

Diagnostic performance of ARFI ultrasound elastography in spleen stiffness measurement to predict esophageal varices

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Abstract: *Background:* Presence esophageal varices are an independent predictor of mortality in patients with cirrhosis. Non-invasive assessment of cirrhotic patients to predict esophageal varices have been increasingly used instead of endoscopy. The aim of this study is to assess the diagnostic performance of ARFI elastography in measuring spleen stiffness to predict esophageal varices with endoscopy as the gold standard and compare these results with platelet count and spleen size. *Methods:* The patients included in the study underwent ARFI elastography and underwent endoscopy to determine esophageal varices stage, platelet count and spleen size values were calculated. The diagnostic performance of spleen stiffness by ARFI elastography, platelet count and spleen size was evaluated using receiver operating characteristic (ROC) curve analysis. Correlations of ARFI Elastography, platelet count and spleen size with endoscopy findings (as the reference standard) were determined using Spearman's correlation coefficient. *Results:* Study included 102 patients of the 58 (56.86%) were grade 0 with mean ARFI elastography value of 20.80±0.92 kPa, 25(26.32%) were grade1 with mean ARFI elastography value of 24.89±2.02kPa, 12(11.76%) were grade 2 with mean ARFI elastography value of 33.50±1.36 kPa, and 07(6.86%) were grade 3 with mean ARFI elastography value of 36.37±0.75 kPa. There was significant positive correlation between different stages of esophageal varices by endoscopy and spleen stiffness detected by ARFI elastography ($r = 0.995$, $p < 0.001$). ARFI elastography spleen stiffness exhibited higher diagnostic accuracy than the platelet and spleen size for the diagnosis of those without varices AUC 0.991 (0.949 to 1.000), 0.973(0.920 to 0.995), 0.968(0.913 to 0.993) and those with high grade varices AUC 1.000(0.964 to 1.000), 0.995(0.955 to 1.000), 0.901(0.826 to 0.952) respectively. *Conclusions:* ARFI elastography spleen stiffness measurement is a novel non-invasive method to use in the clinical practice, for the screening esophageal varices in cirrhotic patients, and thus reducing the number of endoscopic examinations burden with high diagnostic performance.

Keyword: Gastrointestinal bleeding, Cirrhosis, Endoscopy.

Introduction

Esophageal varices accounts for about 10%-15% of Upper gastrointestinal bleeding [1]. 60% of patients with cirrhosis have esophageal varices at the time of diagnosis [2]. And 90% of patients with cirrhosis have esophageal varices after 10 years since diagnosis, and after their appearance progress under the influence of increased portal blood pressure and portal blood flow. Presence esophageal varices is an independent predictor of mortality in the patients [3]. Patients with upper gastrointestinal bleeding should be promptly and correctly evaluated clinically to provide early key

decisions on the initial assessment of the patient with gastrointestinal bleeding [4].

Endoscopy is the way to diagnose esophageal varices and is obligatorily when a liver cirrhosis is diagnosed, considering that esophageal varices are present in 60% of decompensated cirrhosis and 30% of patients with compensated liver cirrhosis[5]. However, these techniques involve considerable endoscopic burden and cost on hence accurate non-invasive technique to predict oesophageal varices is needed.

In recent years, the availability of non-invasive tools for patients with chronic liver disease at the compensated stage of cirrhosis has increased including the routine biological parameters, elastography, the platelet count, spleen diameter [6]. Spleen stiffness is believed to be a direct reflection of portal hypertension and by elastography we can measure this stiffness [7]. It has been postulated that spleen stiffness measurement by ultrasound elastography can be an accurate non-invasive surrogate for Portal hypertension and predicting presence of esophageal varices and high-risk varices in patients with compensated cirrhosis [6].

However, to our knowledge, no major studies have been done in this regard. So, the purpose of this study is to investigate the diagnostic performance of ARFI Elastography to measure spleen stiffness for predicting the presence of esophageal varices in patients with compensated cirrhosis.

Material and Methods

A total 102 patients were examined. This study was approved by the ethical committee of our hospital, and written informed consent was obtained from all patients. Patients with cirrhosis of the liver or portal hypertension regardless of sex were included while patients with ongoing GI hemorrhage or intrahepatic malignancy portal vein thrombosis, pregnant women, and those who did not give consent were excluded.

All patients were subjected to complete clinical examination including age, gender and Body Mass Index (BMI) and laboratory tests which included Platelet count.

Spleen stiffness measurement: After taking informed consent, all patients underwent abdominal ultrasonography; then measurement of Spleen stiffness were done by ARFI technique using 1-5.0 MHZ high frequency curvilinear transducer (C5-1) on Philips Affiniti70 ultrasound machine (PHILIPS medical systems, Bothell, WA) with the subject in supine OR right lateral decubitus position. Subjects were encouraged for shallow breath hold for a few seconds.

The Region of Interest (ROI) was positioned on B-mode image of the spleen about 1.5 to 2 cm beneath the Spleen capsule, and elastography

measurements were obtained. Multiple measurements were made. Median of 10 valid measurements was taken. The values of Spleen stiffness are expressed in kilopascals (kPa). Reliable examination was considered if a success rate of 60%, an inter-quartile range (variability in the validated measures) <30% of the median elasticity

Spleen diameter measurement: Maximum spleen bipolar diameter expressed in cm was estimated by means of an ultrasound scan using the same machine in the same session. All examinations were performed by the same individual.

Upper gastrointestinal endoscopy: Esophageal varices were evaluated for each patient, using upper gastrointestinal endoscopy and were classified into four groups, as follows: Grade 0 as No varices; grade 1 as Small straight varices; grade 2 as Enlarged tortuous varices occupying less than one third of the lumen. And grade 3 as Large coil-shaped varices occupying more than one third of the lumen [8].

Statistical analysis: Correlation between ARFI Elastography and the stages of esophageal varices was estimated using the Spearman's correlation coefficient. The diagnostic performance of ARFI Elastography, platelets and spleen size was determined in terms of sensitivity, specificity, PPV and NPV, as well as likelihood ratio by AUROC curves. The optimal cut-off values between the stages of esophageal varices were determined at the maximised sensitivity and specificity. Analysis of variance (ANOVA) was used to find the significance of study parameters between three or more groups of patients. The p value of $0.05 < p < 0.10$ is considered significant; p value: $0.01 < p < 0.05$ was considered moderately significant and p value: $p < 0.01$ is considered strongly significant with a 95% confidence interval. The Statistical software Statistical Package for the Social Sciences (SPSS) 22.0, and R environment ver.3.2.2 were used.

Results

Patient characteristics: Our study included 102 patients. They were males and females.

Their ages ranged between 26 and 59 years with the mean age was 44.73±8.6 years. The mean body mass index (BMI) was 26.1±2.0 kg/ m². The findings are summarized in table 1.

	Patients (Mean ±SD)	p value
Age (Years)	44.73±8.6	<0.001
Male - n(%)	56 (54.90%)	<0.001
Body Mass Index (kg/m ²)	26.1±2.0	<0.001
Platelet Count (10 ⁹ /L)	138.725±28.86	0.164
Spleen size (cms)	13.7±1.6	<0.01

Endoscopic grades of esophageal varices: According to the endoscopic grades of their esophageal varices (Table 2).

	No. of patients = n (%)
Grade 0	58(56.86 %)
Grade 1	25(26.32 %)
Grade 2	12 (11.76%)
Grade 3	07(6.86 %)

ARFI Elastography of spleen: The mean splenic stiffness measured by ARFI for each esophageal varices stage is summarized in Table 3.

Esophageal varices grade	n=no of patients (%)	Mean stiffness (kP/sec) ±SD
Grade0	58(56.86)	20.80±0.92
Grade1	25(26.32)	24.89±2.02
Grade2	12(11.76)	33.50±1.36
Grade3	07(6.86)	36.37±0.75

The difference between several groups were statistically significant (ANOVA =128.234, p<0.001).

Correlation: Positive correlation was detected between the measured stiffness of spleen by ARFI and esophageal varices stage; correlation coefficient-Spearman rank (r) was 0.955(p<0.0001).95% Confidence interval for r 0.8631 to 0.955 (Talbe-4).

	Correlation coefficient(r)	Significance Level (p)
Spleen ARFI	0.955	<0.0001
Platelet count	-0.927	<0.0001
Splenic size	-0.059	0.5582

Significant figures; *Suggestive significance (p-value: 0.05<p≤0.10); * Moderately significant (p-value: 0.01<p≤0.05); ** Strongly significant (p-value: p≤0.01)

	AUC	95% CI	Cut-off (kPa)	Sensitivity	Specificity	LR+	LR-	PPV	NPV	P value
Grade 0	0.991	0.949 to 1.000	≤22.3	96.55	95.45	21.24	0.036	96.6	95.5	<0.0001
Grade 1	0.742	0.646 to 0.823	>22.3	92.0	72.7	3.37	0.11	91.0	98.6	<0.0001
Grade 2	0.925	0.855 to 0.968	>27.9	100.0	92.22	12.86	0.00	30.0	100.0	<0.0001
Grade 3	0.996	0.957 to 1.000	>35.5	100.0	98.95	95.5	0.00	87.5	100.0	<0.0001

Diagnostic ability of ARFI Elastography to differentiate esophageal varices stage: Spleen stiffness by ARFI Elastography exhibited good diagnostic accuracy in identifying each esophageal varices grade. The optimal cutoff values of ARFI Elastography for different levels of fibrosis are listed in Table 5, with observed AUCs and respective sensitivities, specificities and 95% confidence intervals.

Comparison of ARFI Elastography Splenic stiffness with platelet and spleen size for detecting those with high grade esophageal varices and those without esophageal varices [Table 6 & 7]: AUC value of ARFI Elastography for predicting those without esophageal varices (Grade 0) and those with high grade Varices (Grade 2,3) was significantly higher than those of platelet count or spleen size in both groups.

Table-6: AUC for predicting those without varices (Grade 0)	
	AUC (95% CI)
Spleen stiffness ARFI AUC (95%CI)	0.991 (0.949 to 1.000)
Platelet count AUC (95%CI)	0.973(0.920 to 0.995)
Spleen size AUC (95%CI)	0.968(0.913 to 0.993)

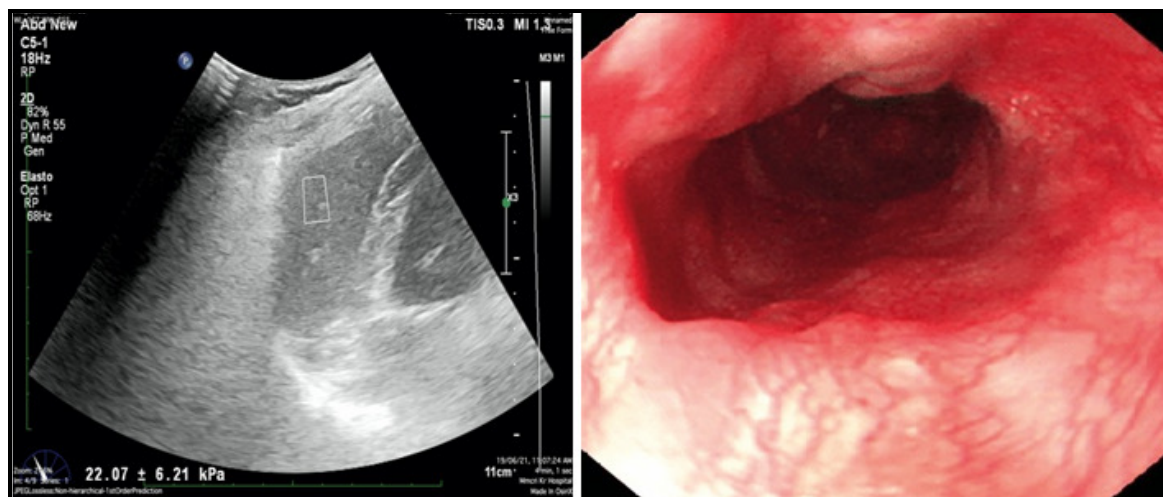
Table-7: AUC for predicting those with high grade varices (Grade 2 & Grade 3)	
	AUC (95% CI)
Spleen stiffness ARFI AUC (95%CI)	1.000(0.964 to 1.000)
Platelet count AUC (95%CI)	0.995(0.955 to 1.000)
Spleen size AUC (95%CI)	0.901(0.826 to 0.952)

Discussion

In the present study, the diagnostic performance of ARFI Elastography for predicting esophageal varices was analysed in 102 patients of which ultrasound image of two cases are shown in (Figure1).

The mean BMI was 26.1±2.0kg/ m² in present study which further confirms the notion that spleen stiffness measurements obtained by ARFI Elastography are not influenced BMI (Table 1). In present study, there was significant positive correlation between different stages of esophageal varices determined by endoscopy and spleen stiffness detected by ARFI Elastography (r=0.955 p <0.0001) (Table 4). Similar results were obtained in a study by kim et al., spleen stiffness was significantly different between patients according to their esophageal varices stage (p<0.001) [9].

Fig-1: Fig 1a shows ARFI Elastography image of spleen of 42 year old patient shows stiffness of 22.07±6.2kPa. Fig 1b Endoscopy of the same patient confirmed Grade I esophageal varices.



The diagnostic performance of spleen stiffness by ARFI Elastography for assessing No/grade 0 varices, grade 1 varices, grade 2 varices, grade 3 varices was significantly high (Table 5). The present study, to the best of our knowledge is one of the few studies to evaluate the diagnostic performance of ARFI Elastography in assessing spleen stiffness in patients with esophageal varices, considering endoscopy as gold standard and providing a comparison with platelets and spleen size.

Present study results are in agreement with previous studies which evaluated ARFI Elastography in measuring spleen stiffness in patients with esophageal varices. Ye et al have reported a significant correlation between spleen elastography and Esophageal varices in patients with chronic Hepatitis B (sensitivity 84.1%; specificity 81%) [10]. Colecchia et al found significant correlation between spleen elastography and Esophageal varices in patients with chronic hepatitis C related liver cirrhosis (sensitivity 98.5%, specificity 60.1%, negative predictive value 98.4%) [11]. In present study, spleen stiffness detected by ARFI Elastography showed high Negative predictive value and specificity in staging esophageal varices (Table 5). Hence, ARFI Elastography can be considered as a screening test and can be useful in daily practice.

In this study, we have compared the diagnostic performances of spleen stiffness by ARFI Elastography, platelet count and spleen size for varices staging. Spleen stiffness by ARFI Elastography exhibited higher diagnostic accuracy than the platelet count and spleen size for diagnosing those without varices and those with high grade varices (Table 6 and Table 7). On review of literature, there were limited previous studies comparing the ARFI Elastography in spleen, platelet count and spleen size. Park et al Showed similar findings and concluded that A univariate analysis revealed that the Platelets, PLT/SD ratio, and spleen elastography variables

were all independently associated with esophageal varices ($p < 0.05$). On multivariate analysis, only spleen elastography was associated with esophageal varices ($p = 0.001$) [12].

Another important point for every newly developed technique is to establish the cut-off values that should be used to differentiate between stages of varices. In present study, author used AUROC curve to know the optimal cut-off values of liver stiffness measurements by ARFI Elastography to differentiate different stages of varices. The optimum cut-off values for Grade 0/No varices, Grade 1, Grade 2, Grade 3 patients is ≤ 22.3 kPa, >22.3 kPa, ≥ 27.9 kPa and ≥ 35.5 kPa. In a similar study by Park et al., the optimal cut-off values for predicting no varices was 16.46 ± 9.4 kPa and those with varices was 40 ± 15.59 kPa, p value < 0.001 , which were comparable to present study [12].

Limitations: Firstly, the sample size was small; however, considering the limitations of endoscopy having large sample size is cumbersome. Those with multiple viral infections or combined causes for liver cirrhosis were not assessed. Other limitation of our study is the uneven distribution of cirrhosis etiologies which makes it difficult to assess the efficacy of splenic stiffness in different etiologies of cirrhosis.

Conclusions

By easily and reliably diagnosing high-risk varices, ARFI elastography can discriminate those who bleed from those who don't. We consider that spleen stiffness measurement by ARFI elastography is a novel optimal method to use in the clinical practice, for the screening of cirrhotic patients, for esophageal varices. reducing the number of endoscopic examinations burden.

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