Operating Characteristics (ROC) curve was fitted to find the cut-off value of LS and SS for presence of any EV as well as presence of LEV in the sampled population. Area Under Curve (AUC) determined for presence of large varices for LS and SS was

compared using Z-test. These analyses were performed in STATA 13 MP, Easy R 1.48 software and SPSS V25.0

Results

A total of 78 CLD patients of various etiology were included. The mean age was 49.79 (±10.92) years. There were 58 (74.4%) males and 20 (25.6%) females showing male preponderance. The laboratory parameters of 78 patients are shown in Table 1.

Table 1: Laboratory parameter of participants

Parameters (mean ± SD)	Esophageal varices		p value
	With EV (n=58)	Without EV (n=20)	
Hemoglobin, gm/dl	11±2	13±1.6	0.001*
Platelet /µL	139879±69742	149850±42011	0.450**
AST, IU/L	69±40	62±41	0.512*
ALT, IU/L	47±33	71±34	0.008*
INR	1.2±0.2	1.07±0.1	0.001**
Creatinine, mg/dl	0.9±0.5	0.8±0.2	0.960*

* Independent samples t-test, ** Welch t-test SD: standard deviation, EV: esophageal varices, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio of 78 patients, 58 (74.4 %) had EV and 20 patients (25.6 %) had no varices in EGD. Among 58 patients with EV, SEV was present in 44.8 % (26) patients and LEV was present in 55.2 % (32) patients.

Forty-one healthy age and sex matched apparently healthy volunteers underwent liver stiffness and spleen stiffness measurements. Seven (8.6 %) patients had an inconclusive SS measurement, even after using XL probe and were not included in the analysis. The reasons were either unable to obtain at least 10 valid measurements, invalid measurements displayed (could be due to BMI >30 kg/m^2, spleen anteroposterior diameter < 4 cm or unexplained reason). Thus, the data of 34 healthy volunteers were analyzed. Of 34 healthy volunteers, Median (IQR) values of LS and SS was 4.75(1.35) and 20.4(9.3) kPa respectively. Of 78 patients, Median (IQR) values of LS and SS was 28.5(41.23) and 39.3(35.25) kPa respectively. The difference was statistically significant; p-value is <0.001.

Median (IQR) values of LS in patients with and without EV were 35.20(35.93) kPa and 9.15 (6.20) kPa, respectively and the difference was significant. Similarly, Median (IQR) values of SS in patients with and without EV were 49.70(35.03) kPa and 21.10(7.6) kPa, respectively and the difference was significant. (Table 2)

Table 2: Median (IQR) values of LS and SS in patients with or without esophageal varices

	Total (n=78)	Esophageal varices		p value
		With varices n= 58	Without varices n= 20	
LS (kPa)	28.5 (41.23)	35.20 (35.93)	9.15 (6.20)	<0.001*
SS (kPa)	39.3 (35.25)	49.70 (35.03)	21.10 (7.6)	<0.001*

* Mann-Whitney U test

Median (IQR) values of LS in patients with SEV and LEV was 26.55 (45.65) kPa and 40.20 (36.03) kPa, respectively and the difference was statistically significant.

Median (IQR) values of SS in patients with SEV and LEV was 32.30 (11.48) kPa and 62.25 (15.88) kPa respectively and the difference was significant (Table 3).

Table 3: Difference in LS and SS in patients with SEV vs. LEV

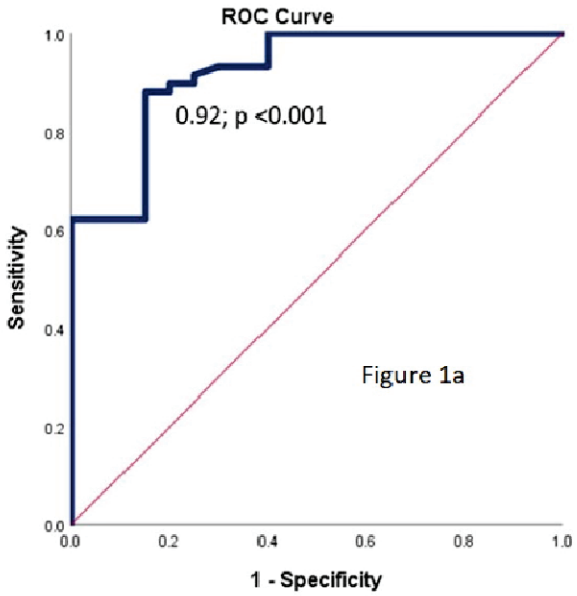
Parameters	Small EV (n=26)	Large EV (n=32)	p value
LS (kPa)	26.55 (45.65)	40.20 (36.03)	0.033
SS (kPa)	32.30 (11.48)	62.25 (15.88)	0.000

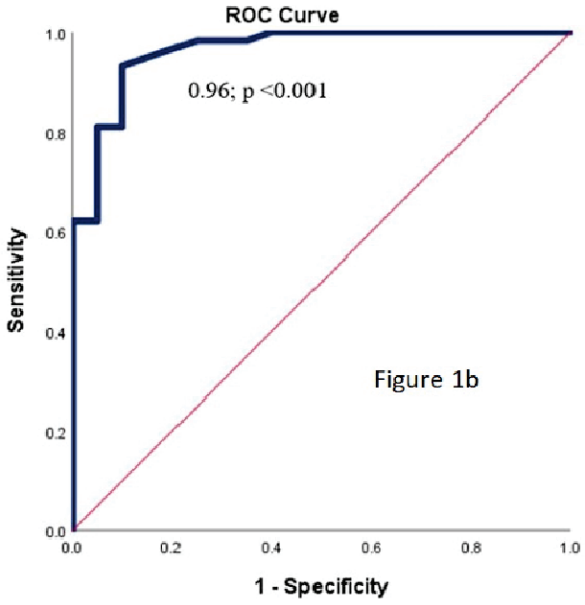
Liver Stiffness higher than 10.4 kPa was found to detect patients with any type of EV and the area under the ROC curve being 0.92 (95% CI: 0.85 – 0.98); p<0.001. It had SN (100.0%), SP (86. 21%), +LR (7.25.00), -LR (0.00) in predicting the presence of any EV. (Figure 1a)

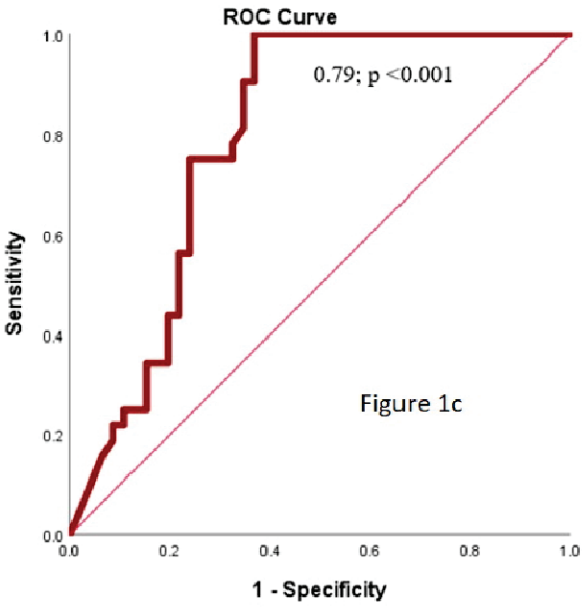
Spleen stiffness higher than 26.0 kPa was found to detect patients with any type of EV and the area under the ROC curve being 0.96 (95% CI: 0.91 – 1.00); p<0.001 and had SN (96.2 %), SP (76.0 %), LR+ (4.0064), LR- (0.0506) in predicting the presence of EV. (Figure 1b)

Liver stiffness higher than 21.7 kPa was found to detect patients with LEV and the area under the ROC curve being 0.79 (95% CI: 0.69 – 0.89); p<0.001. It had SN (100.0%), SP (63%), +LR (2.70), -LR (0.00) in predicting the presence of LEV. (Figure 1c)

Spleen stiffness having a cutoff value of 40 kPa with the area under the ROC being 0.98 (95% CI: 0.96 – 1.00); p<0.001, had SN of 100.0 % and SP of 87.0 % +LR (7.69), -LR (0.03) in predicting the presence of LEV. (Figure 1d)







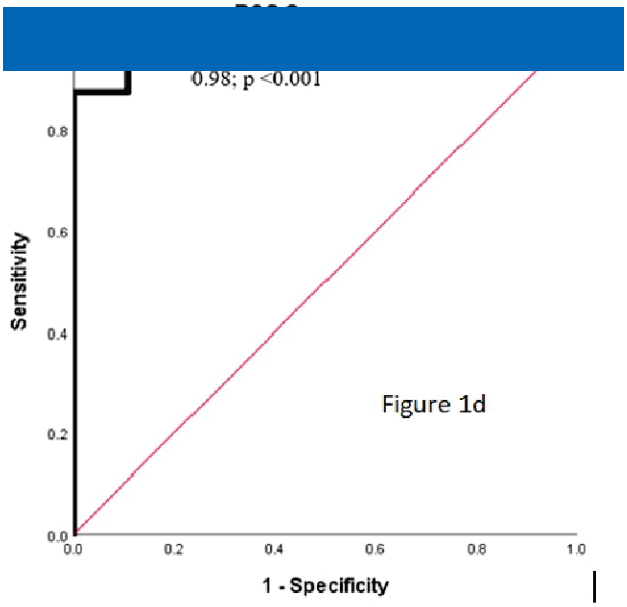


Figure 1: ROC Comparison between liver stiffness and spleen stiffness measurements in predicting large esophageal varices

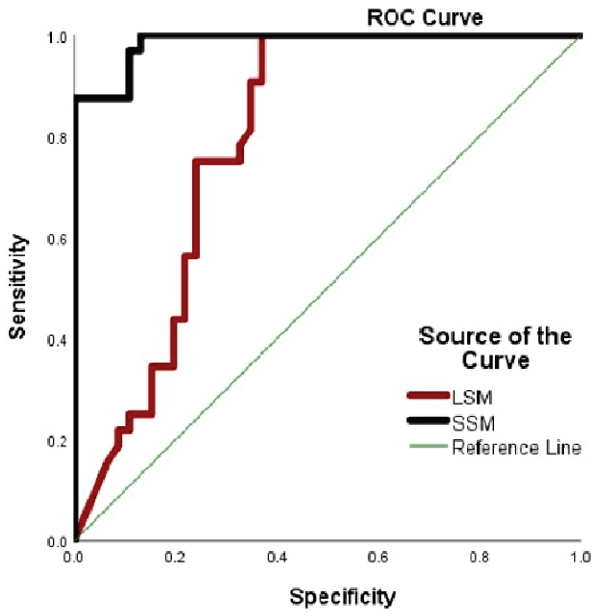


Figure 2: Comparison of ROC between LS and SS measurements in predicting large EV

Table 4: Comparison of ROC between LS and SS measurements in predicting large EV

	95 % Confidence Interval	p-value
Liver Stiffness (LS)	0.79 (0.69 – 0.89)	<0.001
Spleen Stiffness (SS)	0.98 (0.96 – 1.00)	<0.001

Discussion

There has been a large number of studies on LS by transient elastography. Considering all the results and the validations until now, it would be

fair to say that LS measurement shows acceptable diagnostic performance in grading hepatic fibrosis and in detecting CSPH [1,2]. But regarding the prediction of varices, its role is still controversial. Liver stiffness well reflects the structural (fibrosis/cirrhosis) component of PHTN but it lacks in delineating the dynamic (vascular) component of PHTN [5]and it is where SS comes into play. Since the publication of study by Talwalkar et al. [9] in 2009, which showed a highly significant correlation between liver and spleen stiffness in patients with PHTN, there has been increasing interest to see whether SS can be a potential surrogate marker for PHTN.

In this study, liver stiffness higher than 10.4 kPa was found to detect patients with any type of EV and the area under the ROC curve being 0.92 (95% CI: 0.85 – 0.98); p<0.001. It had SN (100.0%), SP (86.21%), +LR (7.25.00), -LR (0.00) in predicting the presence of any EV. Reviewing literature of several studies revealed that the cutoff value of LS in predicting any EV ranges from 17 kPa to 28 kPa, with SN range; 71% to 95%, SP range; 43% to 97.9%, positive likelihood ratio range; 1.4 to 22.6, negative likelihood ratio range; 0.36 to 0.09, diagnostic accuracy range; 71% to 88% and AUROC range from 0.70 to 0.95 [5, 10-22].This wide variation of results between studies is likely due to following factors. Firstly, as explained above, studies enrolled heterogenous groups of patients of various etiology. Secondly, the assessment of size of varices is rather subjective and, in many studies, no details were provided regarding the quality of this assessment (double observers for each endoscopy, assessment of the degree of agreement between the endoscopists). Thirdly, the difference in prevalence of the disease and population may have played a role as well.

In this study, Spleen stiffness higher than 26.0 kPa was found to detect patients with any type of EV and the area under the ROC curve being 0.96 (95% CI: 0.91 – 1.00); p<0.001 and had SN (96.2 %), SP (76.0 %), LR+ (4.0064), LR- (0.0506) in predicting the presence of EV. Several studies revealed that the cutoff value of SS measurement in predicting any EV ranges from 40 kPa to 65 kPa, with SN range; 65% to 94%, SP range; 61% to 96%, positive likelihood ratio range; 1.7 to 17, negative likelihood ratio range; 0.6 to 0.08, diagnostic accuracy range; 80% to 87% and AUROC range from 0.70 to 0.97 [5,10-14,17]. This wide variation of results between studies is likely due to factors explained above. In a recent meta-analysis by Ma et al. [23] with a total of 16 studies (n=1892), In detection of any EV, the summary ROC curve values of LS and SS were 0.81 (95% CI: 0.77±0.84) and 0.88 (95% CI: 0.85±0.91) respectively, and the results had statistical significance (P<0.01). The diagnostic odds ratio of SS (25.73) was significantly higher than that of LS (9.54). The study concluded that SSM was superior to LSM for the diagnosis of any degree of EV, suggesting that SSM may help selecting the patients with advanced liver disease who need to receive an upper gastrointestinal endoscopy screening. Most of the studies included in this meta-analysis used TE to assess LSM und SSM (10/16 studies),

In Summary, the optimal cut-off of liver stiffness and spleen stiffness for predicting varices remains to be defined.

It seems, LS shows a poor correlation with HVPG values ≥ 12 mm Hg [19] and could not differentiate patients with small vs. large varices [5,15]. In this study, LS higher than 21.7 kPa was found to detect patients with LEV and the area under the ROC curve being 0.79 (95% CI: 0.69 – 0.89); p<0.001. It had SN (100.0%), SP (63%), +LR (2.70), -LR (0.00), in predicting the presence of LEV. Calvaruso et al. [12] studied 96 patients of compensated hepatitis C virus related cirrhosis. In his study, LS higher than 19 kPa was found to detect patients with LEV and the area under the ROC curve being 0.71 (95% CI: 0.61-0.80). It had SN (72%), SP (55%), +LR (1.6) and -LR (0.5) in predicting the presence of LEV. However other prospective and retrospective studies (Table 5) have given higher cutoffs ranging from 38 to 48 kPa for predicting the presence of LEV with ROC ranging from 0.76 to 0.77 [21,24].

Table 5: Summary of studies showing characteristics of the diagnostic performance of LS for predicting LEV

	Cut-off (kPa)	n	SN (%)	SP (%)	LR+	LR-	PPV	NPV	AUROC
Calvaruso et al[12]	19	96	72	55	1.6	0.5	38	84	0.71
Stefanescu et al[24]	38	90	89	56	2.13	0.56	70	62	NA
Kazemi et al[18]	19.0	165	91	60	2.3	0.14	48	95	0.84
Pritchett et al[20]	19.8	211	91	56	2.1	0.16	91	55	0.76
Bureau et al[21]	29.3	89	84	71	2.9	0.22	NA	NA	0.76
This study	**21.7**	**78**	**100**	**63**	**2.7**	**0.00**			**0.79**

On the other hand, SS measurements seems to have better predicting ability for the presence of LEV. In almost all the studies till date, it has shown this result. In study by Calvaruso et al. [12], SS having a cutoff value of 54 kPa with the area under the ROC being 0.82 (95% CI: 0.70 - 0.86) had SN of 80 % and SP of 70 % +LR (2.0) and -LR (0.3), in predicting the presence of LEV. In our study, SS having a cutoff value of 40 kPa with the area under the ROC being 0.98 (95% CI:

0.96 – 1.00); p<0.001, had SN of 100.0 % and SP of 87.0 % +LR (7.69), -LR (0.03) in predicting the presence of LEV (Table 6). Spleen stiffness predicts LEV better than LS.

We observed that the diagnostic performance of SSM was better in comparison to LSM for prediction of LEV but yet cutoffs varices between several studies, between the western and eastern studies as well. This observed difference is related potentially to differences in body size and body habitus across these populations and most of all the lack of homogeneity in patients enrolled in the study.

Table 6: Summary of studies showing characteristics of the diagnostic performance of SS for predicting LEV

	Cut-off (kPa)	n	SN (%)	SP (%)	LR+	LR-	PPV	NPV	AUROC
Calvaruso et al[12]	54	96	80	70	2.0	0.3	47	90	0.82
Stefanescu et al[24]	53	90	89	51	1.83	0.21	67	81	NA
This study	**40**	**78**	**100**	**87**	**7.69**	**0.03**			**0.98**

Conclusion

Transient elastography measured by Fibroscan is a useful tool in assessment of patients with chronic liver diseases. Spleen stiffness measurements by transient elastography predicts large esophageal varices better than liver stiffness measurements.

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Conflict of interest: None

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