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ORIGINAL ARTICLE

Evaluation of liver and splenic stiffness by acoustic radiation force impulse for assessment of esophageal varices

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Abstract

Background In routine clinical practice, assessment of portal hypertension (PHT) among patients with liver cirrhosis is done by a upper gastrointestinal endoscopy (UGIE); however, its invasive nature limits its use. Recent advances in ultrasound imaging make it possible to evaluate the tissue stiffness of the liver and spleen reflecting the severity of underlying fibrosis. Liver stiffness and spleen stiffness can be used to predict the presence of esophageal varices/PHT among cirrhotic patients.

Aim To predict the presence or absence of esophageal varices by measuring the stiffness of the liver and spleen by ultrasonography (USG)-based acoustic radiation force impulse (ARFI).

Methods This cross-sectional study included 90 subjects with liver cirrhosis. Liver and splenic stiffness were measured along with the USG abdomen, UGIE and aspartate aminotransferase to platelet ratio index (APRI).

Results Liver and spleen stiffness were significantly higher in cirrhotic patients compared to chronic hepatitis B. The best cut-off value of liver stiffness (LS) obtained by the receiver operating characteristic (ROC) curve was 2.16 m/s for predicting esophageal varices (AUROC 0.78, p 0.0002). The best cut-off value of splenic stiffness (SS) obtained by the ROC curve was 3.04 m/s for predicting esophageal varices (AUROC 0.698, p 0.0274). When both LS and SS were taken together, the accuracy in predicting esophageal varices increased to 92.22%. An equation to predict "esophageal varices = (0.225 LS + 0.377SS) − 0.555" was derived.

Conclusion LS and SS values of ≥ 2.16 m/s and 3.04 m/s, respectively, predict esophageal varices independently; however, combined assessment is better with 92% accuracy.

This study was presented as a poster at DDW 2016 in San Diego and its abstract was published as conference abstract in Gastroenterology. 2016; 150: S1114-5 [24].

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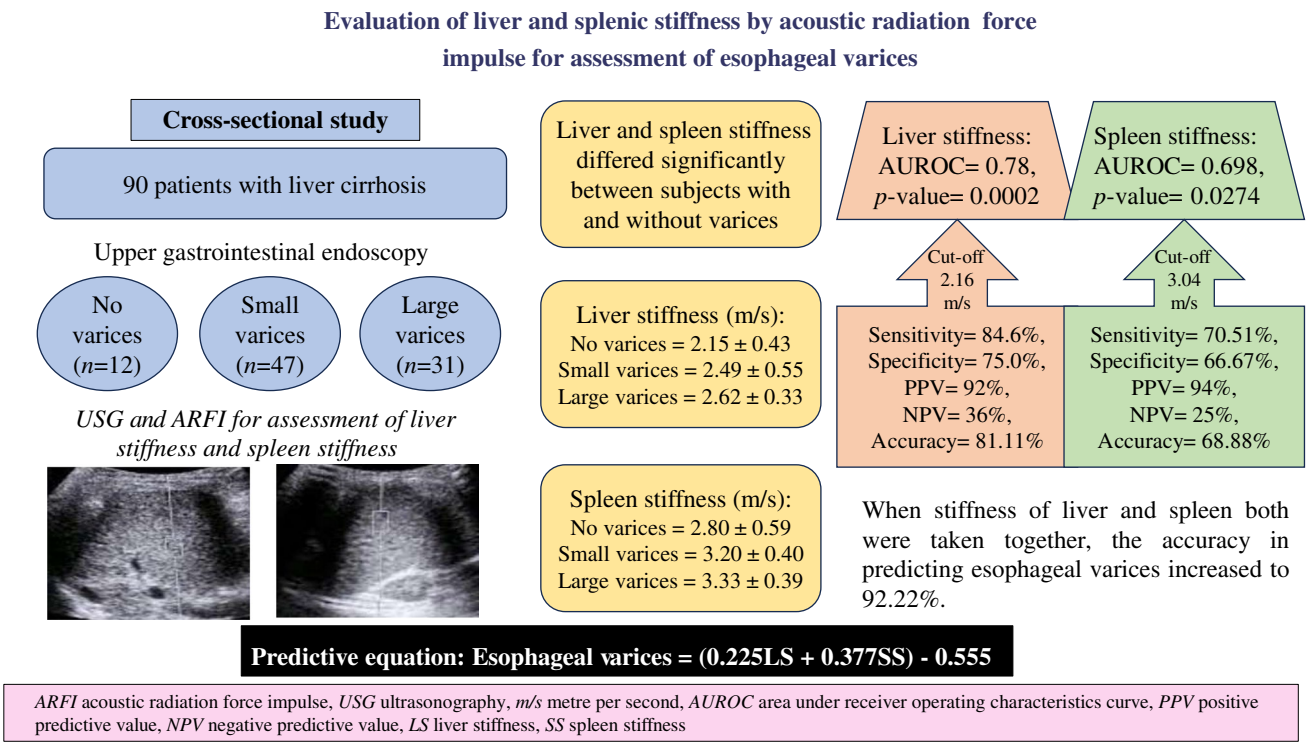
Graphical Abstract



Keywords Acoustic radiation force impulse (ARFI) · Cirrhosis · Clinically significant portal hypertension · Esophageal varices · Liver stiffness · Portal hypertension · Spleen stiffness

Introduction

Portal hypertension is a known sequela of chronic liver disease. In patients with chronic liver disease, fibrosis causes alteration in the architecture of the liver resulting in increased resistance to portal blood flow leading to an increase in portal pressure. Portal pressure of more than 10 mmHg is associated with the development of varices, the most common being esophageal varices (EV). Almost 40% of compensated cirrhotic patients and 60% of decompensated cirrhotic patients have been reported to have varices at first presentation [1]. A further rise in portal pressure, especially above 20 mmHg, may lead to bleeding from these varices. Variceal bleeding in cirrhotic patients is life-threatening with a mortality rate per bleeding episode of approximately 10% to 20% [2, 3] and a survival rate of only 63% [4]. The reference standard technique to assess the presence and severity of portal hypertension (PHT) is a measurement of the hepatic venous pressure gradient (HVPG) [5]. This method is invasive, expensive and available only at specialized centers. Another standard method followed in day-to-day clinical practice to assess clinically significant portal hypertension is upper gastrointestinal endoscopy (UGIE) [6]. Grade-II or more esophageal varices suggest that the patient probably has clinically significant portal hypertension and needs further measures to prevent variceal bleeding. The American Association for the Study of Liver Diseases (AASLD) [7] and American Society for Gastrointestinal Endoscopy (ASGE) [8] guidelines recommend performing screening UGIE in all patients with an initial diagnosis of cirrhosis of the liver. However, UGIE is costly, invasive and perceived as an unpleasant test by most patients, especially if patients are asymptomatic. Therefore, various non-invasive indirect tests have been proposed to predict portal hypertension. But none of these non-invasive tests have been able to replace UGIE in clinical practice. With recent advances in imaging, it is now possible to measure tissue stiffness. Liver stiffness (LS) is a good indicator of the degree of underlying liver fibrosis and can help predict the presence of esophageal varices [9, 10]. Ultrasound-based transient elastography (TE) [11] is reliable and reproducible for rapid and non-invasive measurement of tissue stiffness. But it is expensive and the measurements done using TE are highly operator dependent. Acoustic radiation force impulse (ARFI) imaging [11, 12] has been proposed as an alternative method to assess tissue elasticity with almost similar reliability as TE; however, it is less popular. ARFI imaging utilizes a single ultrasonography (USG) transducer to transmit brief, high-energy, focused acoustic pulses to generate radiation force in tissue causing

tissue displacement. The resulting tissue displacements are detected by USG using correlation-based methods. Local tissue displacement reflects the structure of tissue relative to mechanical properties, including stiffness. In response to the radiation force, soft tissue shows displacement of 1 to 20 μm, reaching peak displacement in less than 1 ms and recovering to its original position in less than 5 ms [13]. The measurement of tissue stiffness using ARFI is based on the principle that while passing through the soft tissue, the radiation force from a focused USG pulse gets attenuated by absorption. The magnitude of radiation force responsible for the displacement of tissue depends on the attenuation by absorption, speed of sound of the tissue and intensity of the acoustic beam. High attenuating media and/or higher diagnostic acoustic frequencies generate appreciable force in the near field, leading to a larger volume of tissue being excited with a more evenly distributed forcing function, whereas less attenuating media and/or lower diagnostic acoustic frequencies result in excitement of smaller volume of tissue [13]. Using ARFI, measurements for stiffness are done with real-time ultrasound under vision [11, 12]. Therefore, we aimed this study at using USG-based ARFI to measure the stiffness of the liver and spleen simultaneously to predict esophageal varices in patients with liver cirrhosis.

Methods

Study design, sample size, sampling technique and study population

This cross-sectional study included 90 subjects with liver cirrhosis. The sample size was calculated using the Scistat.com sample size calculator with the following assumptions.

Type-I error (α) = 0.05
Type-II error (β) = 0.20
Area under ROC = 0.91 (based on previous study) [14]

The convenience sampling technique was employed for the allocation of participants in the study.

Methodology

Study was initiated after obtaining approval from the Institutional Ethics Committee (ECR/204/INST/MP/2013). Only those patients who were willing to participate were included in the study and written informed consent was obtained from patients before enrolling them in the study.

All consecutive patients who presented with symptoms of chronic liver disease for the first time or were incidentally detected to have chronic liver disease were included in the study. The diagnosis of cirrhosis was based on clinical, biochemical, ultrasound findings and histopathology (if needed). Non-alcoholic steatohepatitis (NASH) diagnosis was presumptive, based on the patient's history, laboratory tests and imaging findings provided other disorders had been excluded.

The following patients were excluded:

Patients with active alcohol abuse (last three months),
Patients with space-occupying lesions or hepatocellular carcinoma or any extrahepatic malignancy,
Patients with portal vein thrombosis,
Patients who already had their splenectomy done,
Patients with the transjugular intrahepatic portosystemic shunt (TIPSS),
Patients on beta-blocker therapy or
Patients who had undergone endoscopic therapies such as endoscopic variceal ligation (EVL) or endoscopic sclerotherapy (EST).

All patients underwent detailed clinical examination, biochemical evaluation, whole abdomen USG with portovenous Doppler, UGIE and ARFI of both liver and spleen. The laboratory tests included hemogram, platelet count, bilirubin, aspartate aminotransferase, alanine aminotransferase, albumin, globulin, A:G ratio, international normalized ratio (INR) and serum creatinine. Viral and immunological markers and relevant workup were done as required to establish etiology. Healthy volunteers underwent only clinical examination and USG whole abdomen with ARFI of the liver and spleen.

UGI endoscopy

UGIE was done with Olympus, GIF-160 (Olympus Corporation, Tokyo, Japan). The presence and degree of esophageal varices (EV) were determined by two experienced endoscopists blinded to the patient's disease status. EV was graded from grades I-IV using the Paquet grading system.

Accordingly:

Grade 0: No varices
Grade I: Varices, disappearing with insufflation
Grade II: Larger, clearly visible, usually straight varices, not disappearing with insufflation
Grade III: More prominent varices, locally coil-shaped and partly occupying the lumen
Grade IV: Tortuous, sometimes grape-like varices occupying the esophageal lumen [15].

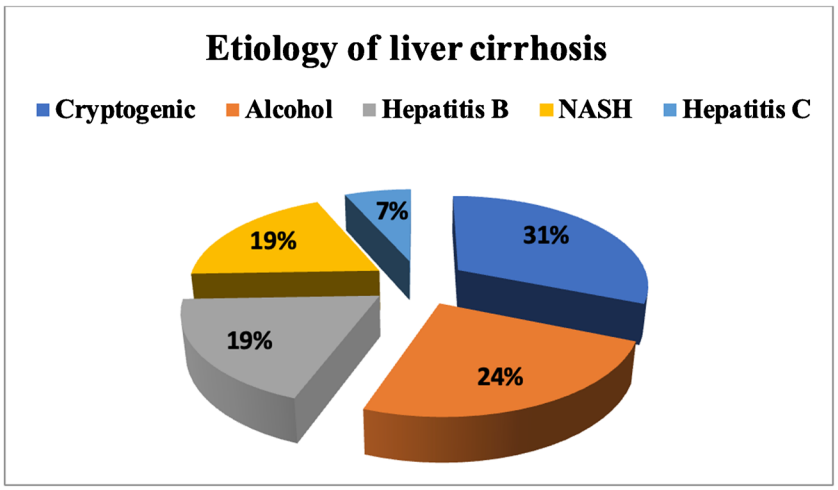


Fig. 1 Etiological spectrum of cirrhotic patients. *NASH* non-alcoholic steatohepatitis

Table 1 Baseline characteristics of patients

Variables	Median (interquartile range)				
	All subjects ($n=90$)	Different grades of esophageal varices			
		No varices ($n=12$)	Small varices ($n=47$)	Large varices ($n=31$)	p-value
Age (in years)	55.00 (44.75–62.00)	58.0 (45.75–67.5)	55.0 (45.0–62.0)	55.0 (42.0–62.0)	.712
BMI	23.00 (20.75–26.00)	23.0 (20.25–25.5)	23.0 (21.0–27.0)	22.0 (20.0–24.0)	.504
Platelet count	1.335 (1.000–1.835)	1.665 (1.000–3.0425)	1.5 (1.0–2.0)	1.20 (1.00–1.37)	.024*
Total bilirubin	1.95 (0.70–3.90)	4.675 (2.875–12.700)	2.14 (0.80–3.8)	1.10 (0.60–2.69)	.003*
SGOT	62.50 (34.75–130.75)	118.0 (25.75–366.0)	66.0 (44.0–122.0)	44.0 (33.0–81.0)	.197
SGPT	32.00 (24.00–68.25)	70.0 (18.5–490.0)	30.0 (26.0–62.0)	32.0 (24.0–56.0)	.662
Albumin	3.1 (2.7–3.6)	3.15 (2.45–3.55)	3.0 (2.7–3.4)	3.1 (2.7–3.8)	.717
Globulin	3.7 (3.2–4.2)	3.500 (3.125–3.700)	3.7 (3.4–4.2)	3.7 (2.8–4.4)	.192
A:G ratio	0.89 (0.70–1.10)	0.92 (0.90–1.095)	0.8 (0.7–1.0)	0.90 (0.63–1.25)	.177
INR	1.4900 (1.2825–1.8025)	1.6600 (1.1725–1.9075)	1.44 (1.24–1.71)	1.51 (1.30–1.80)	.800
Serum creatinine	1.125 (0.925–1.400)	1.4000 (1.0775–2.0625)	1.05 (0.88–1.23)	1.20 (0.98–1.45)	.005*
APRI score	1.2655 (0.7443–2.3798)	1.6530 (1.1533–2.3905)	1.222 (0.7420–2.3680)	1.2720 (0.7160–2.780)	.563

Kruskal-Wallis test. *p-value < .05 was considered statistically

BMI body mass index, *SGOT* serum glutamic oxaloacetic transaminase, *SGPT* serum glutamic pyruvic transaminase, *A: G ratio* albumin: globulin ratio, *INR* international normalized ratio, *APRI score* aspartate aminotransferase (SGOT) to platelet ratio index score

Table 2 Comparison of liver size, spleen size, liver stiffness and spleen stiffness among subjects with different variceal grades

Variable	All subjects	Median (interquartile range)			
		Different grades of esophageal varices			
		No varices	Small varices	Large varices	p-value
Liver size	13.0 (12.0–14.6)	13.15 (12.025–15.725)	14.0 (11.8–15.4)	12.6 (12.0–14.0)	.121
Spleen size	13.45 (11.95–16.0)	11.350 (9.100–12.075)	13.0 (11.0–15.0)	15.7 (13.3–17.0)	.001*
Liver stiffness	2.47 (2.185–2.8825)	2.1000 (1.8825–2.2275)	2.50 (2.19–2.99)	2.59 (2.37–2.90)	.004*
Spleen stiffness	3.200 (2.895–3.505)	3.000 (2.280–3.295)	3.20 (2.90–3.45)	3.3 (3.1–3.6)	.037*

*p-value < .05 was considered statistically significant

Table 3 Comparison of spleen size, liver stiffness and spleen stiffness in patients with different types of varices (post-hoc analysis)

Variable	No varices vs. small varices	No varices vs. large varices	Small varices vs. large varices
Spleen size	.032*	.001*	.001*
Liver stiffness	.007*	.001*	.255
Spleen stiffness	.082	.011*	.189

*p-value < .05 was considered statistically significant

Furthermore, EV were classified dichotomously as large and small EVs; grades III-IV were considered large EVs and grades I-II were considered small EVs.

All cirrhotic patients were classified into three groups based on the presence of esophageal varices as follows: subjects with cirrhosis but no EVs, subjects with cirrhosis and small EVs and subjects with cirrhosis and large EVs [16].

USG abdomen and ARFI liver and spleen

As per protocol, all patients were evaluated with sonography of the upper abdomen along with the measurement of ARFI of the liver and spleen by Siemens Acuson S2000 ultrasound system (Siemens Medical Solutions, Mountain View, CA, USA) by one of the two experienced sonographers, who were blinded to the disease status of the patient. After an overnight fast, each patient first underwent routine sonography of the liver, gallbladder, spleen, pancreas and portovenous system, followed by measurement of ARFI on B-mode imaging. A region of interest (fixed-dimension 1–0.5 cm box; maximum evaluable depth, 5.5 cm) in the liver and spleen parenchyma, free of large blood vessels was selected. Liver stiffness (LS) was measured in the right lobe of the liver, 1 cm below the liver capsule, using the intercostal approach. Splenic stiffness (SS) was measured 1 cm below the spleen capsule using the intercostal approach. The shear wave front was recorded and correlated with elapsed time to measure the shear wave velocity (SWV) (meter/second). Ten valid measurements were performed in each patient's liver and spleen and mean and values were calculated.

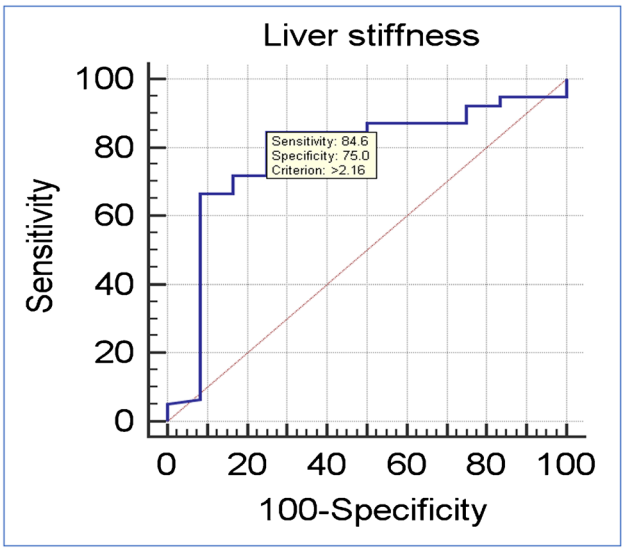


Fig. 2 ROC curve of liver stiffness measured by ARFI for predicting the presence of EVs

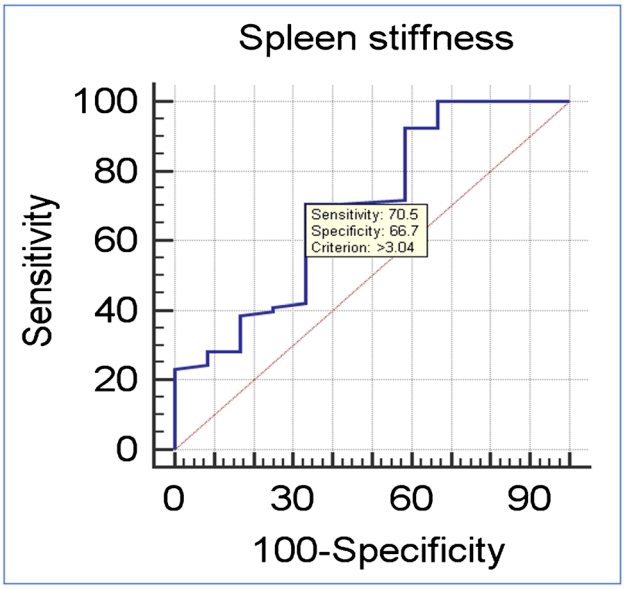


Fig. 3 ROC curve of spleen stiffness measured by ARFI for predicting the presence of EVs

Statistical analysis

The statistical analysis was performed with Statistical Package Mini Tab Version 17.0. Data was analyzed for

Table 4 Validation of derived equation

		Diagnosis using UGIE (esophageal varices)		Total
		Yes	No	
Prediction based on formula	Yes	7	7	14
	No	3	135	138
	Total	10	142	152

Sensitivity: 7/10 = 70.0%

Specificity: 135/142 = 95.07%

Positive predictive value: 7/14 = 50.0%

Negative predictive value: 135/138 = 97.8%

probability distribution using the Kolmogorov-Smirnov test, p-value < 0.05 indicated that the data was not normally distributed and thus, non-parametric tests of significance were applied. A p-value < 0.05 was considered statistically significant. Multiple regression analysis proposed a new equation to predict the presence or absence of esophageal varices.

Results

The study included 90 patients with a median (interquartile range [IQR]) age of 55.0 (44.75–62.0) years. Of 90 cirrhotic patients, 22 were in Child-Turcotte-Pugh (CTP) class A, 40 in CTP class B and 28 in CTP class C. The etiological spectrum of cirrhotic patients is shown in Fig. 1. The most common etiology of liver cirrhosis was cryptogenic (28 [31%]), followed by alcohol (22 [24%]). The median (IQR) of various parameters is described in Table 1. The liver stiffness and splenic stiffness of patients with no, small and large varices differed significantly (p-value < 0.05) (Tables 2 and 3). LS and SS were found to be more in patients with large varices compared to patients with small varices or no varices. The pairwise comparison revealed that liver stiffness and spleen stiffness were significantly higher in patients who had large varices than in patients having no varices (p-value < 0.05) (Table 3).

The receiver operating curve for LS and SS values was built to predict esophageal varices. The best cut-off value of LS obtained by the ROC curve (Fig. 2) was 2.16 m/s for predicting esophageal varices (AUROC = 0.78, p-value = 0.0002, with 84.6% sensitivity, 75.0% specificity, 92% positive predictive value, 36% negative predictive value and 81.11% accuracy). The best cut-off value of SS obtained by the ROC curve (Fig. 3) was 3.04 m/s for predicting esophageal varices (AUROC = 0.698, p-value = 0.0274, with 70.51% sensitivity, 66.67 specificity, 94% positive predictive value, 25% negative predictive value and 68.88% accuracy).

On further evaluation, the combined sensitivity, specificity, positive predictive value, negative predictive value and accuracy of LS and SS for predicting esophageal varices were found to be 94.94%, 72.72%, 96.15%, 66.66% and 92.22%, respectively.

Based on multi-variate regression analysis, including liver and spleen stiffness as variate, the predictive equation was as follows:

$$\text{Esophageal varices} = (0.225\text{LS} + 0.377\text{SS}) - 0.555$$

A value between 1 and 2 indicated a high chance of esophageal varices and a value less than 1 indicated that the occurrence of esophageal varices is unlikely.

This formula was applied retrospectively to all 90 subjects to calculate the predictability and this formula could correctly predict the presence of varices in 90.2% of the patients. Furthermore, the presence of esophageal varices was predicted using the formula to validate and assess its predictive accuracy. A final diagnosis was made using endoscopy prospectively in 152 incidentally detected HBsAg-positive patients (Table 4). The sensitivity of this formula in the correct prediction of varices was 70.0%, but with a high specificity of 95.07% and a negative predictive value of 97.8%.

To further validate the importance of LS and SS, the AST to platelet ratio index (APRI) was calculated in all patients and compared its relation to LS and SS and the severity of esophageal varices. There was no significant association between the APRI index and esophageal variceal grade (Pearson Chi-square = 2.837, df = 4, p-value = 0.585, not significant).

Discussion

In cirrhotic patients, PHT is a common and unavoidable complication [17]. It is responsible for the development of gastroesophageal varices, variceal hemorrhage, ascites, renal dysfunction, portosystemic encephalopathy, hypersplenism and hepatopulmonary syndrome. These complications are significant causes for morbidity and mortality. Takuma et al. [18] measured spleen and liver stiffness in 340 patients. They found that patients with varices had higher SS than patients without varices, with the highest values in those with high-risk varices. They also observed that SS was better than LS in ruling out the presence of varices. Most of the previous studies evaluating ARFI evaluation of the liver and spleen in cirrhosis patients included patients with liver cirrhosis caused by hepatitis B or hepatitis C virus [18, 19]. However, similar to the study done by Sharma et al., the present study evaluated ARFI among the patients with liver cirrhosis irrespective of the etiology [20].

In the present study, the median (IQR) liver stiffness value in cirrhotic patients was 2.47 (2.185–2.8825) m/s, almost similar values have been reported earlier by Takuma et al., Ye et al. and Furuichi et al. [18, 19, 21] LS (1.12 ± 0.23 m/s) of the healthy subject observed in this study was comparable to previously reported data [19, 22].

In our study, the median (IQR) spleen stiffness value was 3.20 (2.895–3.505) m/s, while earlier studies reported splenic stiffness ranging from 3.10 to 3.36 m/s [14, 18, 19, 21]. In the present study on plotting ROC for spleen stiffness, AUROC was 0.698 and accuracy for predicting EVs was 68.88%. Bota et al. [23] found AUROC to be 0.578, at a cut-off value of 2.55 m/s for predicting EVs using SS with 53.1% accuracy. In another study, Bota et al. [14] reported an AUROC of 0.910 and an accuracy of 87.1%. Takuma et al. [17] found AUROC to be 0.94 and an accuracy of

80.9% in predicting EVs using SS in high-risk EV patients. Ye et al. [18] reported an AUROC of 0.83. Our study found liver and spleen stiffness to vary among different variceal grades. The cut-off value of LS was 2.16 m/s and the cut-off value of SS was 3.04 m/s. Another study by Bota et al. [23]. had the best LS cut-off of 2.25 m/s, which was higher than the current study's LS of 2.16 m/s for predicting EVs. The AUROC was 0.596 and the accuracy was 56.5% lower than the AUROC of 0.78% and 81.1% in our study. Ye et al. [19] found no correlation between liver stiffness and variceal grade. However, they found a good correlation between SS and variceal grade. They reported that the best cut-off value of SS was 2.72 m/s, which was lower than the SS (3.04 m/s) obtained in our study. Bota et al. [14] also reported a comparatively lower cut-off value of SS (2.51 m/s). In another study by Bota et al. [23] the cut-off value for SS was 2.55 m/s. Takuma et al. [18] documented that the cut-off value for SS was 3.18 m/s for viral causes and 3.24 m/s for non-viral causes. They further extricated that the SS cut-off values for high-risk EVs were 3.30 m/s for viral causes and 3.41 m/s for non-viral causes. Most ARFI studies were done to determine liver stiffness and to correlate it with the stage of liver fibrosis, very few studies evaluated the predictive accuracy of LS for the prediction of esophageal varices. Our study's findings agree with the findings of the previously done research.

There is an unmet need for simple, non-invasive methods to identify esophageal varices among cirrhotic patients, especially among well-compensated patients who can be managed without screening UGIE. This will not only decrease the burden of GI endoscopy division, but will also be acceptable and affordable to patients. There are limited numbers of studies using LS and SS by real-time USG with ARFI. It is simple and cost-effective and can be reproduced anywhere without any added expertise from a sonologist. It can be an excellent diagnostic tool to predict the severity of varices for patients living in a region, where an endoscopy facility is not available or for patients who refuse to undergo endoscopy or for critically ill patients in ICU. The strength of our study was that a good number of cirrhotic patients with different etiologies were included and compared with disease control. The limitation of our study was that we did not compare the LS and SS with different stages of liver fibrosis by liver biopsy and HVPG. In our study, hepatitis C patients were comparatively lower than other etiology.

It can be concluded that non-invasive assessment of liver fibrosis and spleen done by ARFI (SWV) correlates well with the grade of esophageal varices in patients with liver cirrhosis. Combined LS and SS can predict the grade of esophageal varices with greater accuracy (92%) than individual LS or SS. There was no significant difference in ARFI values of LS and SS based on the etiology of cirrhosis. At last, we proposed a new equation to predict the presence or absence of esophageal varices in cirrhotic patients by the following formula:

$$\text{Esophageal varices} = (0.225\text{LS} + 0.377\text{SS}) - 0.555.$$

Author contribution Conceptualization: Ajay K. Jain, Amit K Bundiwal; methodology: Amit K Bundiwal, Ajay K Jain; formal analysis and investigation: Amit K Bundiwal, Deepika Jain, Suchita Jain, Praveen Agrawal; original draft preparation: Amit K Bundiwal, Ajay K. Jain; writing — review and editing: Ajay K Jain, Amit K Bundiwal, Suchita Jain, Praveen Agrawal, Deepika Jain, Shohini Sircar; final draft manuscript: approved by all authors.

Data availability All data is already part of the manuscript.

Declarations

Competing interests AKJ, AKB, SJ, PA, DJ and SS declare no competing interests.

Ethics statement The study was performed conforming to the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

Ethical approval and consent to participate The present study was conducted after getting ethical approval from the Institutional Ethical Committee (ECR/204/INST/MP/2013).

Human ethics The authors declare that the study was performed to conform with the Helsinki Declaration of 1975, revised in 2000 and 2008, concerning human and animal rights.

Consent for publication Written informed consent was taken from every subject before recruitment in the study.

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