Spleen stiffness: an index marker of oesophageal varices in patients with liver cirrhosis

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Purpose

Development of esophageal varices (EV) is one of the various consequences of portal hypertension in liver cirrhosis, which, when of higher grade may lead to variceal bleeding, sometimes fatal\(^{(1,2)}\). There is historical evidence that variceal bleeding may be life threatening and can cause mortality of around 10-20 % per bleeding episode with one year survival of only 63\%\(^{(3,4,5)}\). Therefore endoscopic screening for varices is recommended in patients diagnosed with liver cirrhosis. Presence of large or medium varices detected on endoscopic screening is an indication for treatment of varices to prevent bleeding whereas all other patients are recommended to undergo periodic surveillance endoscopy. However, at the time of endoscopic screening many patients will not have varices as the prevalence of varices is variable\(^{(6,7)}\).

Endoscopy being an invasive and costly diagnostic procedure, there is a need for finding non-invasive parameters to predict the presence of esophageal varices in patients of liver cirrhosis, and preferably the severity of varices.

Splenic stiffness (SS) is one such potential parameter which can be measured by ultrasound elastography. Longstanding portal hypertension due to liver cirrhosis results in various histological changes in the spleen parenchymal tissue causing raised stiffness\(^{(8)}\). There are various methods for the evaluation of tissue stiffness using ultrasound waves\(^{(9,10)}\) like:

- Acoustic Radiation Force Impulse Elastography (ARFI)
- Transient elastography (TE) (FibroScan)
- Sono-elastography (Real-Time Tissue Elastography) (RT-E)
Fig. 1: PRINCIPLE OF ARFI: Short-duration acoustic pulses (push pulses) are used to mechanically excite the tissue in a region of interest chosen by the examiner. Shear waves thus produced spread away from the region of interest and give rise to localised, micro-scale displacements in the tissue. At the same time, detection waves are also produced whose intensity is lower than that of the push pulses. The shear wavefront at several points are recorded and these measurements are correlated with the elapsed time, to calculate the shear wave velocity (m/s). In general, the shear wave velocity is higher in tissues with higher stiffness.

References: G Davies and M Koenen. ARFI in Distinguishing Hepatic Haemangiomata from Metastases Preliminary Observations, BJR, 84 (2011), 939-943
waves and their complete crossing of the region of interest is determined by moment of interaction between the shear waves and detection waves. The frequency and voltage used by push pulse are different than those of short cycle B-mode pulse. The shear wavefront at several points are recorded and these measurements are correlated with the elapsed time, to calculate the shear wave velocity (m/s). In general, the shear wave velocity is higher in tissues with higher stiffness\(^{(13,14)}\).

In our study we used ARFI to find the role of splenic stiffness using ARFI in predicting the presence of esophageal varices and their grading/ severity.

The aim of this study was

- to measure the value of spleen stiffness (SS) assessed by ARFI in patients of liver cirrhosis.
- to evaluate the diagnostic performance of spleen stiffness (SS) for predicting the presence of esophageal varices (EV) in patients of liver cirrhosis and to correlate it with esophageal endoscopic findings

Images for this section:
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Methods and materials

The study was approved by the scientific committee and the ethical committee clearance was obtained.

Study area: Radiology Department of Apollo Main Hospital, Greams road, Chennai.

Type of study: Prospective observational study

Subjects: Patients with suspected liver disease and referred for ultrasound abdomen to our departments by gastroenterologists.

Study duration: From January 2015 to December 2015.

Inclusion criteria for cases

- Age 18 years or older
- Known cases of liver cirrhosis diagnosed on the basis of combined physical, laboratory, and radiologic findings, including a nodular surface, a coarse echotexture, and an enlarged caudate lobe of the liver on ultrasonography, computed tomography, or magnetic resonance imaging who had or who will be undergoing upper GI endoscopy within 1 month of ultrasound.

Exclusion criteria for cases

- Portal vein thrombosis
- History of treatment for portal hypertension (splenectomy, partial splenic embolization, TIPSS, balloon-occluded retrograde transvenous obliteration, #-blocker therapy, or endoscopic therapies)
- Previous digestive tract hemorrhage because they have high risk of variceal bleeding and endoscopy is certainly indicated in them
- Critically ill patients who could not undergo endoscopic evaluation

Inclusion criteria for the controls

- Age 18 years or older
- No history of chronic liver disease
- Normal serum liver enzyme levels
- Normal findings on abdominal ultrasonography
We enrolled 97 patients in our study who were diagnosed to have liver cirrhosis on the basis of combined clinical, laboratory, imaging findings or based on histopathological examination of liver tissue. Among these, 4 patients were excluded due to portal vein thrombosis, 4 patients did not undergo endoscopy due to critical illness, 6 patients were excluded as they had undergone treatment previously (banding / sclerotherapy). In 5 patients ARFI measurement were unsuccessful due to excessive obesity. Thus data from 78 patients (66 males, 12 females) was finally analysed.

We also included 39 healthy volunteers (21 males and 18 females) as controls who had no history of chronic liver disease, normal serum liver enzyme levels, and normal findings on abdominal ultrasonography, in order to standardize the range of normal reference values.

**Methodology:** Approval by the scientific committee and the ethical committee clearance was obtained prior to the study. Written informed consent was obtained from patients. Measurements were performed with a Siemens Acuson S2000 ultrasound system equipped with virtual touch tissue quantification (VTTQ) software (figure 2) by an experienced radiologist (with more than 20 years of experience) in our department who was blinded to the clinical data throughout the study. A 4C1 curved linear array transducer was used. A region of interest (fixed-dimension 1 × 0.5 cm box; maximum evaluable depth, 8 cm) in the spleen parenchyma, free of large blood vessels, was selected. SS (spleen stiffness) was measured 1 to 4 cm below the spleen capsule using the intercostal approach in right lateral position. Similarly LS (liver stiffness) was measured 1 to 4 cm below the liver capsule in the right lobe of liver using the intercostal approach in left lateral position. ARFI shear wave velocity was measured in meters per second (m/s). More than 10 measurements were performed for each patient and 10 valid measurements of ARFI were noted for spleen and liver of each patient and median value was calculated. Patients underwent upper GI endoscopy to look for esophageal varices by an experienced gastroenterologist (with more than 20 years of experience) who was blinded to ARFI measurements. ARFI measurements and endoscopy were done within 30 days of each other.
Fig. 2: MEASUREMENT OF SPLEEN STIFFNESS BY ARFI. A region of interest (fixed-dimension 1 × 0.5 cm box; maximum evaluable depth, 8 cm) in the spleen parenchyma, free of large blood vessels, was selected. SS (spleen stiffness) was measured 1 to 4 cm below the spleen capsule using the intercostal approach in right lateral position. ARFI shear wave velocity was measured in meters per second (m/s). 10 valid measurements of ARFI of spleen were noted in each patient and median value was taken.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN

Esophageal varices were graded depending on their size [according to Italian liver cirrhosis project\(^{(15)}\)], as follows (figure 3):

- **Small (Grade 1):** small straight varices
- **Medium (Grade 2):** enlarged tortuous varices occupying less than one third of the lumen
- **Large (Grade 3):** large coil-shaped varices occupying more than one third of the lumen.
Based on endoscopic findings, we divided our patients into 2 groups for analysis:

- those without EV (grade 0), and
- those with EV (grade 1, 2, and 3)

The values of SS assessed by ARFI in these two groups were noted and the data analysed to determine whether there is a cut-off level for SS so that we could say EV are highly likely to be absent if the SS is less than this cut-off and endoscopy can be avoided in those patients. Similar analysis was done for the data of LS. The diagnostic performance of SS to predict EV was compared with that of the LS in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under receiver operating characteristic curve (AUROC).
Fig. 4: FINDINGS IN A PATIENT OF LIVER CIRRHOSIS WITH NO EV. (a) ARFI Shear wave velocity in spleen = 2.83 m/s. (b) ARFI Shear wave velocity in liver = 1.88 m/s. (c,d) Endoscopy showing no EV.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
Fig. 5: FINDINGS IN A PATIENT OF LIVER CIRRHOSIS WITH GRADE 1 EV. (a) ARFI Shear wave velocity in spleen = 3.05 m/s. (b) ARFI Shear wave velocity in liver = 2.21 m/s. (c,d) Endoscopy showing grade 1 EV.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
Fig. 6: FINDINGS IN A PATIENT OF LIVER CIRRHOSIS WITH GRADE 2 EV. (a) ARFI Shear wave velocity in spleen = 3.42 m/s. (b) ARFI Shear wave velocity in liver = 2.25 m/s. (c,d) Endoscopy showing grade 2 EV.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
Fig. 7: FINDINGS IN A PATIENT OF LIVER CIRRHOSIS WITH GRADE 3 EV. (a) ARFI Shear wave velocity in spleen = 3.89 m/s. (b) ARFI Shear wave velocity in liver = 2.91 m/s. (c,d) Endoscopy showing grade 3 EV.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN

Statistical Analysis Plan: All the continuous variables were assessed for the normality using Shapiro-Wilk's test. If the variables follow a Gaussian distribution, they were expressed as mean +/- SD, otherwise as median (Interquartile range). All the categorical variables were expressed either as percentage or proportions. Comparison of normally distributed continuous variables were done by either t-test or ANOVA based on the groups available if the variables are normally distributed. Comparison of non-normally distributed continuous variables was done by Mann-Whitney U test or Kruskal-Wallis test. Pearson's correlation co-efficient was computed to evaluate the association between two continuous variables. Comparison of categorical variables was done by Chi-square test or Fisher's exact test based on the number of observations. ROC (Receiver Operating Characteristic) curve analysis was done to assess the diagnostic value for the presence of esophageal varices. The diagnostic value was calculated using sensitivity,
specificity, positive predictive value, negative predictive value and likelihood ratio. All the p-values < 0.05 were considered as significant. Data entry was done in MS Excel spreadsheet. Data validation and analysis was carried out by SPSS version 16.0.

Images for this section:

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Fig. 3: GRADES OF ESOPHAGEAL VARICES ON ENDOSCOPY

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Results

SS and LS values in healthy volunteers: We included 39 healthy volunteers (21 males and 18 females) as controls in our study who had no history of chronic liver disease, normal serum liver enzyme levels, and normal findings on abdominal ultrasonography. The mean value of spleen stiffness by ARFI in normal individuals was 2.04 (+/− 0.35) m/s and that of liver stiffness was 1.32 (+/− 0.53) m/s.

SS and LS values in cirrhotic patients without and with EV: Out of 78 patients with liver cirrhosis included in the analysis, 55 (70.5%) patients (45 males, 10 females) were detected to have EV on endoscopy, while EV were absent in rest of the 23 (29.5%) patients (21 males, 2 females). The group of patients with EV was subdivided according to grades of EV on endoscopy. There were 18 (23.1%) patients (16 males, 2 females) with grade 1 EV, 15 (19.2%) patients (11 males, 4 females) with grade 2 EV, and 22 (28.2%) patients (18 males, 4 females) with grade 3 EV.

The mean value of SS in cirrhotic patients without EV was 2.78 (+/− 0.38) m/s (figure 8) and that of LS was 1.91 (+/− 0.51) m/s (figure 10). In cirrhotic patients with EV, the mean value of SS was 3.34 (+/− 0.34) m/s (figure 8) and that of LS was 2.47 (+/− 0.56) m/s (figure 10). In the further subdivided groups, the mean values of SS in patients with grade 1, 2 and 3 EV were 3.09 (+/− 0.35) m/s, 3.36 (+/− 0.31) m/s and 3.54 (+/− 0.32) m/s respectively (figure 9). The mean values of LS in patients with grade 1, 2 and 3 EV were 2.72 (+/− 0.55) m/s, 2.51 (+/− 0.52) m/s and 2.25 (+/− 0.60) m/s respectively (figure 11).
Fig. 8: SS IN PATIENTS WITH AND WITHOUT EV. The mean value of SS in cirrhotic patients with EV was 3.34 (+/- 0.34) m/s whereas in those without EV it was 2.78 (+/- 0.38) m/s.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
Fig. 9: SS IN DIFFERENT GRADES OF EV The group of patients with EV was subdivided according to grades of EV on endoscopy. The mean values of SS in patients with grade 1, 2 and 3 EV were 3.09 (+/- 0.35) m/s, 3.36 (+/- 0.31) m/s and 3.54 (+/- 0.32) m/s respectively.

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
**Fig. 10**: LS IN PATIENTS WITH AND WITHOUT EV. The mean value of LS in cirrhotic patients with EV was 2.47 (+/- 0.56) m/s whereas in those without EV it was 1.91 (+/- 0.51) m/s.

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Fig. 11: LS IN DIFFERENT GRADES OF EV The group of patients with EV was subdivided according to grades of EV on endoscopy. The mean values of LS in patients with grade 1, 2 and 3 EV were 2.72 (+/- 0.55) m/s, 2.51 (+/- 0.52) m/s and 2.25 (+/- 0.60) m/s respectively.

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There was a statistically significant difference (p < 0.05) in ARFI values of SS between patients with and without EV. Using a cut off value of 2.60 m/s for ARFI of spleen, SS had a sensitivity of 98.2%, specificity of 34.8%, PPV of 87.1% and NPV of 93.8% for differentiating those with EV from those without EV (Table 1). A cut off value of 3.04 m/s for ARFI of spleen showed a sensitivity of 78.2%, specificity of 78.3%, PPV of 89.5% and NPV of 60% for differentiating those with EV from those without EV (Table 1). The area under ROC curve for SS was 0.809 (figure 12).
Table 1: STATISTICAL ANALYSIS VALUES FOR SS

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN

For ARFI of liver with a cut-off value of 1.50 m/s, LS showed a sensitivity of 94.5%, specificity of 39.1%, PPV of 78.8% and NPV of 75.0% (Table 2). At a cut-off value of 2.07 m/s, LS had a sensitivity of 76.3%, specificity of 65.2%, PPV of 84.0% and NPV of 53.6% (Table 2). The area under ROC curve for LS was 0.730 (figure 13).
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**Table 2:** STATISTICAL ANALYSIS VALUES FOR LS

**References:** DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
Fig. 12: ROC CURVE FOR SS (AUROC= 0.809)

References: DEPT OF RADIOLOGY, APOLLO MAIN HOSPITAL, APOLLO MAIN HOSPITAL - CHENNAI/IN
Fig. 13: ROC CURVE FOR LS (AUROC = 0.730)

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**Fig. 13**: ROC CURVE FOR LS (AUROC= 0.730)

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Conclusion

In our study, SS had a high sensitivity and NPV for predicting the presence of EV in patients of liver cirrhosis (Table 1). This indicated that screening endoscopy can be avoided a significant number of patients who had SS values below a certain cut-off level. This would avoid risk of invasive procedure in addition to being cost-effective. The sensitivity and NPV of LS in our study (Table 2) for predicting the presence of EV in patients of liver cirrhosis was much lower as compared to that of SS. The area under ROC curve for LS (0.730) (figure 13) was lesser than that for SS (0.809) (figure 12).

The SS in patients with grade 3 EV was significantly higher than those with grade 1 EV (figure 9). Thus SS could also predict the severity of EV among those who had EV. Although the values of LS in patients with EV were also found to be significantly higher than those without EV (figure 10), however, there was no significant difference in LS within the group of patients who had EV (i.e. among Grades 1, 2 and 3) (figure 11).

A similar study was done by Leonardo Rizzo et al (16). They divided the patients into 2 groups: (a) those without EV (grade 0), and (b) those with EV (grade 1, 2, and 3). However, in their study they included patients of liver cirrhosis caused by hepatitis-C virus infection only, whereas we included all patients of cirrhosis irrespective of the etiology. The most common cause of cirrhosis in our patients was Hepatitis B (69.2 %), followed by alcoholic liver disease (23.1 %), Hepatitis C (5.1%) and cryptogenic (2.6%).

In the study done by Yoshitaka Takuma et al (17), patients were divided into 2 groups: (a) those without significant EV (grade 0 and 1), and (b) those with significant (high risk) EV (grade 2 and 3). The results are depicted in table 3.
Table 3: COMPARISON OF PREVIOUS STUDIES WITH OUR STUDY Leonardo Rizzo et al included in their study the patients of liver cirrhosis caused by hepatitis-C virus infection only, whereas we included all patients of cirrhosis irrespective of the etiology. The NPV value in the above mentioned previously done studies (16, 17) was higher than that in our study. This may be due to the difference in prevalence [51.8% (16) and 38.8% (17) in previous studies vs 70.5% in our study], because NPV decreases as the prevalence increases. The cut-off value of SS by ARFI for optimum sensitivity and NPV in our study (2.60 m/s) was found to be lower than that in the previous studies (16, 17) (3.18 m/s and 3.1 m/s).

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The NPV value in the above mentioned studies done previously (16, 17) was higher than that in our study (Table 3). This may be due to the difference in prevalence (51.8% (16) and 38.8% (17) in previous studies vs 70.5% in our study), because NPV decreases as the prevalence increases. The cut-off value of SS by ARFI for optimum sensitivity and NPV in our study (2.60 m/s) was found to be lower than that in the previous studies (16, 17) (3.18 m/s and 3.1 m/s).

In the study done by Simona Bota et al (18), they concluded that SS assessed by ARFI could not predict the presence of EV. One of the reasons for this discrepancy may be that they did not exclude the patients who were treated for portal hypertension as treatment of portal hypertension may probably alter the spleen stiffness when compared to untreated patients.

Limitations of our study: In a large number of patients, liver biopsy was not used for diagnosis of liver cirrhosis due to which there was unavoidable selection bias caused by clinical, lab and imaging diagnosis of cirrhosis. Portal venous pressure measurements with HVPG (Hepatic venous pressure gradient) was not performed. It was a single-centre study without external validation. No comparison was made with Transient Elastography. Therefore, further studies with larger sample size are needed to overcome these limitations.

Conclusion: Our study concluded that SS assessed by ARFI has a good diagnostic value in predicting the presence of EV as well as their severity in patients of liver cirrhosis. As compared to LS, SS had better diagnostic performance as an index marker for prediction of EV. Assessment of SS by ARFI in patients of liver cirrhosis may help in avoiding screening endoscopy which is an invasive procedure, in a significant number of such patients. It will also help to reduce the financial and disinfection burdens of endoscopy units as well as the medical costs associated with EV.
Table 3: COMPARISON OF PREVIOUS STUDIES WITH OUR STUDY

Leonardo Rizzo et al. included in their study the patients of liver cirrhosis caused by hepatitis-C virus infection only, whereas we included all patients of cirrhosis irrespective of the etiology. The NPV value in the above mentioned previously done studies (16, 17) was higher than that in our study. This may be due to the difference in prevalence [51.8% (16) and 38.8% (17) in previous studies vs 70.5% in our study], because NPV decreases as the prevalence increases. The cut-off value of SS by ARFI for optimum sensitivity and NPV in our study (2.60 m/s) was found to be lower than that in the previous studies (16, 17) (3.18 m/s and 3.1 m/s).

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Fig. 9: SS IN DIFFERENT GRADES OF EV The group of patients with EV was subdivided according to grades of EV on endoscopy. The mean values of SS in patients with grade 1, 2 and 3 EV were 3.09 (+/- 0.35) m/s, 3.36 (+/- 0.31) m/s and 3.54 (+/- 0.32) m/s respectively.
Fig. 11: LS IN DIFFERENT GRADES OF EV The group of patients with EV was subdivided according to grades of EV on endoscopy. The mean values of LS in patients with grade 1, 2 and 3 EV were 2.72 (+/- 0.55) m/s, 2.51 (+/- 0.52) m/s and 2.25 (+/- 0.60) m/s respectively.

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