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ROLE OF 2D SHEAR WAVE ELASTOGRAPHY FOR PREDICTING THE PRESENCE OF OESOPHAGEAL VARICES IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE.

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ABSTRACT

BACKGROUND: Liver cirrhosis and portal hypertension are common outcomes of chronic liver disease. Portal hypertension leads to development of oesophageal varices (EV). Oesophageal variceal rupture is the most common dreaded complication of cirrhosis that proves to be fatal.[1,2,3] In fact, the severity of liver disease can be correlated by the presence and grade of varices. Currently, oesophagogastroduodenoscopy (OGD) is the gold standard investigation for detection and grading of EV's. However, it is invasive, costly and frequently requires sedation. The aim of this study is to investigate the diagnostic performance of 2D shear wave elastography for predicting the presence of oesophageal varices in patients with advanced chronic liver disease (CLD).

METHODS: Study population included 32 cases with CLD and 30 controls without CLD undergoing OGD from August 2019 to August 2021.Prior to undergoing OGD, liver and spleen stiffness elastography were recorded using 2D-SWE. ROC curve was used to find the cut off values for liver and spleen stiffness for prediction of EV.

RESULTS: Using 2D-SWE, the association between liver/ spleen stiffness and presence of EV in CLD cases was found to be statistically significant (p value-<0.001). The optimal cut off values obtained for prediction of EV was 12 kPa and 12.6kPa for liver and spleen respectively (sensitivity of 81.8% and specificity of 82.5%; PPV-72%, NPV- 89.2%).

CONCLUSION: Liver and spleen stiffness values obtained by 2D-SWE were found to be a significant predictive factor for detection of presence of EV's in patients with CLD.

KEYWORDS : 2D-shear wave elastography(2D-SWE), Chronic liver disease (CLD), Esophageal varices (EV), Liver, Spleen

INTRODUCTION:

A serial decline in the function of liver continuing for more than six months is known as chronic liver disease (CLD). As per WHO, liver disease is the tenth most common cause of death in India, affecting about one in five Indians.[4] At the time of diagnosis, about 30% of CLD patients are detected to have varices which increases to 90% in about a decade. For small (grade 1) varices, the one year rate of first variceal bleeding is about 5%, while for large varices (grade 2 and 3) it is pegged at almost 15%.[5] Even though most of these patients are completely asymptomatic, current guidelines require endoscopic screening for oesophageal varices since the fatality rate of variceal bleeding continues to be really high. The gold standard to predict oesophageal varices is oesophagogastroduodenoscopy (OGD). However, it is costly, invasive, uncomfortable and frequently requires sedation. Currently, there are a number of non-invasive tools at our disposal for evaluation of CLD patients (routine biological parameters, elastography, platelet count/spleen diameter ratio and oesophageal capsule endoscopy). The reason for developing newer non-invasive techniques is the necessity for non-invasive predictors to lessen the medical, social, and economic costs. 2D shear wave elastography (2D-SWE) is one such established non-invasive technique. SWE approximates the shear wave velocity to quantitatively estimate the stiffness of tissue. The aim of this study is to investigate the diagnostic performance of 2D shear wave elastography for predicting the presence of oesophageal varices in patients with advanced chronic liver disease and to correlate the stiffness values obtained by 2d shear wave elastography to grade oesophageal varices.

METHODS:

Selection And Description Of Study Participants

Study Setting: Department of Radiology, Amrita Institute of Medical Sciences; Department of Gastroenterology, Amrita Institute of Medical Sciences, Kochi.

Duration of study: for 2 years starting from August 2019 to August 2021 after the approval from the thesis protocol review committee (Scientific, ethical and financial), Amrita Institute of Medical Centre, Kochi, Kerala.

Study design: Diagnostic accuracy study

Study population: 32 cases with cirrhosis and 30 controls without cirrhosis undergoing OGD were randomly selected and their liver and splenic stiffness values were recorded using 2D-SWE. The cirrhotic patients underwent OGD for detecting presence and grading the severity of EV's while the controls underwent OGD for causes unrelated to liver disease.

Inclusion Criteria:

1. All adults meeting the clinical criteria of Chronic Liver disease and willing to participate in the study and with no recent history of hematemesis.
2. Patients without CLD who underwent endoscopy for unrelated reasons and willing to participate in the study.

Exclusion Criteria:

1. Patients with liver tumors, previous endoscopic sclerotherapy or band ligation, or previous beta blockers intake.
2. Technically inadequately assessed elastographic indices.
3. Presence of a contraindication to perform oesophagogastro duodenoscopy (OGD).

Sample size:

Based on the results and statistical analysis of the data obtained in an earlier publication (Measurement of liver and spleen stiffness by shear wave elastography as a noninvasive evaluation of esophageal varices in hepatitis C virus-related cirrhosis; (Al-Azhar Assiut Medical Journal 2017, 15:111–116) and with 20% allowable error and 95% confidence the minimum sample size comes to 10 positive cases and 13 controls and a total of 23.

Technical Information:

OBJECTIVES:

Primary Objective: To investigate the diagnostic performance of 2D shear wave elastography for predicting the presence of oesophageal varices in patients with advanced chronic liver disease.

Secondary Objective: To correlate the stiffness values obtained by 2D shear wave elastography to grade oesophageal varices.

Technique:

Liver stiffness measurement: All patients were subjected to abdominal ultrasound examination and 2D shear wave elastography using convex

C5-1 probe; Philips EPIQ 5G at our Radiology Department. Patients were fasting for at least 4 hours before the examination. The examination was performed in the right lobe of the liver through intercostal spaces, while the patient lay supine or in slight lateral decubitus position with the right arm in extension to enlarge the space between the ribs. Measurement was taken at neutral breathing during a breath hold. The convex probe was placed between the ribs, using the best acoustic window available for liver evaluation. The shear wave elastography box was placed in a uniform zone about 15-20 mm below liver capsule to avoid reverberation artifacts that are often found beneath the capsule. Similarly, perivascular areas and gall bladder fossa were avoided because they alter liver stiffness estimate. The elastography acquisition was repeated three to five times for every patient and for each acquisition real time 2D-SWE color map of the stiffness was frozen after a stabilization of at least 3 seconds. The size of the SWE color box was about 2.7x2.8cm. The measurements were performed in a 1x1cm diameter region of interest (ROI). Ten measurements were taken for each patient and the final result was expressed as the median together with IQR/M. The results were reported in kilopascals (kPa). Since the most important reliability criterion is an IQR/M (interquartile range/median value) of <30%, this was duly followed.

Spleen stiffness measurement: measurements were performed through the left intercostal spaces with left arm maximally extended and applying the same quality criteria as stated for liver stiffness measurement.

All patients were further subjected to oesophagogastroduodenoscopy in the department of Gastro-intestinal medicine of our university for presence of EV's and their grading. OGD was performed using Olympus EVIS EXERA III CLV 190 by an experienced gastroenteroenterologist.

Statistics:
Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables are expressed by frequency and percentage. Continuous variables are presented by mean, median, SD, 25th and 75th percentiles. To find the cutoff value of liver and spleen stiffness for predicting EV and HREV; ROC curve analysis was used. To test the statistical significance of the association of liver and spleen stiffness cutoff with EV and HREV, chi-square test was used and diagnostic measures such as sensitivity and specificity was computed. To test the statistical significance of the difference in the median of liver and spleen stiffness value between EV and HREV, Mann Whitney U test was used.

RESULTS:
Our study comprised a total of 62 participants with 32 cases and 30 controls. Case group includes patients with known chronic liver disease (CLD) while patients without chronic liver disease who are undergoing OGD for other reasons are included in control group.

Among cases, 26 (81.2%) of the participants were males while only 6 (18.8%) of the participants were females. Among controls, 11(36.7%) participants were females while 19(63.3%) were males. Though our sample size is limited, majority of cases were found to belong to male gender.

Regarding age distribution, majority of patients among cases were in the 60-70 years (28.1%) age group. Among controls, majority of patients were in 21-30 years (30%) age group. Among both cases and controls, least number of subjects were in the 71-80 years age group. From this available data, it was found that most of the patients with CLD belonged to an older age group compared to controls.

The most common cause for the development of CLD in our cases was ethanol abuse which comprised 10 (31.1%) out of 32 patients. 4 patients (12.5%) each had NASH and chronic hepatitis related cirrhosis. For 10 patients (31.1%), no cause could be found and they were thus categorized as cryptogenic. Lastly, we had one patient each with cirrhosis due to cardiac causes, myelofibrosis and Wilson's disease.

Out of the total 62 participants (32 patients (51.6 %) with cirrhosis and 30 (48.4%) non cirrhotic patients) undergoing endoscopy, 22 were found to have esophageal varices. 6 patients (9.7%) had grade 1 varices, 15 patients (24.2%) had grade 2 varices and 1 patient (1.6%) had grade 3 varices.

The mean value of LS (liver stiffness) recorded among our control group was 5.81 ±2.30 kPa. The mean value of SS (splenic stiffness) among controls in our study was 7.94 ±2.57 kPa.

Among cirrhotic patients, the mean liver stiffness in patients with EV was found to be 15.1 kPa ± 4.1kPa and without EV was recorded to be 12.5kPa± 3.1kPa. The mean spleen stiffness in cirrhotic patients with EV was 15.9kPa± 3.8 kPa and without EV was found to be 12.1kPa±4.9 kPa. This difference in mean stiffness was found to be significant for splenic stiffness with a p value of 0.021. As far as liver stiffness is concerned, this mean value was not found to be significant with a p value of 0.096. A ROC curve (Figure 2) was plotted to predict presence of esophageal varices. The area under the curve (AUC) of liver stiffness to predict the presence of EV was found to be 0.893 and AUC for splenic stiffness was found to be 0.911 (Table 1).

FIGURES and TABLES

Table 1- ROC curve analysis for prediction of esophageal varices

	Area	Standard error	p value	95% confidence interval	
				Lower bound	Upper bound
Liver	0.893	0.040	<0.0001	0.815	0.970
Spleen	0.911	0.036	<0.0001	0.839	0.982

The cutoff value obtained for liver and splenic stiffness for prediction of EV was 12 kPa and 12.6kPa respectively (Tables 2 and 3) with a sensitivity and specificity of 81.8% and 82.5% respectively and PPV and NPV of 72% and 89.2% respectively. The research shows statistically significant association (p value- <0.001) between LS and SS measurements by 2D-SWE and presence of EV's.

Table 2- Association of liver elastography cut off values for prediction of esophageal varices

Liver Stiffness (in kPa) (number)	Esophageal varices		p value
	Present n (%)	Absent n (%)	
≥12 (25)	18 (72)	7 (28)	<0.001
<12 (37)	4 (10.8)	33 (89.2)	

Table 3- Association of spleen elastography cut off values for prediction of esophageal varices

Spleen Stiffness (in kPa) (number)	Esophageal varices		p value
	Present n (%)	Absent n (%)	
≥12.6 (25)	18 (72)	7 (28)	<0.001
<12.6 (37)	4 (10.8)	33 (89.2)	

Among 25 patients who had liver stiffness of ≥ 12 kPa and spleen stiffness of ≥ 12.6 kPa, 18 (72%) had esophageal varices compared to only 4 (10.8%) patients who had esophageal varices with liver stiffness of <12kPa and spleen stiffness of <12.6 kPa.

A suitable cut off value for prediction of HREV could not be obtained since the AUC of liver (0.547) and spleen stiffness (0.560) is low (Table 4).

Table 4- ROC curve analysis for prediction of high-risk esophageal varices

	Area	Standard error	p value
Liver	0.547	0.162	0.740
Spleen	0.560	0.131	0.941

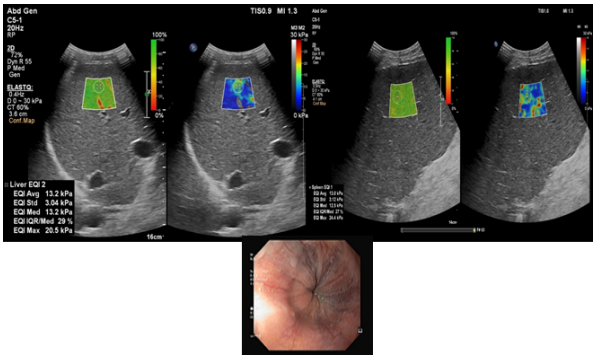

Figure 1: CLD patient with OGD proven grade 2 varices (A) shows liver elastography values of 20.8 kPa (B) shows spleen elastography value of 19.9 kPa. (C) OGD showing medium sized esophageal varices (Grade 2).

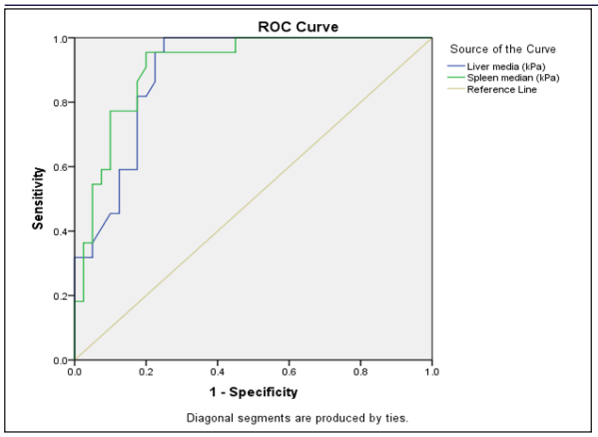

Figure 2- ROC curve analysis of liver elastography and spleen elastography for prediction of esophageal varices.

The mean LS in patients with HREV was found to be 15.1± 4.1kPa (p value-0.740) while the mean SS in patients with HREV was found to be 15.9±4.0kPa (p value-0.941).The results showed statistically no significant difference in the mean and median of liver and spleen stiffness with HREV.

DISCUSSION:

Liver cirrhosis and portal hypertension are common outcomes of chronic liver disease. Portal hypertension leads to development of oesophageal varices. Oesophageal variceal rupture is the most common dreaded complication of cirrhosis that proves to be fatal. [1-3] In fact, the severity of liver disease can be correlated by the presence and grade of varices. Currently, OGD is a gold standard diagnostic procedure to predict oesophageal varices as well as for therapeutic intervention. But we also have to consider the fact that endoscopy is costly, invasive, uncomfortable and frequently requires sedation. Previous studies have reported that LS and SS elastography values when measured by 2D-SWE is a significant predictor for presence of esophageal varices and also for grading of esophageal varices.

The present study was performed to evaluate the performance of LS and SS measured by 2D-SWE for non-invasive assessment of EV in patients with cirrhosis.

The mean value of LS recorded among our control group was 5.81 ±2.30 kPa. This mean value is similar to the values obtained in a study by Hashim et al. [6] which showed a mean LS value of 5.8±1.3 kPa in normal patients. Similar results of LS in normal patients were also recorded by Yoon et al. [7] (4.99 ± 1.42 kPa) and Franchi-Abella et al. [8] (5.96 ± 1.31 kPa).

The mean value of SS among controls in our study was 7.94 ±2.57 kPa. In a study by Hashim et al. [6], the mean value of SS in controls was 16.3±1.5 kPa and in a study conducted by Leung et al. [9] mean splenic stiffness was found to be 17.3 ± 2.6 kPa (range 8.05–24.9 kPa). It was noted that in all of our controls, splenic stiffness was more than liver stiffness. Relatively lower splenic stiffness value recorded in our study may be attributed to factors like small sample size and different make of the machine used in our study. Splenic stiffness measurement is also known to be affected by abdominal wall thickness and spleen size.

The mean value of LS in our patients with cirrhosis was 14.25 ±3.97 kPa, whereas for SS, it was 14.71 ±4.46 kPa. Zaki et al. [10] conducted a study where the mean liver stiffness in patients with CLD was 28kPa. The mean value of LS and SS in cases group was 23.8±10.1 and 51±18.1 kPa respectively in a study conducted by Hashim et al. [6]. This comparatively lower LS and SS mean value obtained in our study again could be due to relatively small sample size and different make of the machine.

In our study, out of the total 62 participants, 22 patients (35.5%) had EV and 40 patients (64.5%) had no EVs. The mean liver elastography value in case group with and without EV was found to be 15.1 kPa ± 4.1 kPa and 12.5±3.1 kPa respectively. While the mean spleen elastography value in case group with and without EV was found to be 15.9 kPa±3.8 kPa and 12.1 ±4.9 kPa respectively. This difference in mean stiffness was found to be statistically significant for splenic stiffness (p value- 0.021). As far as liver stiffness is concerned, this difference in mean value was not found to be statistically significant (p value- 0.096). Fofiu et al.[11] found that mean SS values for low grade varices was 12.71 ± 2.2 kPa for 2D-SWE.In a study conducted by Hashim et al.[6], the mean value of LS in CLD patients with EV was recorded to be 28.1 ± 10.4 kPa and mean value of SS for patients with EV was 61.2 ± 14.2 kPa.

The rate of bleeding from small (grade 1) esophageal varices is around 10% at 2 years while for medium/large varices (grade2/3) it increases to 30% which also depends on the Child-Pugh score.[12] Therefore, it is important to identify patients with EV to start them on prophylactic treatment at the earliest. With this aim in mind, we plotted a ROC curve to predict presence of esophageal varices (Figure 2). The area under the curve (AUC) of liver stiffness to predict the presence of EV was found to be 0.893 and AUC for splenic stiffness was found to be 0.911, proving the excellent ability of the modality to predict the presence of esophageal varices in cirrhotic patients (Table 1). It was also noted that splenic stiffness had a better predictability than liver stiffness which was found to be in agreement with other studies.

The cut off value obtained for liver stiffness for prediction of EV was 12 kPa with sensitivity and specificity of 81.8% and 82.5% respectively and PPV and NPV of 72% and 89.2% respectively (Table 2). The cut off value for spleen stiffness was 12.6 kPa with sensitivity and specificity of 81.8% and 82.5% respectively and PPV and NPV of 72% and 89.2% respectively (Table 3). Kim et al[13] conducted a study on 103 patients with cirrhosis and in this study, the liver stiffness elastography cut off value obtained for patients with EV was 13.9 kPa (sensitivity- 75%; specificity- 88%; AUROC- 0.887), which is almost similar to our values. In a similar study conducted by Hashim et al[6], a cut off value of 16.2 kPa for LS showed 89.8% sensitivity, 57.6% specificity, 79.1% PPV and 76% NPV for prediction for presence of EV. A cutoff value of 42.7 kPa for SWE of spleen was obtained in the same study and showed a sensitivity of 94.9%, specificity of 87.9%, PPV of 93.3% and NPV of 90.6% for differentiating those with EV from those without EV.

A ROC curve was also plotted to predict high risk esophageal varices (grade 2 and 3). The area under the curve of liver stiffness for prediction of HREV was 0.547 (p value-0.740) and AUC for splenic stiffness was 0.560 (p value-0.941) which was not statistically significant (Table 4).

LIMITATIONS:

First and foremost, we had a smaller sample size as compared to other studies which might have played a role in low cut off values obtained for liver and splenic stiffness. Second, our study included patients with mostly compensated cirrhosis whereas other studies had patients with compensated and decompensated cirrhosis. Third, we used a different SWE system that had not been used before for EV prediction. According to European Federation of Societies for Ultrasound in Medicine and Biology guidelines, systems that use the same technique but were developed by different manufacturers had different values owing to different methods to measure the shear wave's speed.[14] If our results are confirmed in larger prospective studies, it may be possible to reduce the endoscopic burden in the patients with compensated cirrhosis.

CONCLUSIONS:

2D-SWE was found to be a good indirect noninvasive tool for prediction of esophageal varices in patients with CLD. We obtained a cut off value of 12 kPa for liver stiffness and 12.6 kPa for spleen stiffness for the prediction of presence of EV. In our study, splenic stiffness value was found to be a more accurate predictor for presence of esophageal varices than the liver stiffness.

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