Hindawi
GastroHep
Volume 2023, Article ID 4912991, 9 pages
https://doi.org/10.1155/2023/4912991

Research Article

Spleen Stiffness Measured by 2D-Shear Wave Elastography and Rebleeding Risk in Cirrhotic Patients Undergoing Endoscopic Variceal Ligation for Variceal Bleeding

Swetha Sattanathan, Krishnadas Devadas, Shanid Ahmed, Atul Hareendran, Arun Prabhakaran, and Nidhin Raveendran

Department of Medical Gastroenterology, Government Medical College, Thiruvananthapuram, Kerala, India

Correspondence should be addressed to Swetha Sattanathan; swethasattanathan@gmail.com

Received 4 February 2022; Revised 21 March 2022; Accepted 5 July 2022; Published 10 January 2023

Academic Editor: Arjun Sugumaran

Background and Aims. Endoscopic variceal ligation (EVL) of esophageal varices alters the portal pressure. We observed the changes in 2D-shear wave elastography (2D-SWE) measurements of spleen and liver following EVL and tried to identify the predictors for rebleeding and mortality at 6 months. *Methods.* A prospective observational study of 202 patients who underwent EVL for bleeding esophageal varices was done. 2D-SWE measurements of liver stiffness (LS) and spleen stiffness (SS) and spleen volume (SV) were measured half an hour before, 1 hour, 2 weeks, and 6 weeks after EVL. All were followed up for 6 months for rebleeding and all-cause mortality. *Results.* 83 patients were in child C (41%). Difference in SV, SS, and LS at 2 and 6 weeks from baseline was noted as Delta 2 (2^{nd} week post-EVL - pre-EVL SV, LS, and SS) and Delta 3 (6^{th} week post EVL - pre - EVL SV, LS and SS), respectively. Mean Delta 2 VOL and Delta 3 VOL were lower in the bleeding and mortality groups. Delta 2 SS, Delta 3 SS, Delta 2 LS, and Delta 3 LS were higher in the rebleeding and mortality groups. These changes were statistically significant. AUROC in predicting rebleeding was the highest for Delta 2 VOL (0.773) and Delta 3 LS (0.764) amongst the USG parameters that performed better than MELD score (0.677). AUROC in predicting mortality was the highest for Delta 3 VOL and Delta 2 VOL-0.873 and 0.842, respectively, and higher than MELD's (0.641). Statistically significant variables in binary logistic regression analysis for rebleeding were Delta 3 LS and Delta 3 SS and none for mortality. *Conclusion.* LS, SS, and SV change after EVL. Changes in liver and spleen stiffness at 6 weeks from baseline had good diagnostic accuracy for predicting rebleeding at 6 months.

1. Introduction

The development of portal hypertension (PHT) in liver cirrhosis is the key factor in increasing mortality and complications. Hepatic venous pressure gradient (HVPG) is the gold standard in diagnosing PHT, and a value more than 10 mm Hg defines clinically significant portal hypertension (CSPH). Since HVPG measurement is scarcely available and invasive, several noninvasive tests are used as surrogate markers of CSPH. Amongst them, elastography techniques measuring liver stiffness (LS) and spleen stiffness (SS) are the extensively studied ones. Though vibration-controlled transient elastography (VCTE) technique is the most commonly available and the most extensively studied method, it needs a special instrument, and hence elastography machines that can be attached to conventional ultrasound (USG) machines are gaining popularity. Amongst them, 2D-shear wave elastography (2D-SWE) is the most recent one, and it assesses stiffness and related parameters by tracking shear waves propagated through a media. Faster imaging techniques and multiple ROI (region of interest) placements when compared to VCTE make them more attractive [1]. But because of its restricted availability, fewer studies on diagnostic performance are available.

Though elastography techniques are routinely used to screen for high-risk varices in compensated cirrhosis, their

role in identifying resolution/persistent varices after a variceal hemorrhage has not yet been studied. Also, endoscopic variceal ligation (EVL), the principal endoscopic modality for bleeding esophageal varices, has been known to alter portal pressure. Hence, we planned this study to investigate whether any changes are happening in the 2D-SWE properties of the liver and spleen after EVL and if changes are happening, whether they are associated with rebleeding and mortality. These changes if identified can help us in better prognostication of patients after a variceal hemorrhage and may even obviate the repeat endoscopy in less risky patients.

Since the survival of patients has improved beyond 6 months in many patients with variceal hemorrhage, we also wanted to explore the percentage of rebleeding and/or mortality at a period of 6 months and its predictors.

2. Materials and Methods

This is a prospective observational study conducted at a university hospital in Kerala, South India, after obtaining approval from the Institutional Ethics Committee (HEC No. 04/27/2019/MCT). 202 patients aged above 18 years, with cirrhosis (diagnosed by standard clinical, radiological, or by histopathological changes) and bleeding esophageal varices undergoing EVL, were taken up for the study. All participants gave written informed consent. We excluded patients with extrahepatic portal vein obstruction, portal/splenic vein thrombosis, mass lesions in the spleen, and who had undergone transjugular intrahepatic portosystemic shunting procedures (TIPSS) or endoscopic sclerotherapy in the preceding 6 weeks.

2.1. Study Protocol. Patients who presented with variceal bleeding and endoscopy showing grade 2 esophageal varices with red color signs or higher grades underwent ligation with multiband ligators. They were treated with vasopressors before and after EVL, followed by an oral nonselective beta-blocker (NSBB) according to the standard treatment guidelines. Patients were followed up, and EVL was repeated every 2 weeks till variceal eradication. Varices were classified as follows:

(i) Grade 1: small, straight varices

(ii) Grade 2: enlarged, tortuous varices that occupy <1/3 of the lumen

(iii) Grade 3: large coil-shaped varices that occupy >1/3 of the lumen

2.2. Shear Wave Elastography Measurements. These patients underwent 2D-SWE measurements using Aixplorer (Supersonic Imagine, France) with a convex probe of 1-6 MHz. 2D-SWE values, expressed in kilopascal (kPa), were mapped with a color-coded two-dimensional image with simultaneous conventional B-mode images. All patients were fasting overnight, as required for their upper GI endoscopy. Two experienced ultrasonologists trained in 2D-SWE image acquisition, who had performed at least 200 2D-SWE measurements obtained measurements. Liver stiffness (LS) was obtained at least 1 cm deep to the liver capsule but less than 6 cm deep from the skin surface. Each LS acquisition consisted of 5 sequential measurements obtained in the upper right hepatic lobe via an intercostal approach with breath held at end-expiration and the patient in a supine position. A 10 mm region of interest was chosen, and size changed if necessary, according to the amount of measurable parenchyma and the locations of large vessels, avoiding blood vessels or portal tracts. The mean value was used. After LS measurement, spleen was visualized in the right lateral decubitus position with the left arm at maximum abduction, and the depth of breathing adjusted to increase the visibility of the spleen and its size measured. Spleen stiffness (SS) and LS were measured similarly. A stiffness measurement was considered valid when it has a stability index > 90%. The measurement was considered inconclusive when the spleen/liver parenchyma did not provide a properly color-coded elastography or a valid stiffness value was not obtained.

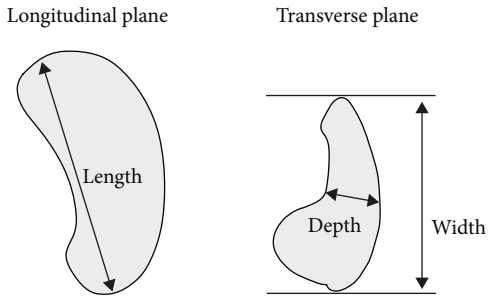

Figure 1: Measurement of spleen dimensions by ultrasound.

Splenic volume (SV) was calculated using the standard prolate ellipsoid formula (length × width × depth × 0.5232) (Figure 1).

The readings obtained were as follows:

(1) Pre-EVL (30 min before EVL) (SV0, SS0, LS0) (SV: splenic volume; SS: spleen stiffness; LS: liver stiffness)

(2) Post-EVL (1 hour after EVL) (SV1, SS1, LS1)

(3) First relook (at 2 weeks from EVL) (SV2, SS2, LS2)

(4) 6^{th} week (at 6 weeks from EVL) (SV3, SS3, LS3)

The changes in each value during serial measurements were denoted as Delta where

(1) Delta 1 = 1 hour post-EVL – pre-EVL (Delta 1 SV, Delta 1 SS, Delta 1 LS)

(2) Delta 2 = 2^{nd} week post-EVL – pre-EVL values (Delta 2 SV, Delta 2 SS, Delta 2 LS)

(3) Delta 3 = 6^{th} week post-EVL – pre-EVL values (Delta 3 SV, Delta 3 SS, Delta 3 LS)

All these patients will be followed up with a telephonic conversation at 6 months regarding the rebleeding episodes

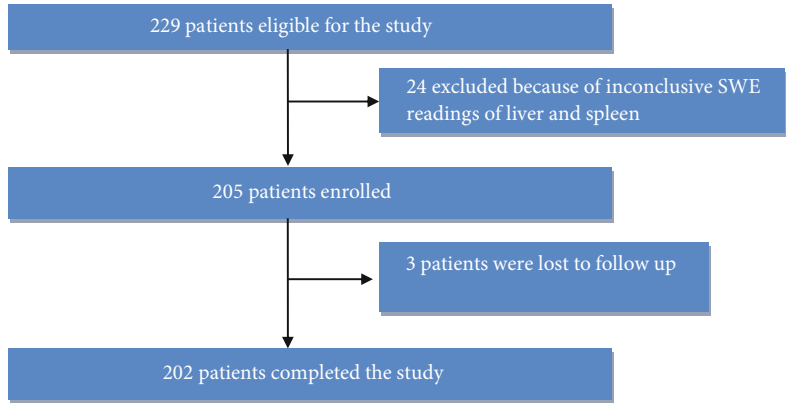

Figure 2: CONSORT diagram of the study.

and/ or all-cause mortality. Throughout the article, the following references are used:

(1) Delta 1 VOL = (1 hour post-EVL splenic volume − pre-EVL splenic volume)

(2) Delta 2 VOL = (2^{nd} week post-EVL splenic volume − pre-EVL splenic volume)

(3) Delta 3 VOL = (6^{th} week post-EVL splenic volume − pre-EVL splenic volume)

(4) Delta 1 SS = (1 hour post-EVL splenic stiffness − pre-EVL splenic stiffness)

(5) Delta 2 SS = (2^{nd} week post-EVL splenic stiffness − pre-EVL splenic stiffness)

(6) Delta 3 SS = (6^{th} week post-EVL splenic stiffness − pre-EVL splenic stiffness)

(7) Delta 1 LS = (1 hour post-EVL liver stiffness − pre-EVL liver stiffness)

(8) Delta 2 LS = (2^{nd} week post-EVL liver stiffness − pre-EVL liver stiffness)

(9) Delta 3 LS = (6^{th} week post-EVL liver stiffness − pre-EVL liver stiffness)

2.3. Ethical Concerns. Upper GI endoscopy with EVL for treatment of esophageal varices was performed on all subjects as per AASLD guidelines on the treatment of portal hypertension and variceal hemorrhage. Ultrasound abdomen and shear wave elastography, which are noninvasive procedures, were carried out as part of the study.

2.4. Statistical Analysis. The statistical analysis was performed using IBM SPSS version 25. Continuous variables were reported as mean and standard deviation (SD). Categorical variables were reported as frequency and percentage. Comparison between groups was performed using the independent *t*-test for continuous variables with normal distribution and the Chi-square test or Fisher's exact test for categorical variables. The paired *t*-test was used to assess the significance of changes in different parameters in different subgroups following EVL. Baseline variables were analyzed, and univariate analysis was performed to find out factors predicting rebleeding and mortality at 6 months. Variables found to have $p < 0.05$ on univariate analysis were evaluated with binary logistic regression analysis.

3. Results

202 patients who underwent EVL as secondary prophylaxis were enrolled, and the CONSORT diagram is shown in Figure 2. The demographics and baseline parameters are given in table 1.

The commonest etiology of liver cirrhosis in males was alcohol (52.6%) and in females, it was NASH (58.6%).47 (23.3%) patients had a rebleeding episode, and 41 (20.2%) patients had died within 6 months. The various parameters of patients were compared between patients those who had a rebleeding episode and those without and those who died and those who survived by univariate analysis. The results are tabulated in Tables 2 and 3.

The Receiver Operating Characteristic ROC was plotted for MELD, and the USG parameters found to have significant association in univariate analysis. With regard to rebleeding, the Area Under Receiver Operating Characteristics (AUROC) of Delta 2 VOL, Delta 2 LS, Delta 3 LS, and Delta 3 SS was higher than that of MELD's. With respect to mortality within 6 months, AUROC of all the USG parameters found to be significantly associated with mortality at 6 months in univariate analysis had a higher AUROC than that of MELD's. The AUROC values and the optimum cut-offs of various parameters and their sensitivity and specificity values are shown in Table 4. The AUROC curves of USG parameters and MELD are given in Figures 3–6.

The variables identified in univariate analysis to have a significant association with rebleeding and mortality were subjected to binary logistic regression analysis, and the results are tabulated in tables 5.

4. Discussion

Acute esophageal variceal bleeding is a common but severe, life-threatening complication in patients with cirrhosis and portal hypertension. EVL has largely reduced mortality due

Table 1: Baseline characteristics of the study population.

Characteristic	Value
Age (years)	54.4 ± 11.2 (45-64)
Male	173 (85.6%)
Aetiology of cirrhosis (*n*, %)	
Alcohol	91 (45%)
BASH	40 (19.8%)
NASH	39 (19.3%)
HBV	23 (11.3%)
HCV	5 (2.5%)
Others	4 (2.1%)
Comorbidities	
Diabetes mellitus	62 (50.8%)
Systemic hypertension	46 (37.7%)
Dyslipidaemia	14 (11.4%)
Child status	
A	47 (23.3%)
B	72 (35.6%)
C	83 (41.1%)
MELD	17.96 ± 4.36 (15-20)
Platelet count (lakh/mm^3)	0.9 ± 0.3 (0.7-1.2)
Albumin (mg/dL)	3.0 ± 0.4 (2.5-3.3)
Hepatocellular carcinoma	16 (7.9%)
Compliance to treatment	141 (69.8%)
Post 2 weeks repeat EVL required	88 (43.6%)
3rd EVL required	20 (9.9%)
Pre-EVL SV (cm^3)	797.7 ± 314.2 (560.5-933.5)
Pre-EVL LS (kPa)	31.9 ± 12.1 (23-35.8)
Pre-EVL SS (kPa)	69.4 ± 13.7 (61-80.5)
Delta 1 VOL (cm^3)	42.5 ± 178.3 (-59.4-121.9)
Delta 1 SS (kPa)	−2.8 ± 15 (-12.1-4)
Delta 1 LS (kPa)	−12.3 ± 20.9 (-25-1.2)
Delta 2 VOL (cm^3)	−50.4 ± 723.2 (-99.7-193.3)
Delta 2 LS (kPa)	2.6 ± 12.5 (1.1-7.4)
Delta 2 SS (kPa)	10.9 ± 11 (6-15.4)
Delta 3 VOL (cm^3)	−26.4 ± 413.3 (-242.3-231)
Delta 3 LS (kPa)	11.0 ± 10.6 (6-17.4)
Delta 3 SS (kPa)	16.1 ± 20.6 (10.2-24)
Patients with rebleeding at ≤6 months	45 (23.3%)
Patients who died at ≤6 months	41 (20.2%)

BASH: both alcoholic and nonalcoholic steatohepatitis; NASH: nonalcoholic steatohepatitis; HBV: hepatitis B virus; HCV: hepatitis C virus; MELD: model for end stage liver disease.

to variceal bleeding. Guidelines recommend repeating endoscopies in patients who had their varices tackled by EVL till the varices are demonstrated to be obliterated since there are no noninvasive methods to reliably predict the obliteration of varices [2, 3]. This adds to the burden on both the patients and the infrastructure. Hence, there is a need for a simple, reproducible, and noninvasive predictor of recurrent varices in follow-up endoscopies.

It has been shown that EVL alters the portal pressure by Lo *et al*. They demonstrated that the majority of patients experienced elevated portal pressure after EVL. The patients who had a reduction in portal pressure after EVL had other major collaterals apart from esophageal varices, compared to patients with elevated portal pressure. This elevation of portal pressure after EVL ligation and lack of collateral circulation was postulated to be an important factor in variceal rebleeding [4].

Recent studies demonstrated that SS is a good predictor of PHT since it reflects both the hepatic and extrahepatic components of PHT. SS > 54 kPa reliably predicts high-risk esophageal varices according to the BAVENO VI consensus [5]. No studies are available that measure the change in SS happening as a result of changes in portal pressure induced by EVL, and whether these changes can be related to rebleeding and mortality at 6 months. Hence, we planned this study to measure the same.

Our study involved 202 patients. 114 (56.4%), 88 (43.6%), and 20 (9.9%) required one, two, and three sessions of EVL, respectively. This was similar to the observation by Ahmed *et al*. wherein 25 (36.2%) patients had variceal obliteration after the first EVL, while 32 (46.4%) and 12 (17.4%) required two and three sessions, respectively [6].

In our study, 47 (23.3%) patients had a rebleeding episode at 6 months. Though studies on the rebleeding frequency at 6 months following EVL are not available, this can be extrapolated from the rebleeding frequencies of 40.5% at 1 year in the study by He *et al* and 19% in the median follow-up of 15 ± 12 months in the study by Kumar *et al*. [7, 8].

Of the 47 patients who had rebleed, 14, 12, and 21 (29, 16, and 25%) were in child A, B, and C groups, respectively, $p = 0.216$. This could be due to the confounding effect of HCC, as the proportion of patients who had rebleed was 10 : 11 : 16 (27, 30, and 44%) in child groups A, B, and C, respectively, when HCC was excluded.

The endoscopy findings that had a significant association with rebleeding were the presence of portal hypertensive gastropathy (PHG) and gastroesophageal varices (GOV) at first relook scopy. PHG was mild in 30 (20%) and severe in 17 (34%) patients. GOV 1 and GOV 2 were found in 18 (46%) and 2 (13%) patients who bled again. This can be explained based on the fact that PHG has been significantly associated with the severity of portal hypertension as noted by Kumar *et al* and Kim *et al* [9, 10].

On univariate analysis, MELD was found to be higher in patients who have had a rebleeding episode (19.64 ± 3.48 vs. 17.45 ± 4.50, $p = 0.002$). This is in concurrence with the observations by Chen *et al*. and Wang *et al* who had validated the utility of MELD scores in predicting rebleeding at 6 weeks [11, 12].

In this study, 41 (20.2%) patients had died by the end of 6 months which can be again extrapolated from the mortality rates of 40% observed at 1 year by Sharma *et al*. [13].

On univariate analysis, child distribution (A:B:C) (8 : 7 : 26), (17 : 9 : 31%, $p = 0.003$) and higher mean MELD scores (19.34 ± 5.75 vs. 16.96 ± 3.907, $p = <0.001$) were found to be significantly associated with mortality. This is

Table 2: Association of qualitative variables with rebleeding at 6 months.

Univariate analysis	Rebleeding at 6 months			Mortality at 6 months		
Parameter	Frequency (percentage)	p value	Chi^2	Frequency (percentage)	p value	Chi^2
Male/female	40 : 7 (23 : 24)	0.905	0.014	39 : 2 (23 : 7)	0.053	3.759
Child status (A:B:C)	14: 12: 21 (30 : 17 : 25)	0.216	3.068	8 : 7 : 26 (17 : 9 : 31)	**0.003**	11.53
Pre-EVL largest column (grade 2 : 3)	11 : 36 (19 : 25)	0.403	0.701	31 (21)	0.54	0.37
Largest column at first relook (1 : 2 : 3)	15 : 7 (25 : 19 : 29)	0.51	1.348	23 : 11 : 7 (23 : 14 : 29)	0.177	3.469
Change in varix grade at first relook-0 : 1 : 2	—	—	—	5 : 15 : 21	0.103	4.546
Change in varix number at first relook (-1 : 0 : 1:2 : 3)	—	—	—	4 : 25 : 5 : 5 : 2 (9 : 26 : 15 : 55 : 8)	**0.005**	14.9
Pre-EVL PHG (mild/severe)	39 : 8 (23 : 26)	0.716	0.132	34 : 7 (19 : 22)	0.731	0.128
Relook PHG (mild/severe)	30 : 17 (20 : 35)	**0.03**	4.731	28 : 13 (18 : 26)	0.213	1.554
Pre-EVL other varices (no: GOV1/GOV2)	18 : 3 (33 : 23)	0.118	4.28	11 : 2 (20 : 15)	0.9	0.211
Other varices at first relook (GOV1/GOV2)	18 : 2 (46 : 13)	**0.001**	14.36	10 : 2 (25 : 13)	—	1.183
Post 2 weeks repeat EVL required	24 (27)	0.237	1.401	20 (22)	0.451	0.569
Post 4 weeks 3rd EVL required	2 (10)	0.139	2.189	3 (15)	0.535	0.385
Compliance	30 (21)	0.309	1.036	27 (19)	0.537	0.38
Poor control of comorbidities	12 (42)	0.332	0.94	10 (35.7)	0.123	2.376

Table 3: Association of quantitative parameters with rebleeding and mortality at 6 months.

Univariate analysis	At 6 months			At 6 months		
Parameter	Rebleeding	No rebleeding	p value	Mortality	No mortality	p value
Age (years)	56.2 ± 12.4	53.9 ± 10.8	0.209	56.9 ± 13.2	53.8 ± 10.6	0.114
MELD	19.64 ± 3.48	17.45 ± 4.50	**0.002**	20.07 ± 5.34	17.42 ± 3.94	<0.001
Platelet count (lakh/mm^3)	1.01 ± 0.37	0.92 ± 0.33	0.098	1.06 ± 0.38	0.91 ± 0.33	0.01
Albumin (g/dL)	2.97 ± 0.47	2.94 ± 0.42	0.68	2.82 ± 0.44	2.98 ± 0.42	0.031
Pre-EVL SV (cm^3)	750.7 ± 194.3	811.9 ± 341.6	0.243	743.2 ± 260.5	811.6 ± 325.7	0.214
Pre-EVL LS (kPa)	36.3 ± 16.2	30.6 ± 10.2	0.014	31 ± 11.5	32.1 ± 12.3	0.609
Pre-EVL SS (kPa)	69.6 ± 13.2	69.3 ± 13.8	0.905	70.3 ± 12.7	69.1 ± 13.9	0.621
Delta 1 VOL (cm^3)	53.8 ± 155.9	39.2 ± 184.9	0.624	3.44 ± 125.2	52.5 ± 188.5	0.116
Delta 1 SS (kPa)	−6.41 ± 20.7	−1.66 ± 12.71	0.058	−5.31 ± 16.43	−2.12 ± 14.65	0.226
Delta 1 LS (kPa)	−13.92 ± 18.2	−11.83 ± 21.73	0.551	−20.10 ± 19.53	−10.34 ± 20.87	20.87
Delta 2 VOL (cm^3)	40.18 ± 43.24	250.78 ± 300.33	<0.001	28.24 ± 33.77	245.97 ± 295.61	<0.001
Delta 2 SS (kPa)	16.38 ± 8.05	12.29 ± 10.17	0.012	21.31 ± 14.83	11.19 ± 6.78	<0.001
Delta 2 LS (kPa)	10.31 ± 7.08	5.35 ± 5.20	<0.001	12.07 ± 7.35	5.09 ± 4.75	<0.001
Delta 3 VOL (cm^3)	140.85 ± 97.46	263.99 ± 261.28	**0.002**	66.07 ± 81.01	278.44 ± 246.99	<0.001
Delta 3 SS (kPa)	24.07 ± 10.07	16.90 ± 9.55	<0.001	22.56 ± 9.06	17.55 ± 10.14	0.004

in concurrence with the previous observation by Chen *et al* that MELD is a good predictor of mortality after variceal bleeding at 6 weeks [11, 14, 15].

In our study, mean Delta 2 VOL and mean Delta 3 VOL were significantly lower in patients who had rebleeding than in those who did not. The values of mean Delta 2 VOL and Delta 3 VOL were 40.18 ± 43.24 vs. 250.78 ± 300.33 cm^3, p = <0.001, and 140.85 ± 97.46 vs. 263.99 ± 261.28 cm^3, p = 0.002, respectively. Similarly, mean Delta 2 VOL and mean Delta 3 VOL were lower in the mortality group (28.24 ± 33.77 vs. 245.97 ± 295.61 cm^3 and 250.78 ± 300.33 vs. 263.99 ± 261.28 cm^3, respectively) than in the survivors.

Mean Delta 2 SS and Delta 3 SS were significantly higher in the rebleeding group (16.38 ± 8.05 vs. 12.29 ± 10.17 kPa, p = 0.012) (24.07 ± 10.07 vs. 16.90 ± 9.55, p = <0.001), respectively. Similarly, Delta 2 SS and Delta 3 SS were higher in the group with mortality than in the group that remained alive at 6 months. The values were 21.31 ± 14.83 vs. 11.19 ± 6.78 kPa, p = <0.001, and (22.56 ± 9.06 vs. 17.55 ± 10.14 kPa, p = 0.004), respectively.

Table 4: AUROC and cut-off of various parameters in predicting rebleeding.

USG parameter		AUROC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
Delta 2 LS (kPa)	Rebleeding	0.743 (0.677-0.802)	>3.9	97.8	45.8
	Mortality	0.841 (0.784-0.889)	>11.9	63.4	93.1
Delta 2 SS (kPa)	Rebleeding	0.674 (0.604-0.738)	>9.8	87.2	43.8
	Mortality	0.754 (0.689-0.812)	>13.9	70.7	70.2
Delta 2 VOL (cm^3)	Rebleeding	0.773 (0.709-0.829)	≤46.9	76.6	72.9
	Mortality	0.842 (0.784-0.889)	≤44	85.3	74.5
Delta 3 LS (kPa)	Rebleeding	0.764 (0.699-0.820)	>12.9	78.7	62.6
	Mortality	0.717 (0.649-0.778)	>17	95.1	42.2
Delta 3 VOL (cm^3)	Rebleeding	0.638 (0.568-0.704)	≤173	59.5	56.7
	Mortality	0.873 (0.819-0.916)	≤58	75.6	93.2
Delta 3 SS (kPa)	Rebleeding	0.706 (0.638-0.767)	>21	63.8	72.2
	Mortality	0.668 (0.598-0.732)	>17	68.2	63.4
MELD	Rebleeding	0677 (0.608-0.741)	>19	51.1	76.7
	Mortality	0.641 (0.569-0.706)	>19	48.8	75.2

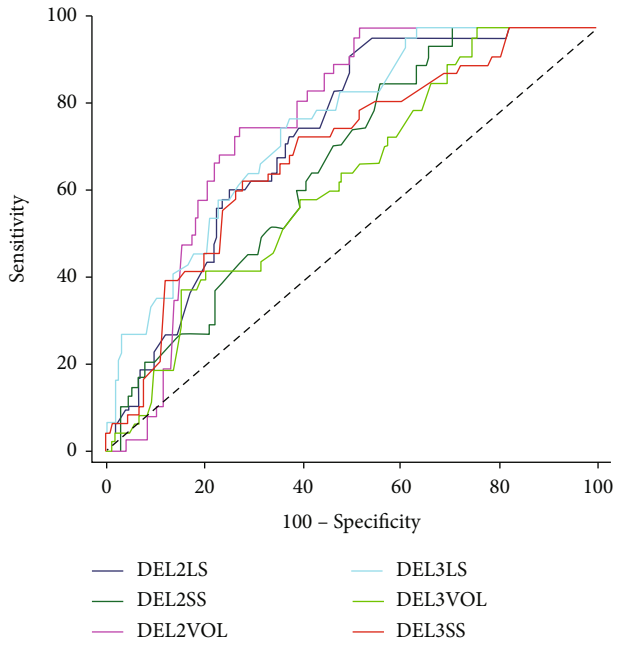

Figure 3: AUROC of USG parameters in predicting rebleeding.

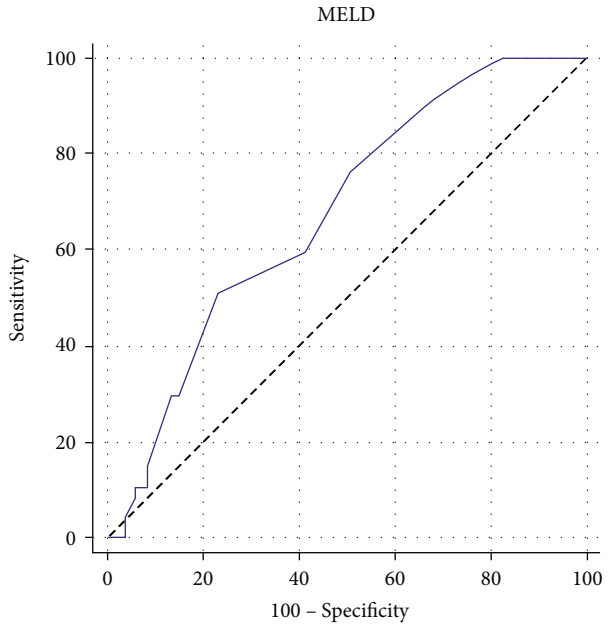

Figure 4: AUROC of MELD in predicting rebleeding.

This reduction in SV with an increase in SS in the rebleeding and mortality group can be hypothesized to the lack of collaterals and worsening of PHT. This impact of collateral circulation has been shown by Tarantino *et al* that the median splenic vein flow velocity in patients with splenorenal shunts was significantly inferior to that of patients without them [16]. This reduction in splenic vein flow velocity could be the explanation for the decrease in SS in patients with significant extra esophageal collaterals and consequently no rebleeding episodes at 6 months. They are probably having less severe PHT and fewer complications.

Another observation in our study was that Delta 2 LS and Delta 3 LS were significantly higher in the rebleeding group than in the other (10.31 ± 7.08 vs. 5.35 ± 5.20 kPa, $p < 0.001$) and (19.25 ± 7.72 vs. 11.99 ± 6.75 kPa, $p = <0.001$), respectively. Also, Delta 2 LS and Delta 3 LS were significantly higher in the mortality group than in the survivors. The values were 12.07 ± 7.35 vs. 5.09 ± 4.75 kPa, $p = <0.001$, and 18.04 ± 7.20 vs. 12.57 ± 7.33 kPa, respectively.

This can be explained based on the observation by Piecha *et al* who evaluated the changes in HVPG with EVL and TIPS. They noted that LS increased transiently in the majority following EVL and in few after TIPS. They postulated that the collateral circulation determines the changes in stiffness happening after EVL/TIPS. Patients with more fibrosis/severe disease can have an increase in stiffness while

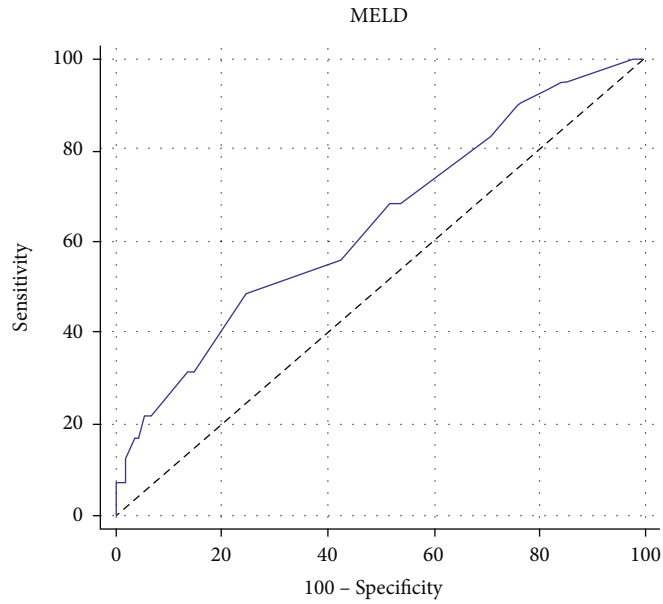

Figure 5: AUROC of MELD in predicting mortality.

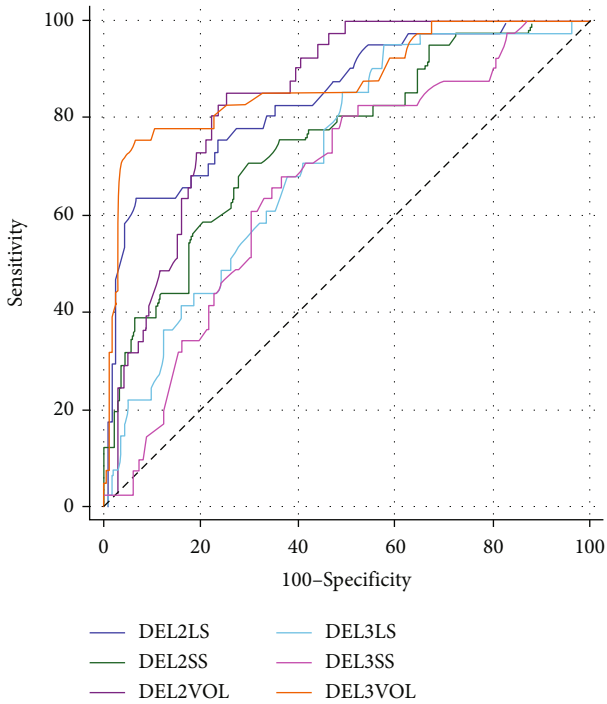

Figure 6: AUROC of USG parameters in predicting mortality.

those with lesser fibrosis and/or more collaterals had a reduction in stiffness [17]. Those who had rebleeding/mortality had probably lesser collaterals and consequent worsening of PHT.

The variables identified to be significant in univariate analysis were subjected to binary logistic regression analysis. Delta 3 SS and Delta 3 LS were found to have a significant positive correlation with rebleeding with an odds ratio (OR) of 1.075, 95% CI (1.03-1.12), and 1.156 95% CI (1.08-1.23), respectively. None of the variables were predictive of mortality.

The AUROC of MELD for the prediction of the rebleeding episode and mortality was 0.677 and 0.641, respectively. With a cut – off > 19, the sensitivity and specificity were 51% and 76%, respectively, for a rebleeding episode and 48% and 75%, respectively, for predicting mortality.

The AUROC of Delta 2 VOL, Delta 2 SS, and Delta 3 SS for predicting rebleeding was 0.773, 0.674, and 0.706, respectively, and higher than that of MELD. With a cut-off of $\leq 46.9\,cm^3$, the sensitivity and specificity of Delta 2 VOL were 76% and 72%, respectively. The cut-offs for Delta 2 SS and Delta 3 SS were >9.8 and >21 kPa, respectively. The sensitivity and specificities were 87% and 43% for Delta 2 SS and 63% and 72% for Delta 3 SS, respectively.

The AUROC of all the ultrasound parameters in predicting mortality was more than that of MELD's. The highest among them were for Delta 2 VOL (0.842) and Delta 2 LS (0.841). At a cut-off of $\leq 44\,cm^3$, the sensitivity and specificity of Delta 2 volume were 85% and 74%, respectively. The cut-off of Delta 2 LS was >11.9 kPa, and sensitivity and specificity were 63% and 93%, respectively.

Though there are studies regarding the utility of 2D-SWE in diagnosing CSPH, no studies are available regarding the change in the elastography parameters that happen as a result of EVL-induced changes in portal pressure. Our study shows that significant changes are happening after EVL, and they can be used to predict rebleeding and mortality. Especially, the difference in LS and SS at 6 weeks from the baseline is found to be statistically significant in binary logistic regression analysis to predict rebleeding at 6 months. Our study needs further validation in a larger cohort.

We admit that the study has limitations. The exact reason for the varied response in portal pressure could not be ascertained. The presence of significant portosystemic collaterals was hypothesized to be the reason but it was not

Table 5: Binary logistic regression analysis of variables to predict rebleeding and mortality.

	Rebleeding		Mortality	
	p value	Odds ratio	p value	Odds ratio
Change in varix number	0.088	0.686 (0.444-1.058)	0.559	0.819 (0.42-1.599)
PHG at first relook	0.121	2.321 (0.8-6.729)	—	—
MELD	0.227	1.058 (0.966-1.158)	0.395	1.061 (0.925-1.218)
Delta 3 VOL (cm^3)	0.027	0.997 (0.994-1)		0.979 (0.97-0.988)
Delta 3 SS (kPa)	0.001	1.075 (1.03-1.122)	0.985	0.985 (0.93-1.044)
Delta 3 LS (kPa)	<0.001	1.156 (1.084-1.233)	0.054	1.088 (0.999-1.185)
Child status	—	—	0.228	1.719 (0.713-4.145)

objectively demonstrated. But to the best of our knowledge, this is the first study of its kind to look at changes happening in elastography properties of the liver and spleen and its usefulness in predicting rebleeding and mortality at 6 months in patients undergoing secondary prophylaxis for esophageal varices.

If validated in larger cohorts, these noninvasive tests can identify people at increased risk of recurrent variceal hemorrhage and mortality enabling increased surveillance in this high-risk population.

5. Conclusion

Liver and spleen stiffness as measured by 2D-SWE and spleen volume changes after endoscopic variceal ligation and is reflective of the dynamic nature of portal hypertension. The difference in spleen volume from baseline at 2 weeks and 6 weeks after EVL is significantly lower in both the rebleeding and mortality group than in the nonrebleeders and survivors. Also, the difference in spleen and liver stiffness at 2 weeks and 6 weeks after EVL is higher in the rebleeding group and those who had died by the end of 6 months than in the nonrebleeding group and group who survived. The difference in liver and spleen stiffness at 6 weeks had a good diagnostic accuracy for rebleeding at 6 months.

Data Availability

The data used to support the findings of this study are included within the manuscript.

Disclosure

This research paper was presented in the Indian National Association for the Study of the Liver-28th Annual scientific Meeting held virtually from 6th to 8th August, 2021, in Young Investigator Award session.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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