



Splenic and Liver Elastography in Prediction of Esophageal Varices and Variceal Severity in Patients with Chronic Liver Disease: A Diagnostic Validation Study

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J Gastrointestinal Abdominal Radiol ISGAR

Abstract

Keywords

- ▶ liver stiffness
- ▶ splenic stiffness
- ▶ chronic liver disease
- ▶ shear wave elastography
- ▶ esophageal varices
- ▶ upper gastrointestinal endoscopy
- ▶ ultrasonography

Objective The aim of this study was to assess the value of shear wave elastography (SWE) to predict the presence of esophageal varices (EVs) and to predict high-grade EV in patients with chronic liver disease (CLD).

Methods A cross-sectional observational study was conducted. One hundred twenty-one CLD patients were recruited. Liver stiffness (LS) and splenic stiffness (SS) were measured using SWE.

Results Evaluation of LS is superior to SS in predicting the presence of EV. Evaluation of SS is more valuable than LS in grading EV.

Conclusion LS and SS have good diagnostic performance in predicting and grading varices. SWE is simple to incorporate into standard ultrasonography assessments in patients with CLD. SWE can be used as an adjunct to upper gastrointestinal endoscopy to screen and monitor CLD patient.

Introduction

Progressive deterioration of liver functions over a period of at least 6 months denotes chronic liver disease (CLD). CLD can be caused by a wide variety of factors, ranging from alcohol abuse and infections to congenital metabolic and autoimmune disorders. CLD leads to fibrosis and ultimately to cirrhosis of the liver parenchyma because of inflammation and simultaneous destructive and regenerative processes.¹

CLD leads to portal hypertension and subsequent recruitment of portosystemic collaterals. Esophageal varices (EVs) are dilated submucosal distal esophageal veins, acting as portosystemic collaterals. Rupture and bleeding of EV bears

high mortality in CLD patients. Upper gastrointestinal endoscopy (UGIE) is the gold standard for detecting EV.²

Shear wave elastography (SWE) is a novel technique. It can quantify the changes in liver stiffness (LS) and splenic stiffness (SS) occurring due to hemodynamic and microscopic changes in the course of CLD.

The objective of the study is to assess the value of SWE to predict the presence of EV and to predict high-grade EV in patients with CLD.

Material and Methods

This was a cross-sectional diagnostic validation study. It was conducted over a period of 18 months, from January 2021 to

DOI <https://doi.org/10.1055/s-0044-1790233>.
ISSN 2581-9933.

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June 2022. The institutional ethics committee permission was obtained. A total of 121 patients, diagnosed with CLD, visiting the Department of Medical Gastroenterology were included in the study.

Patient Selection

Patients older than 18 years diagnosed with CLD were selected for the study.

The study methodology was thoroughly explained to the patients. Written informed consents was obtained. Fresh and follow-up cases were included.

Patients with the following conditions were excluded: ascites, history of therapeutic procedure for EV or portal hypertension, liver or splenic tumors, infiltrative disorders involving the spleen such as lymphoma, sarcoid, metastases, history of splenectomy or splenic embolization, portal or splenic vein thrombosis, congestive heart failure, acute viral hepatitis, cholestatic jaundice, and very sick patients who could not undergo elastography.

A thorough history and comprehensive clinical examination were elicited. Laboratory test values of complete blood count, platelet counts, serum bilirubin, serum albumin, liver enzymes (alanine transaminase and aspartate aminotransferase), and international normalized ratio (INR) were recorded.

Liver and Spleen Ultrasound and SWE Protocol

We performed all ultrasound elastography procedures adhering to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) updated guidelines and recommendations on the clinical use of liver ultrasound elastography for diffuse liver disease.³

All ultrasound and elastography examinations were performed using Esaote MyLab 9 eXP equipment (Esaote, Genoa, Italy) by a radiologist with more than 10 years of experience in abdominal and hepatobiliary imaging. Patients were asked to observe fasting for at least 4 hours before the ultrasound examination. Abdominal ultrasound evaluated the echotexture and morphology of the liver and spleen, the portal vein diameter, the splenic longitudinal dimension, and the presence of ascites and other features of CLD.

To widen the intercostal window for optimal examination, the examination was done in the supine or lateral decubitus position, depending upon the patient's habitus. A convex transducer C1–C8 (1–8 MHz) was used. Short breath-hold of 5 to 6 seconds was required to minimize motion artifacts. Tissue stiffness was assessed by SWE, using the elastography point quantification feature, to measure the stiffness of the liver and spleen. The elastography region of interest was positioned between 1.5 and 3 cm from the liver or spleen capsule across a region of the parenchyma free of major blood vessels or biliary ducts and far from the heart and other organs like the kidney. We considered the average (median) value of 10 accurate measurements that were successful and expressed in kilopascals (kPa) for each organ. This information was automatically reported and calculated as a sample report that listed 10 measurements along with their average

(median) and standard deviation. They were obtained from several locations in the right lobe of the liver (segments V, VII, and VIII), and from the upper and lower poles as well as the interpolar region of the spleen to ensure reproducibility.

Intraobserver variations were analyzed and found to have good reliability (93% agreement; intraclass correlation coefficient: 0.92; 95% confidence interval: 0.91–0.94).

Upper Gastrointestinal Endoscopy Protocol

All UGIE procedures were performed by the single gastroenterologist with 5 years of experience. The procedures were done at the Endoscopy Unit of the Medical Gastroenterology Department using the Olympus Evis Exera III CV-190 endoscope (Olympus EU, Hamburg, Germany). Endoscopy evaluated the absence or presence of varices and the severity of varices if present.

According to the American Association for the Study of Liver Diseases (AASLD) guidelines, patients were divided into three groups: group 1—patients with CLD and no varices (F0); group 2—patients with CLD and varices (F1); and group 3—patients with CLD and varices (F2).⁴

Classification of varices as per the AASLD guidelines⁴:

- F0: no varices.
- F1: small varices with diameter less than 5 mm.
- F2: large or high-grade varices with diameter \geq 5 mm.

Liver biopsy was not a part of our study. Liver cirrhosis stages included in our study were pre-ascites patient. Patients with ascites were excluded from our study as intraperitoneal free fluid alters elastography measurements. Hence, patients with a decompensated stage of CLD were not a part of our study.

Statistical Analysis

Data entry was done using Microsoft Excel spreadsheet software. Data analysis was done using IBM SPSS Statistics version 23. Values for LS, SS, and other parameters were recorded as mean \pm standard deviation. The Mann–Whitney *U* test was performed to compare two groups. The diagnostic performance of LS-SWE and SS-SWE in predicting EV and high-grade F2 EV was evaluated using the receiver operating characteristic (ROC) analysis. Area under the ROC curve assessed diagnostic accuracy.

Results

Our study included 121 CLD patients, consisting of 77 males and 44 females. No patients were dropped out because of missing data or loss to follow-up.

Out of 121 patients, EVs were present in 74 patients (61.2%) and EVs were absent in 47 patients (38.8%). The mean age of the patients with EVs was 47.61 ± 12.78 years. The mean age of the patients without EVs was 43.77 ± 14.78 years.

The group of the patients with EVs consisted of 51 (66.2%) men and 23 (52.3%) women. The group of patients without EVs consisted of 26 (33.8%) men and 21 (47.7%) women.

Table 1 Distribution of the patients based on etiology ($n = 121$)

Etiology	Frequency	Percentage	95% CI
Alcoholic	68	56.2	46.9–65.1%
Viral	33	27.3	19.8–36.3%
NAFLD	8	6.6	3.1–13.0%
Cryptogenic	7	5.8	2.6–12.0%
AIH	5	4.1	1.5–9.9%

Abbreviations: NAFLD, nonalcohol fatty liver disease; AIH, autoimmune hepatitis.

Table 2 Distribution of the patients in terms of varix grade ($n = 121$)

Varix grade	Frequency	Percentage	95% CI
F0 (no varices)	47	38.8%	30.2–48.2%
F1 (small varices: diameter <5 mm)	41	33.9%	25.7–43.1%
F2 (large varices: diameter \geq 5 mm)	33	27.3%	19.8–36.3%

Abbreviations: CI, confidence interval.

There was no statistically significant correlation between the two study groups' demographic characteristics in the current investigation.

The most common underlying cause of CLD in our study was alcohol abuse (68 patients, 56.2%), followed by viral hepatitis (33 patients, 27.3%; ► **Table 1**).

- F0 grade: absent varices—47 patients (38.8%).
- F1 grade: small EVs with diameter less than 5 mm—41 patients (33.9%).
- F2 grade: large EVs with diameter \geq 5 mm—33 patients (27.3%; ► **Table 2**).

All the cases in our study were compensated liver disease, that is, stages I and II. We excluded cases with decompensated liver disease, that is, stage III and IV cirrhosis. Out of 121 cases, varices were absent (stage I CLD) in 47 patients (38.8%) and EVs were present (stage II CLD) in 74 patients (61.2%).

Performance of LS and SS in Predicting EV

► **Table 3** and ► **Fig. 1** show a comparison of the diagnostic performance of LS and SS values measured by SWE in patients with and without EVs.

Liver Stiffness

The mean value of LS in patients without EVs was 13.65 ± 3.55 kPa. The mean value of LS in patients with EVs was 22.81 ± 4.56 kPa. To predict the presence of EVs,

the cutoff value was 16.5 kPa for LS (sensitivity: 94.6%; specificity: 85.1%; AUC: 0.95).

Splenic Stiffness

The mean value of SS in patients without EVs was 21.32 ± 3.92 kPa. The mean value of SS in patients with EV was 31.40 ± 7.15 kPa. To predict the presence of EVs, the cutoff value was 27.3 kPa for SS (sensitivity: 79.7%; specificity: 95.7%; AUC: 0.882).

With a cutoff value of 16.5 kPa, LS is superior to SS in predicting the presence of EV (► **Fig. 1**).

Performance of LS and SS in Predicting EV Grade

► **Table 4** and ► **Fig. 2** show a comparison of the diagnostic performance of LS and SS values measured by SWE in patients with an EV grade.

F1 Grade Esophageal Varices

- The mean value of LS in patients with an F1 grade EV was 20.54 ± 2.96 kPa.
- The mean value of SS in patients with an F1 grade EV was 27.49 ± 5.87 kPa.

F2 Grade Esophageal Varices

- The mean value of LS in patients with an F2 grade EV was 25.87 ± 4.04 kPa.

Table 3 Comparison of the diagnostic performance of various predictors in predicting varices: present vs. varices—absent ($n = 121$)

Predictor	AUROC	95% CI	<i>p</i>	Sn	Sp	PPV	NPV	DA
Liver stiffness (SWE), kPa	0.950	0.912–0.987	< 0.001	95%	85%	91%	91%	91%
Spleen stiffness (SWE), kPa	0.882	0.819–0.945	< 0.001	80%	96%	97%	75%	86%

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; DA, diagnostic accuracy; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; SWE, shear wave elastography.

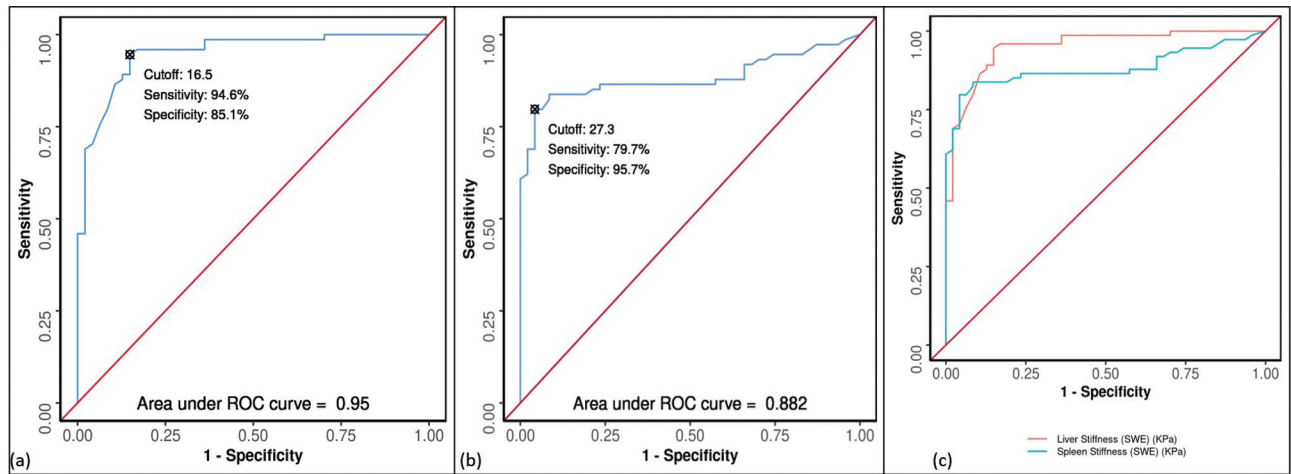


Fig. 1 Receiver operating characteristic (ROC) curves showing diagnostic performance of (a) liver stiffness (LS), (b) splenic stiffness (SS), and (c) their comparison in predicting the presence of esophageal varix (EV; $n = 121$).

Table 4 Comparison of the diagnostic performance of various predictors in predicting grade of varices: F2 vs. grade of varices: F1 ($n = 74$)

Predictor	AUROC	95% CI	p	Sn	Sp	PPV	NPV	DA
Liver stiffness (SWE), kPa	0.857	0.764–0.951	< 0.001	82%	85%	82%	85%	84%
Spleen stiffness (SWE), kPa	0.920	0.846–0.994	< 0.001	91%	90%	88%	92%	90%

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; DA, diagnostic accuracy; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; SWE, shear wave elastography.

- The mean value of SS in patients with an F2 grade EV was 36.55 ± 4.68 kPa.
- To predict the F2 grade EV, the cutoff value was 23.6 kPa for LS (sensitivity: 81.8%; specificity: 85.4%; AUC: 0.857).
- To predict the F2 grade EV, the cutoff value was 33.8 kPa for SS (sensitivity: 90.9%; specificity: 90.2%; AUC: 0.920).

The mean and cutoff values for variceal grades were higher for SS than for LS, denoting early involvement of splenic circulation in portal hypertension pathogenesis (**→Figs. 6 and 7**). The box and whisker plots in **→Figs. 6 and 7** demonstrate the distribution of stiffness values in various variceal grades.

SS performed better than LS at predicting the EV grade F2 (**→Fig. 2**).

Both LS and SS increased with the grade of varices progressing from F0 to F2 (**→Figs. 3–5**).

Discussion

Application of an external mechanical push or focused acoustic beams on an organ causes distortion of the tissue

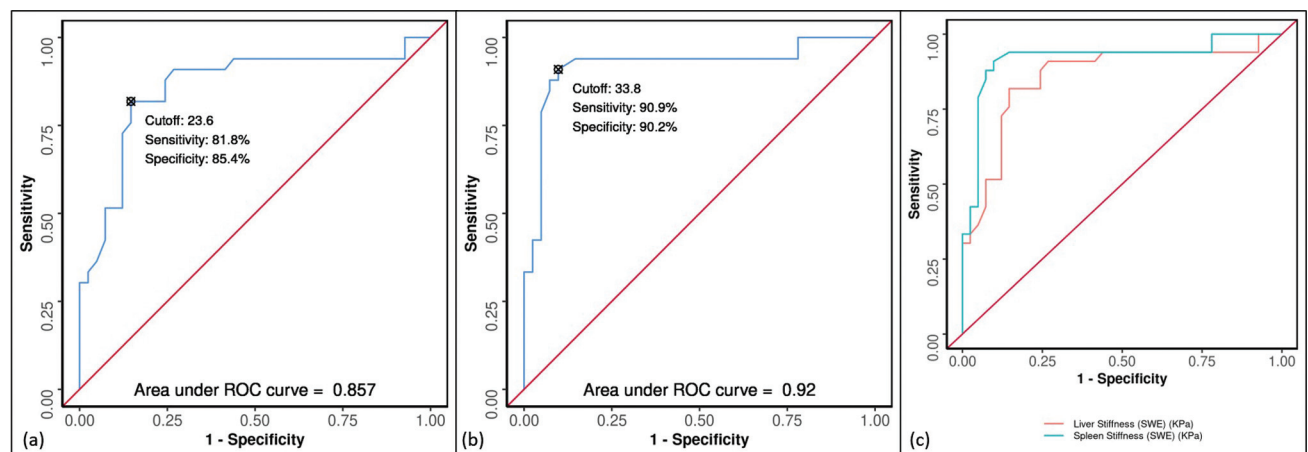


Fig. 2 Receiver operating characteristic (ROC) curves showing diagnostic performance of (a) liver stiffness (LS), (b) splenic stiffness (SS), and (c) their comparison in predicting F2 grade esophageal varix (EV) versus F1 grade EV ($n = 74$).

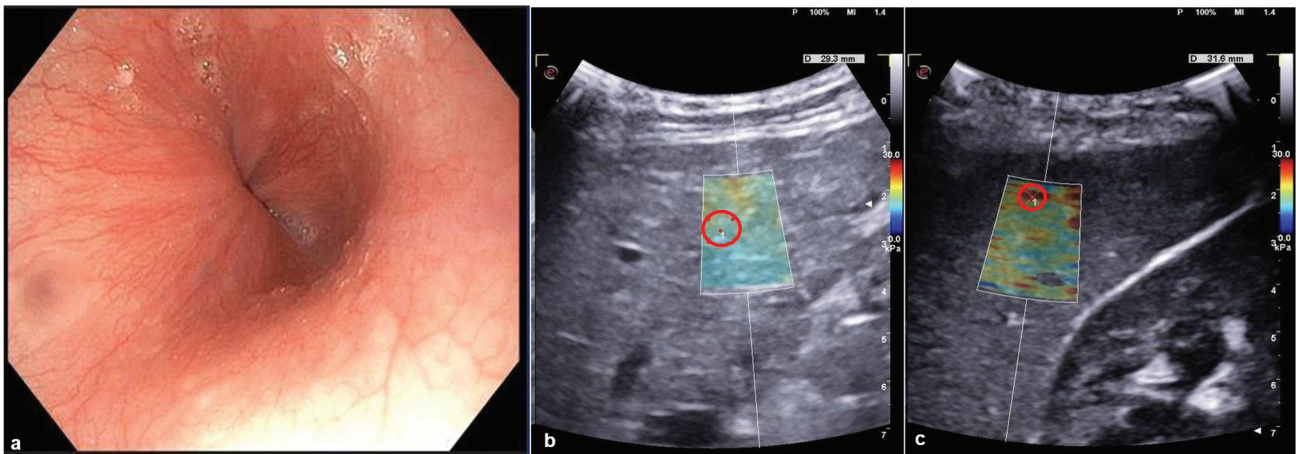


Fig. 3 (a) Endoscopic image in a patient with grade F0 esophageal varix (EV). Shear wave elastography (SWE) images showing (b) liver stiffness (LS) measurement of 13.14 kPa and (c) splenic stiffness (SS) measurement of 22.37 kPa.

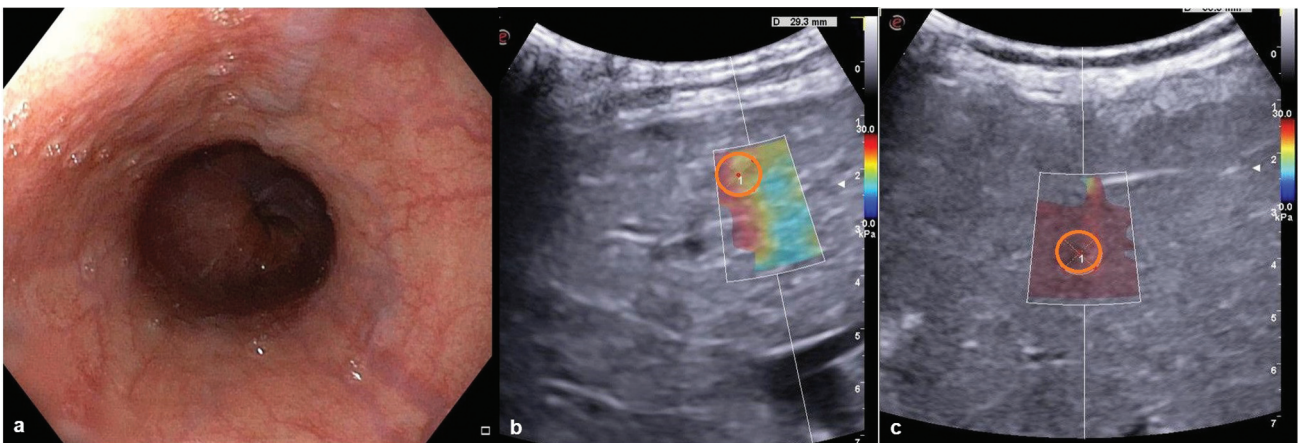


Fig. 4 (a) Endoscopic image in a patient with grade F1 esophageal varix (EV). Shear wave elastography (SWE) images showing (b) liver stiffness (LS) measurement of 21.54 kPa and (c) splenic stiffness (SS) measurement of 32.52 kPa.

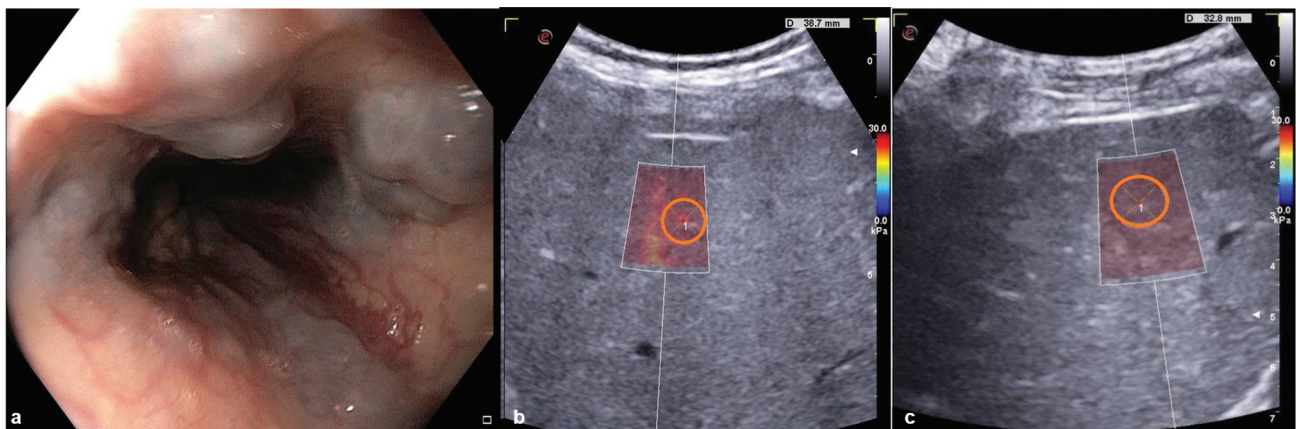


Fig. 5 (a) Endoscopic image in a patient with grade F2 esophageal varix (EV). Shear wave elastography (SWE) images showing (b) liver stiffness (LS) measurement of 28.63 kPa and (c) splenic stiffness (SS) measurement of 53.13 kPa.

as the mechanical or sonic wave traverses through the tissue. The way a tissue reacts to such external stimulus depends upon the internal structure of the tissue. Different solid organs behave differently, depending upon elasticity or

plasticity. Tissue elasticity changes in healthy and disease states can be measured by elastography. Ultrasound elastography is a noninvasive, convenient, and affordable technique that can be performed bedside and can be repeated multiple

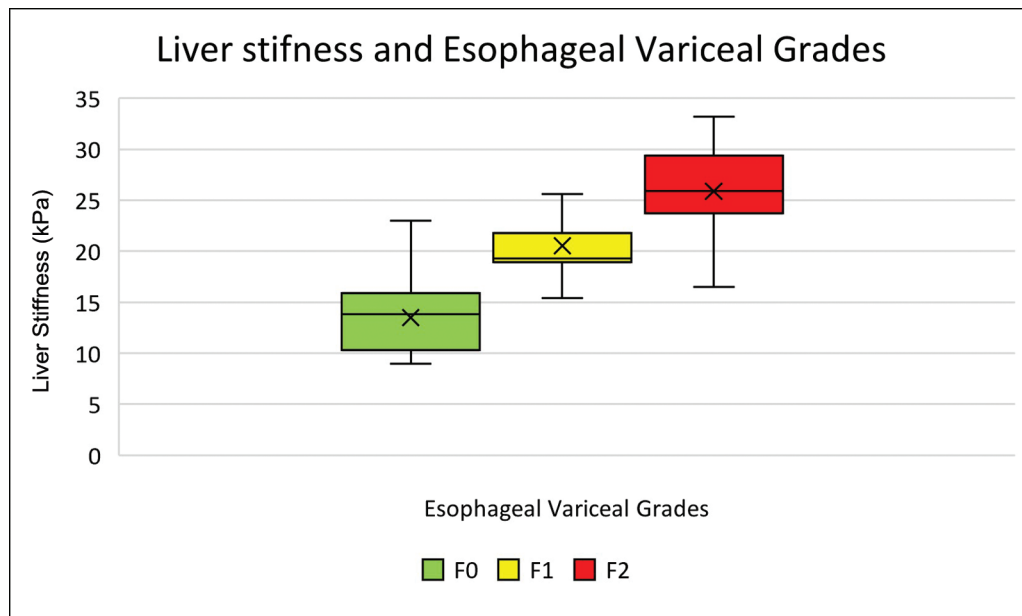


Fig. 6 The box and whisker plot depicting the distribution of liver stiffness values (in kPa) in three types of esophageal varices. The middle horizontal line represents the median value, the upper and lower bounds of the box represent the 75th and the 25th centiles, respectively, and the upper and lower extent of the whiskers represent the Tukey limits in each of the groups.

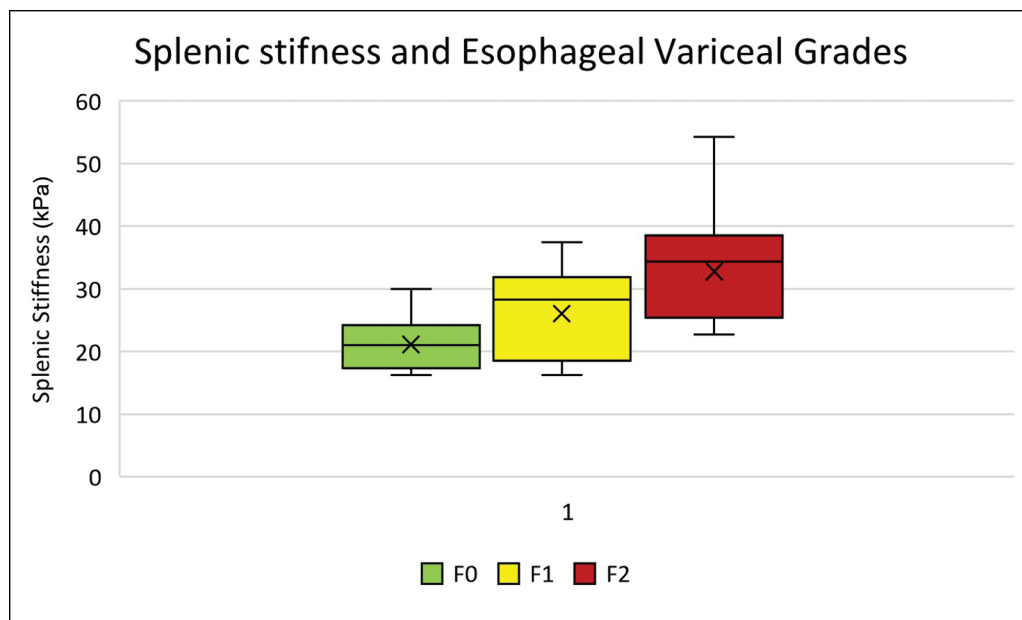


Fig. 7 The box and whisker plot depicting the distribution of splenic stiffness values (in kPa) in three types of esophageal varices. The middle horizontal line represents the median value, the upper and lower bounds of the box represent the 75th and the 25th centiles, respectively, and the upper and lower extent of the whiskers represent the Tukey limits in each of the groups.

times without hazards of ionizing radiation. Ultrasound elastography utilizes various techniques like SWE, acoustic radiation force impulse (ARFI), SWE imaging, and real-time elastography. Perturbations in the organ caused by mechanical wave or sonic wave are measured using ultrasound probes and specialized software.³ In CLD patients, the liver and spleen can be studied well by elastography because of their superficial location in the abdomen and both are affected in CLD. Hepatic inflammation, fibrosis, and its effects on the liver and spleen can be similarly evaluated

by elastography. Hepatic inflammation increases intrahepatic vascular congestion. Increased portal venous flow and pressure lead to an increase in the stiffness and rigidity of the liver and spleen. Derangement of both LS and SS is the continuum of a single pathology. Hence, both are connected with raised portal venous pressure. But SS derangements are more severe. The mean and cutoff values to predict the presence of EVs and variceal grade are higher for SS than for LS ($p < 0.001$). LS and SS do not show derangements in isolation.

In advanced CLD, cirrhosis leads to scarring and fibrosis, and further increase in stiffness. As tissue stiffness increases, SWE shows higher shear wave velocity or Young's elastic modulus readings in patients with CLD.³ Hence, SWE may be utilized to track the evolution and progression of CLD.^{5,6}

EVs are portal systemic collaterals, formed to bypass high-resistance portal circulation. Variceal pressure and risk of rupture increases with severity and duration of CLD and extent of portosystemic shunting. Variceal bleeding is a major cause of morbidity and mortality in CLD patients. All CLD patients should undergo endoscopic screening at the time of diagnosis to identify varices with a high risk of bleeding and for primary prevention.⁵ Despite being a gold standard for detection of EV, UGIE is an invasive procedure and requires technical expertise, which may not always be available at outlying centers. Hence, an alternative modality to screen high-risk patients and stratify them to definitive endoscopic management is required. The purpose of this study was to offer an accurate and simple adjunct method for detection and monitoring of CLD complications such as EVs.

We aimed to measure the LS and SS using SWE and to demonstrate their capability to predict the presence and severity of EV in CLD patients.

- The SS measured with SWE can predict the presence of high-grade EV in CLD patients.
- The LS measured with SWE can predict the presence or absence of EV in CLD patients.
- SS was always higher than LS on SWE. This result results from the fact that the liver receives 75% of its blood supply from portal circulation, a low-pressure vein. The spleen is supplied by a splenic artery, which has a greater perfusion pressure. The cutoff values for SS described in previous studies were higher than those for LS.⁷⁻⁹

Our findings agreed with previous studies that evaluated the prediction of clinically significant portal hypertension using LS and SS by SWE with LS and SS by transient elastography (TE). The measurement of LS by SWE was found to be superior to other modes of elastography. The LS cutoff value with SWE for clinically significant portal hypertension detection is 24.6 kPa.⁸

The Baveno VII renewed guidelines for CLD accepted elastography as a noninvasive tool to rule out CLD and emphasized its importance as a noninvasive and inexpensive method for evaluation. LS less than 10 kPa and SS less than 21 kPa rule out CLD in the absence of other clinical/imaging signs. The Baveno VII consensus and previous studies utilized transient elastography and obtained stiffness cutoff values.⁷⁻⁹

Magnetic resonance elastography (MRE) was performed by Morisaka et al to evaluate SS and LS. They concluded that increased values of SS and LS were related to the presence of EV. SS showed good correlation with the severity of EV.¹¹ MRE is more expensive and technically demanding than ultrasound elastography, and hence limits its use as a screening tool.^{10,11}

Rifai et al evaluated LS and SS using the ARFI elastography, and found that LS was superior to SS in the prediction of clinically significant portal hypertension.¹²

Bastard et al used a novel transient elastography (TE) technique for SS assessment and showed that SS might be used to predict large EVs.¹³

Ma et al found splenic rigidity to be more preferable in EV severity prediction. The summary receiver operating characteristic (SROC) curve values are 0.88 for SS and 0.81 for LS.¹⁴

The difficulty in comparing the data acquired by the various elastography techniques may be due to different terminology, technical parameters, and shear wave frequencies used.¹⁵

In contrast to our study, Castera et al concluded that SS evaluated by ARFI showed good performance in determining the existence of EV and in grading of EV in patients with chronic hepatitis B. Their results differed with our study due to the inclusion of patients with a single etiology of CLD—viral hepatitis.¹⁶

Etiologies like sinistral portal hypertension, lymphoma, and splenic neoplasm tend to generate earlier and more severe splenomegaly, which causes increased SS. We did not include such cases in our study.¹⁷

Filiz et al performed SWE in patients with viral hepatitis-induced liver fibrosis. The SWE values showed significant correlation with severity of liver fibrosis on histopathology.¹⁸

Advantages of SWE over Conventional TE Techniques

A meta-analysis by Jiang et al¹⁹ compared the accuracy of TE and SWE in measuring liver fibrosis. The AUC values were comparable for TE and SWE for detection and stratification of liver fibrosis. TE is well validated by the current literature as a technique to evaluate LS. The TE technique is widely used with the FibroScan device (Echosens, Paris, France).

TE does not use direct ultrasound visualization. SWE shows a simultaneous grayscale B-mode image on the screen and allows the operator to study the liver parenchymal area. This avoids large blood vessels, reduces artifacts and repeat examinations, and improves throughput. TE had over 10-fold higher failure rates as compared with SWE in study by Jiang et al.¹⁹ This makes SWE a more preferred technique over the conventional TE technique. We measured the LS and SS values with the SWE technique alone. We did not compare the TE and SWE findings.

A systemic review by Medyńska-Przęczek et al²⁰ explored the scope of SWE as an alternative method to biopsy in pediatric patients with liver fibrosis. They acknowledged that SWE cannot replace biopsy for diagnosis of fibrosis, but it can satisfy the growing need of a noninvasive method for diagnosis.

Strengths and Limitations of the Study

Previously published studies have utilized TE, while we have used SWE. The advantages of SWE over TE are already discussed. SWE offers many advantages over conventional TE by combining real-time ultrasonography evaluation with elastography evaluation.

Our study had a small cohort of CLD patients with various etiologies and varying severity and stage of cirrhosis, which had an impact on the values of LS. Age-matched controls

were lacking. Hence, a multicenter study with a large sample is required on this subject to make a large cohort with a homogeneous distribution of various etiopathologies of CLD.

Conclusion

SWE cannot replace UGIE. The role of SWE can grow as an adjunct modality to screen and stratify CLD patients needing UGIE. This can reduce the number of screening endoscopy examinations and reduce the burden on endoscopy facilities. Our study showed the following:

- LS is a better indicator to predict the presence of EVs.
- SS has a better correlation with the severity of EVs.
- However, both these indices require larger validation studies.

Ethical Statements

This study was conducted after approval of the institute's ethics committee. No animal experiments were done. Informed written consent was obtained from all study participants.

Authors' Contribution

T.P. contributed to data collection, manuscript preparation, and data analysis. K.K.N. contributed to manuscript preparation and editing, and data processing. P.S. and I.P. contributed to data collection. U.C. contributed to the study design and conceptualization, and manuscript editing.

Funding

None.

Conflict of Interest

None declared.

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