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Shear Wave Elastography of Spleen in Predicting Esophageal Varices in Chronic Liver Disease

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Abstract

Background: Chronic liver disease (CLD) is a major causative factor accountable for deaths, with multifactorial complications increasing the severity of the disease process. The most commonly cited reasons for people diagnosed with CLD has shown a 5.1% prevalence rate for alcohol abuse with a trail of 62.9% liver cirrhosis mortality rate. Acoustic radiation force impulse (ARFI) imaging has gained popularity as the novel modus operandi provides the diagnostician with rapid as well as noninvasive quantification of the tissue elasticity and its properties.Aims & Objectives: To calculate the shear wave velocity of spleen in clinically suspected cases of chronic liver disease and to correlate elastographic findings with upper GI endoscopy**Material and Methods:**It is a Hospital based prospective study consisting of 42 patients above the age of 18 years who were clinically suspected to have CLD, undergoing shear wave elastography of spleen along with upper GI endoscopy in M S Ramaiah Hospitals, Bengaluru.**Results:**42 patients of chronic liver disease with acoustic radiation force impulse and compared with upper gastro-intestinal endoscopy, which is the gold standard investigation for diagnosing the esophageal varices. The spleen stiffness was measured with ARFI. Mean velocity among subjects with varices was 3.16 ± 0.33 m/s and among those without varices was found to be 3.30 m/s. The mean spleen stiffness cutoff value of 3.35 m/s identified patients with varices with a 36.6% sensitivity and 100% specificity.**Conclusion:**The diagnostic accuracy of ARFI in predicting esophageal varices in chronic liver disease has many rewards like being non-invasive, easy to perform, minimal/no chances of complication and also cost-effective in nature. Hence the use of ARFI as a non-invasive diagnostic tool in the current scenario without any substitute plays an indispensable role in the diagnostic process.

Keywords: Splenic stiffness, Elastography, Esophageal varices, Acoustic radiation force, Impulse.

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Introduction

Chronic liver disease (CLD) is a major causative factor accountable for deaths, with multifactorial complications increasing the severity of the disease process. It is a global

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burden across the globe with India being a heavy baggage for the same disease process and United States contributing approximately 150,000 CLD diagnosed cases.[1,2,3]

The most commonly cited reasons for people diagnosed with CLD has shown a 5.1% prevalence rate for alcohol abuse with a trail of 62.9% liver cirrhosis mortality rate being predicted by the WHO published data in the year 2014. Further, 36,000 patients lose their lives because of complications of decompensated cirrhosis and/or hepatocellular cancer.[2,3]

Portal hypertension (PH) is defined as a clinical syndrome characterized by an upsurge in the venous pressure gradient in the liver, which is a clinical sign of the progression of CLD disease process.[4] PH has the high risk of severe complications which includes but is not limited to upper digestive bleeding from gastrointestinal varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy. Esophageal varices (EVS) are most commonly seen in about 50% patients with CLD with a mortality rate of variceal bleeding ranging from 20-30%.[5]

It is important to screen upper gastrointestinal tract endoscopically to detect EVS in all CLD patients to understand the disease process. The diagnostic process ranges from a simple routine endoscopic screening to the most newfangled innovative diagnostic techniques. Nonetheless, routine endoscopic screening comes with the potentially associated complications under the protocol of sedation with its economic burden being an added briny to it.

Amongst the various imaging methods, acoustic radiation force impulse (ARFI) imaging has gained popularity as the novel modus operandi provides the diagnostician with rapid as well as noninvasive quantification of the tissue elasticity and its properties.[6] Further, the capability of ARFI imaging to be used synchronously with real time B-mode imaging acts as a bonus with the ultrasound based practice working on the ideology of shear wave velocity being gauged to weigh the elastic properties of target tissue in comparison with the normal tissues. Therefore, we were interested to evaluate and understand the splenic stiffness (SS) value determined by the ARFI technique and also whether it can be used as an initial screening test to predict EVS.

Aims & Objectives

1. To calculate shear wave velocity of spleen in clinically suspected cases of chronic liver disease.
2. To correlate elastographic findings with the upper GI endoscopy findings

Material & Methods

Source of Data

It is a Hospital based prospective study consisting of 42 patients above the age of 18 years who were clinically suspected to have CLD, undergoing shear wave elastography of spleen along with upper GI endoscopy in M S Ramaiah Hospitals, Bengaluru from the time period of November 2018 to June 2020 formed the part of our study with an informed consent approval from the patient and an ethical committee approval before inclusion/start of our study protocol.

Exclusion Criteria

Patients with history of

1. Liver transplant.
2. Focal splenic lesions.
3. Splenic vein, Superior mesenteric vein, Portal vein thrombosis.
4. Transjugular intrahepatic portosystemic shunt.
5. Gross ascites.

Study Protocol

Clinical data was recorded and analyzed if the subjects formed the part of the study.

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B-Mode Ultrasonography and Acoustic Radiation Force Impulse [ARFI] elastography was performed on suspected patients who fulfilled our inclusion criteria.

The patient was placed in the supine and left lateral position for assessment of the liver and right lateral decubitus position for assessment of the spleen as well as the SSM. The maximum window for spleen free from rib shadow was obtained and a region of interest (ROI) box measuring 1 x 1 cm was placed on the spleen with the preferred site for obtaining values 3-5 cm from the splenic capsule and away from the major vessels.

A total of 6 velocities was obtained from the region of interest during elastography in suspended respiration and recorded onto the patient proforma.

Further, the study population was subjected to upper GI endoscopy after elastography for confirmation of esophageal varices and the elastographic findings was correlated with the endoscopic findings.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent 't' test was used as test of significance to identify the mean difference between two quantitative variables.

Results

Table 1: Age distribution among subjects

		Count	%
Age	<40 years	5	11.9%
	41 to 50 years	10	23.8%
	51 to 60 years	17	40.5%
	>60 years	10	23.8%
	Total	42	100.0%

We found that the majority of the subjects were in the age group 51 to 60 years (40.5%), consisting of 78.6% males and 21.4% males.[Table1]

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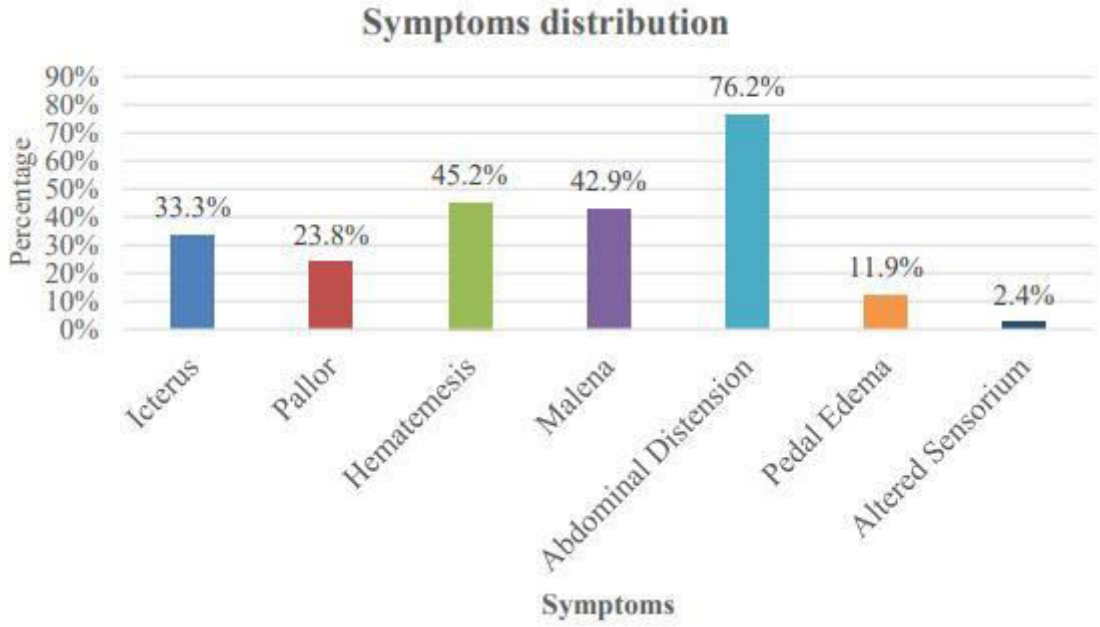
Table 2: Mean of laboratory parameters distribution among subjects

	Mean	SD	Minimum	Median	Maximum
Alkaline Phosphatase U/L	141.76	55.74	69	125	300
AST U/L	74.38	18.17	40	76	116
ALT U/L	48.21	17.66	20	46	96
GGT U/L	100.76	73.36	35	71	350
Total Bilirubin mg/dl	1.46	0.82	0.53	1.05	3.43
Direct Bilirubin mg/dl	0.96	0.55	0.32	0.75	2.40
Total Protein gm/dl	5.26	.57	4.20	5.00	6.50
Albumin gm/dl	3.01	.53	1.90	3.00	4.00
Globulin gm/dl	2.71	.33	2.00	2.80	3.50
A/G Ratio	1.10	.29	.60	1.05	1.60
Liver Size	13.36	1.06	11	13	16
Spleen Size	13.52	1.49	12	13	20
Portal Vein Diameter	13.35	1.22	11.00	13.05	16.70
Mean Velocity	3.17	0.33	2.6	3.2	3.6

Mean Velocity was 3.17 ± 0.33.



Graph 1: Bar diagram showing symptoms distribution among subjects

About 76.2% patients had Abdominal Distension, 42.9% had malena and 45.2% had Hematemesis. Further, 33.3% patients were found to have icterus followed by pallor in 23.8% patients and a meagre 11.9% had pedal edema with about 2.4% showing altered sensorium.[Table2][Figure1]

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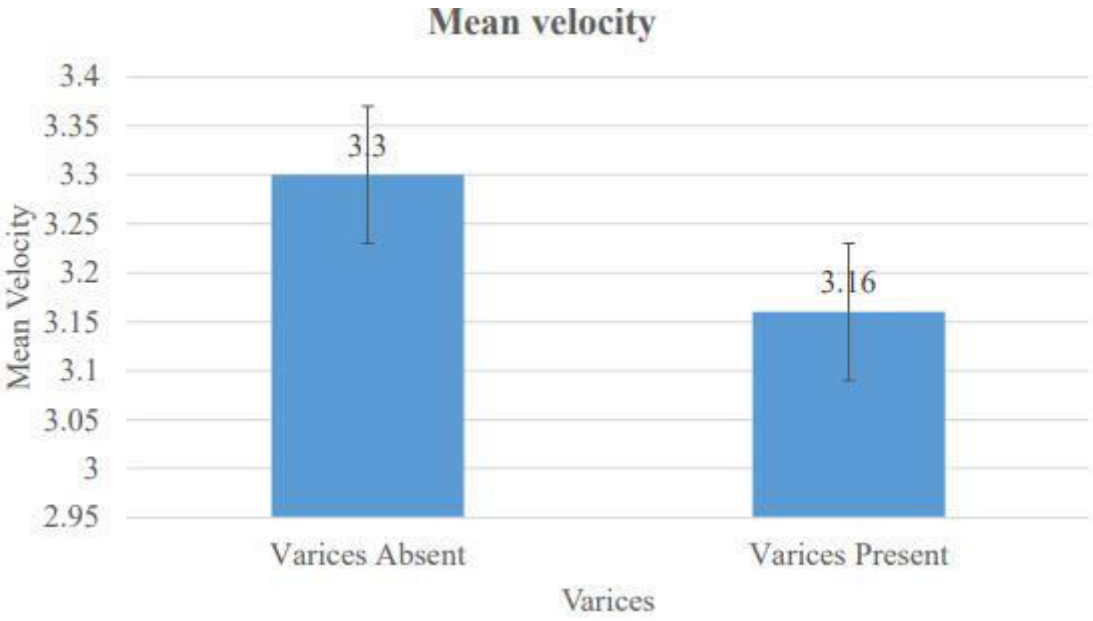
Table 3: Mean velocity among endoscopy findings (Varices)

		Mean Velocity					P value
		Mean	SD	Minimum	Median	Maximum	
Endoscopy	Varices Absent	3.30	.	3.3	3.3	3.3	0.684
	Varices Present	3.16	.33	2.6	3.2	3.6	



Graph 2: Bar diagram showing mean velocity among endoscopy findings (Varices)

41 subjects had Varices of various grades with a mean velocity of 3.16 ± .33, whereas it was 3.30 in subjects without varices.[Table3]

Table 4: Association between endoscopy findings and elastographic findings

		Endoscopy					
		Varices Present		Varices Absent		Total	
		Count	%	Count	%	Count	%
Elastographic Impression	Varices Present	30	73.2%	1	100.0%	31	73.8%
	Varices Absent	11	26.8%	0	0.0%	11	26.2%
	Total	41	100.0%	1	100.0%	42	100.0%

$\chi 2 = 0.363$, df = 1, p = 0.547

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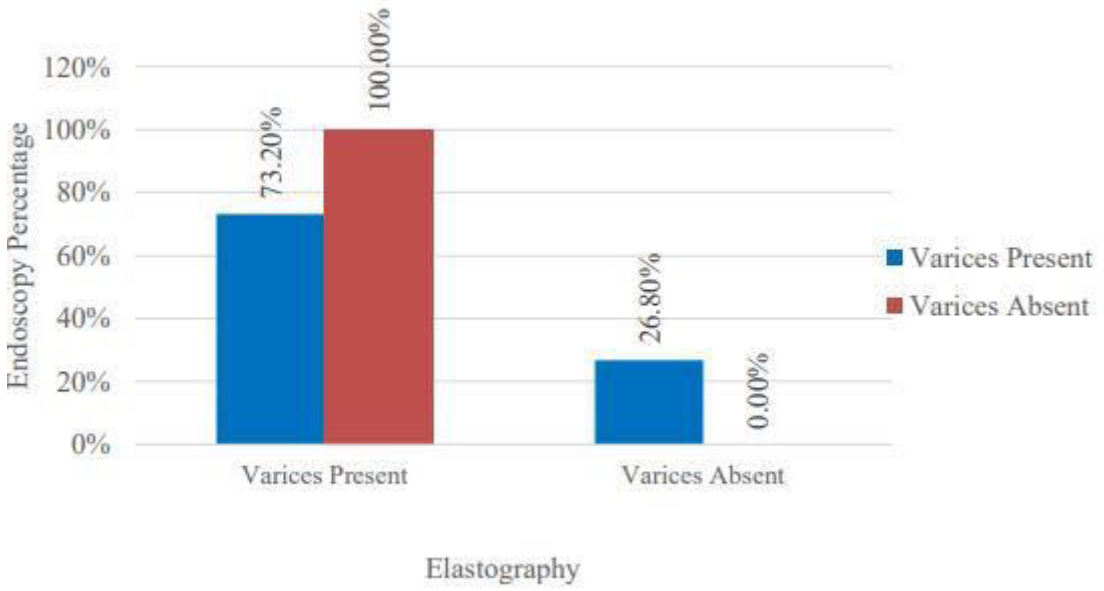
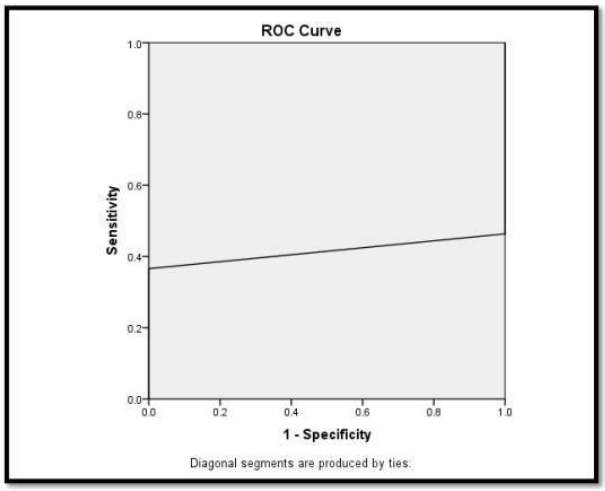


Graph3: Bar diagram showing association between endoscopy findings and elastographic findings

Amongst 41 subjects with varices detected in endoscopy, 73.2% showed varices in Elastography and 26.8% were not detected (False negative). However, in contrast the 1 subject without varices in endoscopy was positive for Elastography (False positive), which also showed no significant association between Elastography and Endoscopy findings.[Table4]

Table 5: Validity of mean velocity in predicting varices

Test Result Variable(s): Mean Velocity				
Area	SE	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.415	0.082	0.773	0.254	0.575



Graph 4: ROC curve showing validity of mean velocity in predicting Varices

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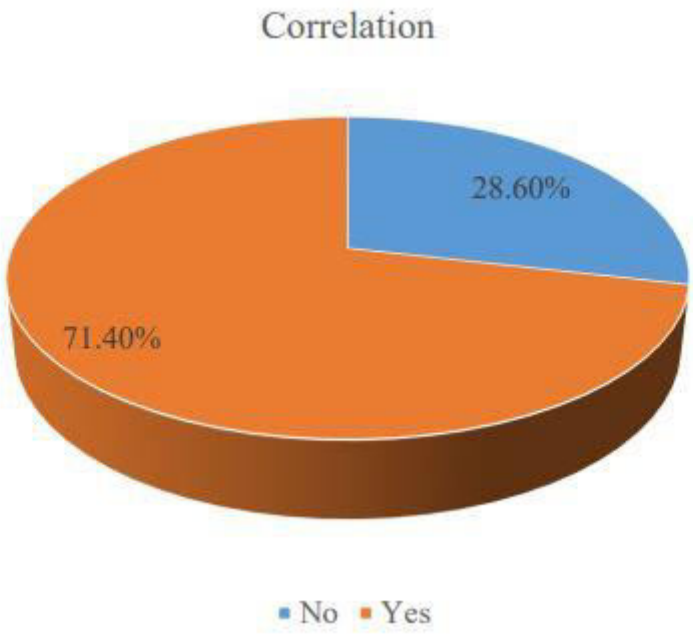
The mean velocity at 3.16 m/s showed a 100% sensitivity and 0% specificity, whereas at 3.35 m/s, the sensitivity was 36.6% and specificity was 100%. [Table5].

Table 6: Endoscopic findings among subjects

		Count	%
Endoscopic Impression	Small, Grade I Varices	3	7.2%
	Grade II Varices	1	2.4%
	Grade III Varices	37	88.1%
	No Varices	1	2.4%

Table 7: Correlation between endoscopy and elastographic findings

		Count	%
Correlation	No	12	28.6%
	Yes	30	71.4%



Graph 5: Pie diagram showing correlation between endoscopy and elastographic findings

Other findings on Endoscopy included Mild Portal Hypertensive Gastropathy in 85.7% & Mild Portal Hypertensive Gastropathy, Fundal Varix in 11.9%. Further correlation of elastographic findings against endoscopic findings was found to be 71.4%.[Table6,7].

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Discussion

Portal hypertension has been deemed as a trail of catastrophic snags as a part of chronic liver disease. Portal Hypertension occurs due to the remodeling procedure consisting of passive congestion, enhanced angiogenesis as well as fibrogenesis, all of which will alter the extrahepatic hemodynamic condition and contributes to the stiffness of the spleen[7,8] The complications of clinically significant PH include ascites, hepatic encephalopathy and bleeding from the gastroesophageal varices, which is associated with a high mortality rate.

Upper Gastrointestinal endoscopy is considered as the gold standard investigation for screening as well as diagnosis of the esophageal varices, which cannot be implemented in all patients because of its invasive nature as well as its complications and their cost. Hence, there is a dire need to replace it with a non-invasive detection technique for esophageal varices in CLD patients.

ARFI is the novel newfangled type of real time shear wave ultrasound based technique used for determining the splenic stiffness which is amalgamated onto conventional ultrasound images, for a better understanding of the disease process.

Shear wave elastography has high reliability as well as reproducibility in gauging splenic stiffness. A literature review demonstrated that SWE has higher success rate and better diagnostic value for detecting portal hypertension.[9]

The present study was performed to evaluate the performance of SSM by ARFI for non-invasive assessment of the EVS in patients of CLD. The majority of the patients belonged to the age group of 51 to 60 years (40.5 %) and was male (78.6 %). Out of 42 patients assessed majority came to hospital with multiple clinical features with the most common being the abdominal distension (76.2 %) and the majority of the patient showed altered liver function tests.

In patients with portal hypertension, splenomegaly is instigated by portal congestion in amalgamation with tissue hyperplasia.[10] On the contrary, literature has evidence that there is no significant association between the PH and splenomegaly.[11] Further, data from some studies also suggests that splenomegaly in the chronic liver disease is almost always expression of PH and EVS.[23,13]

In our study, all the 42 patients had splenomegaly with the mean size of the spleen measured to be 13.52 cm. The average liver span was 13.6 cm. In addition most of the patients had dilated portal vein with the mean portal vein diameter was 13.3 mm.

Except 1 patient, all 41 patients had varices which were graded, with the most common being grade III varices (88.1 %). Majority of the patients reported mild portal hypertensive gastropathy (85.7 %) as well as fundal varix on upper GI endoscopy. The mean SSM velocity was 3.17, with a range of 2.6 - 3.6 and the mean SSM velocity amongst the patients without varices was 3.3. [Figure2]

According to our study, the SS cutoff value of 1.6 m/s had 100 % sensitivity and 0% specificity, whereas at 3.35 m/s, the sensitivity and specificity was found to be 36.6 % and 100 % respectively for EVS prediction. A study conducted by Takuma et al.,[14] an SSM cutoff value of 3.18 m/s identified patients with EVS with a 98.4% negative predictive value, 98.5% sensitivity and 75.0% accuracy. An SSM cutoff value of 3.30 m/s identified patients with high-risk EVS with a 99.4% negative predictive value, 98.9% sensitivity and 72.1% accuracy. The SSM values less than 3.3 m/s ruled out the presence of high-risk varices in patients with cirrhosis.

Another study conducted by Bota et al.,[15] that SSM evaluated by ARFI had a SS cut-off value of 2.51 m/s for predicting the presence of varices but could not predict the presence or severity of EVS. According to Carmen et al.,[16] the cut-off values of SSM to rule out and rule in the varices at risk for bleeding were < 3.20 and ≥ 3.80 ms/s respectively. For a SSM cutoff

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value of 3.20 m/s has 99 % negative predictive value for excluding the cases with varices needing treatment.

Amongst the 41 cases of EVS detected by gastrointestinal endoscopy, the elastography technique was able to predict the presence of esophageal varices in 30 cases (73.2 %) only and the other 11 cases could not detect the varices, which provided us with a false negative value of 26.8 %. On the contrary, the 1 case without EVS as observed on endoscopy, predicted the presence of esophageal varices by the elastography technique, providing us with a false positive result. However, there was no significant association between the elastography and endoscopy findings.[Figure3]

The Limitations of our study can be overcome by increasing the sample size and conducting the study across various hospitals/centers in a systematic protocol and conglomerate the data to produce sufficient evidence while reducing the error rate. Further, selection bias should be minimized and inter-observer variability in assessment of the disease process in either of the techniques should be carried out with an experienced diagnostician.

Over the years, there have been enormous technological advancements which have become a game changer ranging from the conventional self-monitoring devices to the smart watch. These have rewards like being non-invasive, easy to perform, minimal/no chances of complication and also cost-effective in nature. Similarly, elastography has all the advantages in comparison to that seen in gastrointestinal endoscopy.

The spleen stiffness was measured with ARFI. Mean velocity among subjects with varices was 3.16 ± 0.33 m/s and among those without varices was found to be 3.30 m/s. The mean spleen stiffness cutoff value of 3.35 m/s identified patients with varices with a 36.6% sensitivity and 100% specificity.[Figure4,5]

Conclusion

Diagnosis forms a triad of history, clinical & laboratory investigations with the aim to reach a definitive diagnosis with minimal error rate. Endoscopy has been deemed as the gold standard in diagnosis of esophageal varices of chronic liver disease. Similarly, the diagnostic accuracy of ARFI in predicting esophageal varices in chronic liver disease has many rewards like being non-invasive, easy to perform, minimal/no chances of complication and also cost-effective in nature. However, the diagnostic accuracy of ARFI still has not accomplished the accuracy levels of endoscopy but can be definitely be used as a preliminary test prior to endoscopy after correlation with clinical signs and symptoms. Hence the use of ARFI as a non-invasive diagnostic tool in the current scenario without any substitute plays an indispensable role in the diagnostic process.

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