ISSN 2515-8260 Volume 10, Issue 01, 2023

Liver Elastography to Predict Presence of Esophageal Varices: A Cross Sectional Study

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Background: Esophageal varices are portosystemic collaterals developed in cirrhotic patients with portal hypertension. Noninvasive assessment of cirrhotic patients to predict esophageal varices have been increasingly used instead of endoscopy. Shear wave elastography is a non- invasive technique which is based on an ultrasound device which has been developed to detect liver stiffness. We aim to assess the diagnostic performances of Shear Wave Elastography liver for the noninvasive detection of the presence of esophageal varices. **Subjects and Methods:** The patients included in the study underwent shear wave elastography (SWE) of liver and underwent endoscopy to determine presence of esophageal varices, Platelet count and spleen size values were calculated. The diagnostic performance of liver stiffness by SWE, platelet count and spleen size were evaluated using receiver operating characteristic (ROC) curve analysis. Correlations of SWE, 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 SWE of 16.32±1.28 kPa, 25 (26.32%) were grade1 with mean SWE of 18.16±1.00kPa;12 (11.76%) were grade2 with mean SWE of 24.42±0.70kPa, and 07(6.86%) were grade3 with mean SWE of 26.50±0.53kPa. There was significant positive correlation between different stages of esophageal varices by endoscopy and liver stiffness detected by SWE ($r = 0.9178$, $p < 0.001$). AUC (95% Cl) for diagnosing grade 0, grade 1, grade 2 and grade 3 esophageal varices SWE elastography is 0.926(0.857 to 0.969);0.655 (0.555 to 0.747) ;0.922 (0.852 to 0.966) and 1.000 (0.964 to 1.000) respectively. A cutoff value of >19.3kPa and >25.3kPa was 100% sensitive in diagnosing grade2 and grade 3 esophageal varices respectively. SWE liver stiffness exhibited higher diagnostic accuracy than the platelet and spleen size for the diagnosis of those with high grade varices AUC 1.000(0.964 to 1.000), 0.995 (0.955 to 1.000), 0.913(0.841 to 0.960) respectively. **Conclusion:** Shear Wave Elastography (SWE) is a novel noninvasive independent variable for predicting high-risk esophageal varices in cirrhotic patients. Since SWE technique can be easily integrated into conventional ultrasound during a conventional liver ultrasound examination it helps to reduce medical, social, and economic costs particularly the endoscopic burden and also improve patient compliance.

Keywords: Shear wave elastography, esophageal varices, liver stiffness.

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Introduction

Esophageal varices are portosystemic collaterals developed in cirrhotic patients with portal hypertension.[1] Esophageal varices are one of the main complications of liver cirrhosis. Upper gastrointestinal endoscopy is the gold standard for the detection of esophageal varices.[1] Every year, a percentage of patients with cirrhosis (3-12%) develop esophageal varices and in 8-12% of patients, progression from small to large varices is detected.[2]

Clinically Significant Portal Hypertension leads to development of portosystemic collaterals, such as

ISSN 2515-8260 Volume 10, Issue 01, 2023

esophageal-, umbilical-, fundal- and/or rectal-varices. Detection of Clinically Significant Portal Hypertension most commonly relies on endoscopic screening for esophageal varices (EV) but may be (earlier) identified by hepatic venous pressure gradient (HVPG) measurements showing HVPG ≥ 10 mmHg.[3]

Endoscopy is an invasive procedure, requiring training and specialized infrastructure and is not well perceived by patients. Therefore, in recent years, several studies have investigated liver elastography as a non-invasive method for the diagnosis of esophageal varices and varices needing treatment.[3]

Shear wave elastography is one such non- invasive technique which is based on an ultrasound device which has been developed to detect liver stiffness.[4,5]

The ultrasound transducer in Shear wave elastography (SWE) emits many pulse wave beams at increasing depths, allowing the synchronous evaluation of the velocity of several shear wave fronts over a wide frequency range.[6]

However, not many studies have been done in this regard. So, in the present study, we aim to assess the diagnostic performances of Shear Wave Elastography liver for the noninvasive detection of the presence of esophageal varices.

Subjects and Methods

A total 102 patients were examined from June 2018 to February 2019. This study was approved by the ethical committee of our hospital, and written informed consent was obtained from all patients.

Cirrhosis either biopsy-proven or diagnosed on combined physical, biological, and radiological evidence Were included in the study. Patients with idiopathic portal vein thrombosis, presence of trans jugular intrahepatic portosystemic shunt, cardiac congestive liver, regenerative nodular hyperplasia, and hepatocellular carcinoma were not included in the study.

Dilwale Dulhania Le Jayenge, also known by the initialism DDLJ, is a 1995 Indian Hindi-language musical romance film written and directed by Aditya Chopra in his directorial debut and produced by his father Yash Chopra. Released on 20 October 1995, the film stars Shah Rukh Khan and Kajol. The plot revolves around Raj and Simran, two young non-resident Indians, who fall in love during a vacation through Europe with their friends. Raj tries to win over Simran's family so the couple can marry, but Simran's father has long since promised her hand to his friend's son. The film was shot in India, London, and Switzerland, from September 1994 to August 1995.

With an estimated total gross of ₹2 billion[3][4] ($60 million) worldwide,[5] Dilwale Dulhania Le Jayenge was the highest-grossing Indian film of 1995 and one of the most successful Indian films in history. It won 10 Filmfare Awards—the most for a single film at that time—and the National Film Award for Best Popular Film Providing Wholesome Entertainment. Its soundtrack album became one of the most popular of the 1990s.

Kuch Kuch Hota Hai (transl. Something Happens) also known as KKHH or K2H2, is a 1998 Indian Hindi-language romantic comedy-drama written and directed by Karan Johar and produced under Dharma Productions. It stars the popular on-screen pair of Shah Rukh Khan and Kajol in lead roles, along with Rani Mukerji and Salman Khan. It also features Sana Saeed in a supporting role. The plot combines two love triangles set years apart. The first half covers friends on a college campus, while the second tells the story of a widower's young daughter who tries to reunite her dad with his old best friend.

Filmed in India, Mauritius and Scotland, this was Johar's directorial debut. One of his goals for the film was to set a new level for style in Hindi cinema. The music was composed by Jatin–Lalit, which was the biggest seller of the year. Kuch Kuch Hota Hai was released on 16 October 1998, in India and United Kingdom and received positive reviews from critics who praised the setting, music, direction, cinematography, screenplay, performances and overall presentation. The film was successful in India and abroad, becoming the highest-grossing Indian film of the year and the third highest-grossing Indian film at that time. Outside India, the film was the highest-grossing Hindi film ever until its record was broken by

The film received various accolades, including the National Film Award for Best Popular Film Providing Wholesome Entertainment and Best Film at the Filmfare Awards, Screen Awards, Zee Cine Awards and Bollywood Movie Awards. Kuch Kuch Hota Hai won 8 Filmfare Awards and was the only film to win all four acting awards (Best Actor, Best Actress, Best Supporting Actor, and Best Supporting Actress) until Gully Boy.[7].

Liver stiffness measurement: After taking informed consent, all patients underwent abdominal ultrasonography; then measurement of hepatic stiffness were done by SWE technique (Elast PQ) using 1-5.0 MHZ high frequency curvilinear transducer (C5-1) on Philips Affiniti 70 ultrasound machine (PHILIPS medical systems, Bothell, WA) with the subject in supine or slight (30°) left lateral decubitus position. Subject was encouraged for shallow breath hold for a few seconds. The Region of Interest (ROI) was positioned on B-mode image of the liver in the right lobe of liver (typically segment VII or VIII) about 1.5 to 2 cm beneath the Glisson capsule, perpendicular to the liver capsule and elastography measurements were obtained. Multiple measurements were made. Median of 10 valid measurements was taken. The values of liver 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.[7]

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 SWE and the stages of esophageal varices was estimated using the Spearman's correlation coefficient. The diagnostic performance of SWE, platelets and spleen size were 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 maximized 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. Their ages ranged between 26 and 59 years with the mean age was 44 .73±8.6years. The mean body mass index (BMI) was 26.1±2.0kg/m^2. The findings are summarized in [Table 1].

Table 1: Patient characteristics

	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)	13.778431±1.6	<0.001

Table 2: Endoscopy esophageal varices grades

	No. of patients =n (%)

Grade 0	58 (56.86 %)
Grade 1	25 (26.32 %)
Grade 2	12 (11.76%)
Grade 3	07 (6.86 %)

The mean liver SWE stiffness values measured for each esophageal varices stage is summarized in [Table 3].

Table 3: Mean liver stiffness SWE in each grade of varices

Esophegeal varices grade	n=no of patients (%)	Mean stiffness (kPa)±SD
Grade0	58(56.86)	16.32 ±1.28
Grade1	25(26.32)	18.16 ± 1.00
Grade2	12(11.76)	24.42 ±0.70
Grade3	07(6.86)	26.50 ± 0.53
The difference between several groups were statistically significant ($p < 0.001$)		

Correlation: Positive correlation was detected between the measured stiffness of Liver by SWE and esophageal varices stage; correlation coefficient-Spearman rank (r) was 0.9178 ($p < 0.0001$). 95% Confidence interval for r.

Table 4: Correlations of the results of liver SWE;platelet count; splenic size with endoscopic esophageal varices stage

	Correlation coefficient (r)	Significance Level(P)
Liver SWE	0.9178	<0.0001
Platelet count	-0.927	<0.0001
Splenic size	-0.059	0.5582
Significant figures; +Suggestive significance (p-value: $0.05<p\leq0.10$); * Moderately significant (p-value: $0.01<p\leq0.05$); ** Strongly significant (p-value: $p\leq0.01$)		

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

Table 5: The optimal cutoff values of ElastPQ for different levels of fibrosis with observed AUCs and respective sensitivities, specificities, positive predictive value, negative predictive values and 95% confidence intervals.

	AUC	95%CI	Cut-off	Sensitivity	Specificity	LR+	LR-	PPV	NPV	P value

			(kPa)							
Grade 0	0.926	0.857 to0.969	<17.3	79.31	90.91	8.72	0.23	92.0	76.9	<0.0001
Grade 1	0.655	0.555 to 0.747	>17.3	84%	59.74%	2.09	0.27	40.4	92.0	<0.0001
Grade 2	0.922	0.852 to 0.966	>19.6	100.0	92.2	12.86	0.00	63.2	100.0	<0.0001
Grade 3	1.000	0.964 to 1.000	>25.3	100.0	100.0	-	0.00	100	100	<0.0001

Comparison of SWE with platelet and spleen size for detecting those with high grade esophageal varices [Table 6].

AUC value of SWE for predicting those with high grade Varices (Grade 2,3) was significantly higher than those of platelet count or spleen size .

Table 6: AUC for predicting those with high grade varices (Grade 2 & Grade 3)

	AUC (95%CI)
SWE AUC (95%CI)	1.00 (0.964 to 1.000)
Platelet count AUC (95%CI)	0.995 (0.955 to1.000)
Spleen size AUC (95%CI)	0.913 (0.841 to 0.960)

Discussion

In the present study, the diagnostic performance of liver shear wave elastography (SWE) for predicting esophageal varices was analyzed in 102 patients of which ultrasound elastography image of a case is shown in [Figure 1a & 1b].

Different treatment protocol is required According to different endoscopic levels of esophageal varices. Hence, in cirrhotic patients, it is very important to predict the level of esophageal varices for proper treatment protocols. However, endoscopy has its limitations being limited by its cost, invasiveness, and the discomfort for the patients. Hence in this study we assess the diagnostic performances novel non-invasive Shear wave elastography (SWE) technique to diagnose the presences of esophageal varices.

The new technology of shear wave elastography (SWE) to measure liver stiffness, enables a better determination of overall liver fibrosis distribution. Shear wave elastography has high reliability and reproducibility in assessing liver stiffness.[9] The advantage of shear wave elastography is that it can be integrated into conventional ultrasound images, which can be performed using conventional ultrasonic probe, greatly improving the diagnosis accuracy and reproducibility in assessing liver stiffness.[10]

The mean stiffness of liver SWE is given in table 3 ranged from 16.32 ±1.28 in no/Grade0 varices to 26.50 ± 0.53 in patients with grade 3 varices. Similarly in study done by Kim et al. reported SWE range of 13.1–30.3 kPa.[11]

Shear wave elastography also found that as liver stiffness increase, the more is the increase in the size of the varices [Table 3].

In present study, there was significant positive correlation between different stages of esophageal varices determined by endoscopy and liver stiffness detected by Shear wave elastography (SWE) (r= 0.9178, p <0.0001) [Table 4].

Few studies have been done to known our knowledge which evaluates the diagnostic performance of SWE in assessing liver stiffness in patients with esophageal varices, considering endoscopy as gold standard and providing a comparison with platelets and spleen.

ISSN 2515-8260 Volume 10, Issue 01, 2023

In our study the diagnostic performance of shear wave elastography (SWE) for assessing No varices (grade0) and high-risk varices (grade 2 and grade 3) was significantly high. [Table 5].
A test with high Negative predictive value and specificity can be considered as a screening test. In our present study, liver stiffness detected by Shear wave elastography showed high Negative predictive value and specificity and can be useful in daily practice as a screening test.
In this study, we have compared the diagnostic performances of liver stiffness by SWE, platelet count and spleen size for varices staging [Table 6]. Liver stiffness SWE exhibited higher diagnostic accuracy than the platelet count and spleen size for diagnosing those without varices and those with high grade varices.
On review of literature, there were limited previous studies comparing the SWE measurements and platelet count and spleen size. In a study by Kim et al The AUROC of liver stiffness for prediction of esophageal varices was significantly higher than the AUROCs of platelet count, and spleen diameter (P = .025; P = .001; P = .027).[11]
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, we used AUROC curve to know the optimal cut-off values of liver stiffness measurements by SWE to differentiate different stages of varices. The optimum cut-off values for Grade 0, Grade1, Grade2, Grade3 patients is <17.3 kPa ;> 17.3 kPa; >19.6 kPa and >25.3 kPa.
The optimal cut-off values for predicting the presence of esophageal varices and high-risk varices were 13.9 kPa and 16.1 kPa respectively in study done by Kim et al.[11]
The minor increase in stiffness in our study compared to this study by Kim et al may be attributed to different study group with different etiologies. Particularly in our study there were more patients with alcoholic liver disease and it has been known that patients with alcoholic liver disease tends to have higher liver stiffness compared to patients with viral hepatitis.[12]

Limitations

Our study had several limitations. First, it involved a small number of patients in a single institution however, considering the limitations of endoscopy having large sample size itself is cumbersome.
In previous studies we know that liver stiffness in alcoholic liver disease is higher than in viral hepatitis[12] . In our study, there was various diverse etiologies causing liver disease including alcoholic liver disease, viral hepatitis, and autoimmune hepatitis. The role of different etiologies on stiffness score is not accounted for.

Conclusion

Shear Wave Elastography (SWE) is a novel noninvasive independent variable for predicting high-risk esophageal varices in cirrhotic patients. Since SWE technique can be easily integrated into conventional ultrasound during a conventional liver ultrasound examination it helps to reduce medical, social, and economic costs particularly the endoscopic burden. And also improve patient compliance.
However further studies with larger study group are needed, particularly evaluating various etiologies causing cirrhosis and its complications.

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