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Original Research Article

Prediction of esophageal varices in cirrhosis by using splenic stiffness measurement

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ABSTRACT

Background: Predicting esophageal varices in cirrhosis using the measurement of splenic stiffness is an exciting area of study. Vein enlargement in the lower esophagus, known as varices, is a common symptom of cirrhosis caused by portal hypertension. These varicose veins are potentially fatal since they bleed easily. The present study aims to predict the OV in cirrhosis patients by splenic stiffness in and around this region.
Methods: After receiving permission from the Institutional Ethics Committee, the study was performed. The present study authors measured splenic stiffness and liver stiffness by using FibroScan in 112 consecutive cirrhotic patients who met the inclusion criteria. Patients were also assessed by hepatic venous pressure gradient (HVPG), upper gastrointestinal endoscopy, liver stiffness, liver spleen diameter to platelet ratio score, and platelet count to spleen diameter ratio.
Results: Among 112 patients enrolled, 64 patients had valid liver stiffness and splenic stiffness measurement, and 64 patients had EV (small, n=23 and large n=42). There was a significant difference in median liver stiffness (54.2 vs. 21.3 kPa, $p<0.05$), splenic stiffness (56.1 vs. 30 kPa, $p<0.05$), liver spleen diameter to platelet ratio score (6.3 vs. 2.7, $p<0.05$), and platelet count to spleen diameter ratio (798 vs 1,241, $p<0.05$) between patients with OV and those without OV.
Conclusions: Non-invasive markers, such as splenic stiffness, may help identify individuals with cirrhosis who are at risk of having esophageal varices, especially large ones, and who are at risk of bleeding, the study's authors conclude.

Keywords: Esophageal varices, Liver stiffness, Platelet score, Portal hypertension, Splenic stiffness, Transient elastography

INTRODUCTION

The utilization of splenic stiffness assessment to predict the occurrence of esophageal varices (EV) in individuals with cirrhosis is a captivating field of research. Varices, which refer to the dilation of veins in the lower esophagus, are a prevalent manifestation of portal hypertension-induced cirrhosis. Varicose veins possess a significant fatality risk due to their propensity to hemorrhage readily.[1,3]

Portal hypertension (PHTN) and development of EV are one of the major complications of liver cirrhosis. Bleeding from EV is a life-threatening event with 10-20% mortality with each episode. Current guidelines recommend that all cirrhotic patients should undergo screening endoscopy at diagnosis to identify patients with varices.[3] This approach increases the burden upon endoscopy units, and repeated testing over time may decrease patient compliance. Upper gastrointestinal endoscopy (UGIE) is deemed to be the gold standard against which all other tests are compared but is not

without its limitations.[1] Splenomegaly is a common finding in patients with cirrhosis and noncirrhotic PHTN, and is commonly ascribed because of blood congestion, increased portal pressure, augmented resistance to splenic vein outflow, and increased angiogenesis and fibrogenesis.[4] Splenic stiffness, often assessed using non-invasive imaging techniques like transient elastography (TE), has been suggested as a potential indicator of portal hypertension.[2,3] In cirrhosis, increased resistance to blood flow in the liver can lead to increased pressure in the portal vein, causing blood to be diverted into alternative pathways, such as the development of EV.

The rationale behind using splenic stiffness to predict EV is that as portal hypertension increases, the spleen may become congested and stiffer due to the increased pressure. For the diagnosis of fibrosis and its complications, one needs an ideal noninvasive method with good diagnostic accuracy, which will be easy to perform and will be easily reproducible, and its correlation with Hepatic venous pressure gradient (HVPG) being the gold standard for the diagnosis of PHTN. Various studies have explored the correlation between splenic stiffness and the presence of EV in cirrhosis.[4,5] Another non-invasive technique is to know the platelet count to spleen diameter ratio less than 909 is one of the several parameters proposed for the noninvasive prediction of EV.[6,7] Some studies have shown that splenic stiffness and liver stiffness were more accurate than other noninvasive parameters in identifying patients with EV and different degrees of PHTN. These studies aim to establish whether there is a strong association between increased splenic stiffness and the presence of significant EV, as well as the potential to predict their occurrence. Hence, the present study aims to predict the EV in cirrhosis patients by splenic stiffness in and around this region.

METHODS

After receiving approval from the Institutional Ethics Committee, the current investigation was initiated. This is a descriptive observational study. Between May 2021 and May 2023, a total of 112 patients from Department of Hepatology SCB MCH Cuttack with cirrhosis (aged 18-70 years) were enrolled in the investigation. Cirrhosis was diagnosed based on clinical, biochemical, imaging (ultrasound and computed imaging), and, when necessary, liver biopsy data. Patients were excluded if they had moderate to severe ascites, active alcohol consumption (any amount) within the previous 4 weeks, acute or chronic liver failure according to the Asian Pacific Association for the Study of the Liver guidelines hepatocellular carcinoma or any space-occupying lesion of the liver, portal vein thrombosis, biliary obstruction, or cardiac failure, or if they were unwilling to participate in the study.[1,2] 64 out of 112 patients were precluded due to moderate to severe ascites, hepatocellular carcinoma with portal vein thrombosis, hepatitis B reactivation, and active alcohol consumption, respectively.

Every single patient underwent a TE examination of the liver and spleen to assess liver stiffness and splenic rigidity. All patients were evaluated for EV using upper endoscopy per AASLD guidelines.[6] Endoscopic investigators were unaware of the FibroScan ((GE LOGIQ™ S8 XDclear; C1-6-D convex transducer 16MHz, GE Healthcare, Milwaukee, WI USA) values. In the event of any uncertainty regarding the subjectivity of diagnosing the extent of EV, the opinion of another senior author was sought, and a decision was made accordingly. For data analysis, the initial endoscopic findings of patients undergoing endoscopic band ligation for primary or secondary prophylaxis of esophageal variceal bleeding were recorded. Before TE, all patients had variceal bleeding. Every patient's routine biochemical parameters were recorded, including complete hemogram, platelet count, international normalized ratio, aspartate aminotransferases, alanine aminotransferases, albumin, bilirubin, serum creatinine, and relevant workup for etiology of liver disease evaluation. All patients also underwent liver and splenic diameter ultrasonography. Patients who consented to HVPG also underwent HVPG within one week of liver rigidity and splenic stiffness measurements. In all patients, the research protocol was completed within one week. The operator has extensive experience with both TE measurements and ultrasonographic examinations of the abdomen and has performed over a thousand TE measurements. The nature of the study was conveyed to all patients, and all patients provided written consent. The research adheres to the principles of the Helsinki Declaration.

Using a flexible video gastroscope, all patients underwent upper endoscopy. EV were classified as tiny (5 mm) or large (>5 mm) according to their size.[1,6] After a fasting of one night, HVPG was measured according to a standard protocol. In each instance, the average of three readings was determined after triplicate measurements were obtained. If the difference between readings was greater than 1 mmHg, all readings were repeated. The difference between wedge and free hepatic venous pressure was used to calculate HVPG.[4,6]

After an overnight fast, patients underwent a comprehensive ultrasound examination of the upper abdomen. Using LOGIQ shear wave elastography (GE LOGIQ™ S8 XDclear; C1-6-D convex transducer 16MHz, GE Healthcare, Milwaukee, WI, USA as per our hospital protocol, TE was performed in the morning hours on the same day, after patients had eaten breakfast, using a 16-MHz ultrasound transducer probe mounted on the axis of a vibrator. In this study, we did not search for diurnal variations in liver stiffness and splenic stiffness, as all measurements were performed in the morning. The tip of the transducer (M-probe) was covered with a drop of gel and situated perpendicularly in the intercostal space with the patient in the dorsal decubitus position and the right arm in the maximal abduction position. Under control, in time motion, and in A-mode, the operator selected a liver segment within the right lobe that was at

least 6 centimeters thick and devoid of significant vascular structures, as well as the gallbladder. On a cylinder of hepatic tissue measuring 1 cm in diameter and 2-4 cm in length, rigidity was measured. The patient was placed in a supine position with his left arm in maximum abduction and the transducer was placed in the left intercostal spaces, typically on the posterior axillary line or immediately over the palpable spleen just below the costal space, in order to assess splenic stiffness. We utilized ultrasonography to visualize the spleen parenchyma, select the optimal location for splenic rigidity measurement, and determine the spleen diameter (long axis). As a representative of the liver stiffness and splenic stiffness measurements, the median of 10 successful acquisitions, expressed in kpa, was retained. Failure to measure liver and splenic stiffness was recorded when no value was obtained after at least ten attempts. Under the following circumstances, the results were deemed unreliable: Valid, inconclusive measurements of splenic and/or hepatic stiffness (less than 10 shots, success rate 60%, or interquartile range/liver stiffness >30).[10]

After an overnight fast, the patient venous blood was drawn and analyzed for routine liver function tests and hematologic parameters, as well as for viral markers such as hepatitis B and hepatitis C. In addition, abdominal ultrasound and computed tomography were conducted to determine the size of the liver and spleen, as well as a Doppler study for abdominal vessels and, if necessary, a liver biopsy. All patients were evaluated for varices using UGIE. For each patient, the liver spleen diameter to platelet ratio score, and platelet count to spleen diameter ratio were calculated using the formula liver stiffness x spleen diameter/platelet count.[1,6,8]

Statistical analysis

The SPSS program, version 15.0, from SPSS in Chicago, Illinois, was used to conduct statistical analysis. The range (minimum and maximum values) and median values for the continuous variables were shown. For continuous and categorical variables, respectively, the Mann-Whitney U-test and the 2-test were used to compare the data. Spearman's correlation coefficients were used to describe the relationships between the parameters. Utilizing sensitivity, specificity, positive predictive value, and negative predictive value, the diagnostic performance of LS and SS was evaluated. By using multiple regression binary logistic with forward conditional elimination, multivariate predictors were identified for OV, and their odds ratios and 95% confidence intervals were calculated. Statistics were considered significant for p values under 0.05.

RESULTS

A total of 112 participants initially participated in the study. However, 18 patients were subsequently eliminated from the analysis due to either inability to provide valid measurements or the presence of unreliable data. Specifically, a valid measurement was defined as having a value of at least 10, an interquartile range greater than 30% of the median value, or a success rate below 60%. Liver stiffness and splenic stiffness measures were unsuccessful in 10 out of the 18 patients, despite the utilization of an XL instrument. This failure can be attributed to the patients' high body mass index (BMI), which had a median value of 35 kg/m^2. In a further 20 individuals, the measurement of splenic stiffness was not feasible due to the absence of spleen enlargement or the presence of lung or intestinal gas, resulting in the lack of reliable measurements. Splenic stiffness was shown to be quantifiable in a sample of 10 individuals, exhibiting a substantial interquartile range over 30%. A comprehensive screening for OV was conducted on all individuals diagnosed with cirrhosis, utilizing the method of upper gastrointestinal endoscopy (UGIE).

The causes of cirrhosis in the sample of 112 individuals were alcohol (n=10), hepatitis B (n=18, 13.2%), hepatitis C (n=11, 16.7%), and cryptogenic (n=32, 25.9%). A total of 82 patients were identified with EV. Out of the total sample of 18 patients who were eliminated from the study, 11 individuals were diagnosed with EV. Specifically, 7 patients had small EV, whereas 4 patients had large EV. Table 1 presents the fundamental characteristics of a cohort including 112 individuals. There were substantial differences observed in hemoglobin levels, total leukocyte count, platelet count, Child Turcotte Pugh score, and spleen diameter between patients diagnosed with EV and those who did not have EV, as indicated in Table 1. Nonetheless, the Child Turcotte Pugh score did not exhibit any noteworthy disparity between patients who experienced variceal hemorrhage (n=5) and those who did not encounter variceal bleed (n=13) (p=0.99).

All patients consented to biochemical tests, abdominal ultrasound, and TE, as well as measurements of liver rigidity, splenic stiffness, liver stiffness measurement, spleen diameter to platelet ratio score, and platelet-spleen-score ratio. The median duration for patients with variceal bleeding to receive these tests was six days (3-10 days). There was significant difference in median liver stiffness (56.2 vs. 26.8 kpa, p<0.05), splenic stiffness (58 vs. 30 kpa, p<0.05), liver stiffness measurement -spleen diameter to platelet ratio score (5.9 vs. 2.9, P<0.05), and platelet-splenic-score ratio (921 vs. 1,412, P<0.05) between patients with EV vs. those without EV. We categorized the patients based on alcoholic (n=10) and nonalcoholic (n=102) patients. There was a significant difference (p<0.05) between patients with varices and those without varices in both the categories (alcoholic: liver stiffness, 59.8±21.4 kpa vs. 28.1±12.1 kpa ; splenic stiffness, 61±8.9 kpa vs. 34±11.9 kpa; liver stiffness measurement-spleen diameter to platelet ratio score,6.9±1.8 vs.3.2±1.2; platelet-splenic-score ratio 884 (188.9-2854) vs. 1243 (387.3-2,489); and nonalcoholic: liver stiffness, 58.9 kpa (14-79) vs. 27.2 kpa (18-39);

splenic stiffness, 62 kpa (38-78) vs. 35 kpa (16-59); liver stiffness measurement-spleen diameter to platelet ratio score, 6.1 (1.5-18.1) vs. 3.2 (1.3-6.7), and platelet-splenic-score ratio 912.8 (352.1-1999) vs. 1,301 (403-2598).

Table 1: Information about the study's subjects at the outset.

Variables	Total	Patients with EV (n=82)	Patients without EV (n=30)	P value
Age (years)	48.2±14.3	47.8±11.2	48.1±12.1	>0.05
Male:Female	84 : 28	62 : 20	22 : 8	>0.05
BMI	27.1±2.1	27.2±4.1	27.9 ±3.2	>0.05
Hemoglobin (Hb%)	12±2.1	9.8±1.9	13.1±4.1	<0.05
Total leukocyte count (TLC per cu mm)	7.4±2.9	7.0±2.7	8.3 ±3.8	<0.05
Platelet (per cu mm)	141±49.3	101±51	133±73	<0.05
Total bilirubin (mg/dl)	1.9±0.7	3.8±0.7	1.4±0.2	<0.05
Albumin (mg/dl)	3.8±1.2	3.2±0.5	3.0±1.1	<0.05
Alanine transaminase (ALT; IU/l)	42± 21.2	49±14	38±11	>0.05
Aspartate transaminase (AST; IU/l)	58±12	61±14.1	40.1±8.1	<0.05
Spleen diameter (cm)	15.1±1.1	15.8±2.1	13.9±2.5	<0.05
CTP score	7.1±1.2	7.3±1.6	6.7±1.6	<0.05

The relationship between HVPG and non-invasive measurements

HVPG was measured in a subgroup of patients who gave consent for it. Only 64 of 112 patients underwent HVPG. Of 64 patients who underwent HVPG. 23 patients had small varices and 42 patients had large varices. None of the patients without EV underwent HVPG. Median HVPG was significantly higher in patients with large EV compared with patients with small EV (20 mmHg vs.17 mmHg, p<0.051) and it was significantly higher in bleeder compared with non-bleeder (20.5 mmHg vs.17 mmHg, p<0.05). The median time of getting HVPG done in patients with variceal bleed was 7 days (5-16 days). HVPG showed correlation with splenic stiffness (r=0.532, p<0.05), liver stiffness measurement-spleen diameter to platelet ratio score (r=0.436, p<0.05), and platelet-splenic-score ratio (r=−0.327, p<0.05), but not with liver stiffness (r = 0.238, p>0.05), when we took all patients (n = 112). When we included only those patients (n = 64) who had HVPG, liver stiffness, splenic stiffness, liver stiffness measurement-spleen diameter to platelet ratio score, and platelet-splenic-score ratio done, HVPG showed correlation with only splenic stiffness (r=0.398, P<0.05) and liver stiffness measurement-spleen diameter to platelet ratio score (r=0.452, p<0.05), but not with liver stiffness (r=0.246, p>0.05) and PSR (r=-0.302, p<0.05). However, at higher HVPG (≥20 seen in 14 patients (large varices, n=11; small, n=3), splenic stiffness did not show any correlation with HVPG (r=0.01, p>0.05).

DISCUSSION

The findings of this study demonstrated that those diagnosed with EV exhibited higher liver stiffness, splenic stiffness, higher platelet-splenic-score ratio, spleen diameter to platelet ratio score than patients without EV. Those with extensive varices and those with variceal bleeding can be distinguished by splenic stiffness and HVPG.

Previous studies have found that measuring liver stiffness with a TE device is a simple, repeatable procedure that can help identify patients with varices and correlate with HVPG.[1,3,5,7,10] However, liver stiffness does not distinguish between patients with small vs. large varices, patients who had variceal bleeds vs. those who had none, and patients with HVPG values of 12 mmHg.[1,10,12,13] With a positive predictive value of 89% and a diagnostic accuracy of 86%, the current study's liver stiffness cutoff value of 27.3 kPa was able to distinguish between patients with EV and those without EV. However, liver stiffness was unable to distinguish between patients with larger EVs and those with smaller EVs, and there was no difference in liver stiffness between patients with EV bleeds and those without.

The most accurate way to assess PHTN is with HVPG, which has a strong correlation with PHTN-related problems.[13-15] However, liver stiffness did not correlate with HVPG in this investigation; this may be because only patients who provided consent were tested, and most of these patients had EV. The median HVPG in the study was 17.6 mmHg, and LSM had a weak relationship with higher HVPG values (12 mmHg). This may be because extrahepatic factors are becoming more important in determining how PHTN progresses.[10] To evaluate the same, we require several patients. However, liver stiffness did not correlate with HVPG in patients who also had all the other non-invasive indicators, although splenic stiffness did.

One of the several criteria suggested for the non-invasive prediction of EV is the platelet count-to-spleen diameter

ratio of 909.[6] However, a recent meta-analysis found that the test properties of the Platelet count to spleen diameter ratio of 909 might not be sufficient to fully replace UGIE in its current form.[16-18] However, according to other published studies, the diagnostic accuracy of this study's cutoff value of 909 for the prediction of EV was 68%, while the diagnostic accuracy of its cutoff value of 1,024 was 74%. Splenic stiffness and the ratio of platelet count to spleen diameter were significantly correlated. However, the Platelet count to spleen diameter ratio was unable to distinguish between individuals with large EV and those with small EV, as well as between bleeders and non-bleeders.

The findings of the current study also highlight the diagnostic precision in patients with cirrhosis of various etiologies, such as LSPS, a test that has only been studied in individuals with cirrhosis caused by the hepatitis B virus and hepatitis C virus thus far.[3,4] Splenic stiffness, liver stiffness, HVPG and the platelet count to spleen diameter ratio were all significantly correlated with the liver stiffness measurement-spleen diameter to platelet ratio score. In this study, the splenic and liver stiffness measurements' diagnostic accuracy was compared using the spleen diameter to platelet ratio score. Other noninvasive markers, however, were unable to distinguish between patients at risk of PHTN hemorrhage and those with large varices.

Splenomegaly is common in both cirrhotic and non-cirrhotic PHTN patients. It is often caused due to high portal pressure, resistance to splenic vein outflow, and more angiogenesis and fibrogenesis.[2] In an animal model, magnetic resonance elastography was used to measure the direct portal vein pressure gradient and the splenic stiffness. The results showed that the stiffness of the spleen and the pressure gradient in the direct portal vein were related in a positive way. The average stiffness of the spleen went up by more than twice what it was at the start of the study and stayed the same after 8 weeks, which was in line with changes in portal pressure. In a study on people with chronic liver injury, real-time tissue elastography was used to measure the liver and spleen's elasticity, figure out HVPG, and do UGIE.[17] Splenic elasticity had the strongest connection with the HVPG-related variables. Similar findings were made in another study, who discovered that patients with EV had considerably higher splenic stiffness evaluated by TE than those without. Greater than the liver stiffness estimate, the splenic stiffness value had diagnostic accuracy for EV prediction. Splenic stiffness revealed only a weak connection with HVPG in this study for patients who received HVPG measurements and none at greater HVPG (>19 mmHg). In this study, we also discovered that splenic stiffness, with a cutoff value of 40.4 kPa, could predict EV with a diagnostic accuracy of 90%, which is higher than that of other noninvasive parameters like platelet count to spleen diameter ratio and liver stiffness measurement-spleen diameter to platelet ratio score, though comparable with liver stiffness. However, splenic stiffness was greater in those who bled than in those who did not, and it was greater in those who had large varices as opposed to those who had small varices. We advocate measuring splenic stiffness in all patients with cirrhosis and validating our findings in further patient cohorts since when liver stiffness is combined with it, the specificity of predicting the existence of EV is enhanced. In this study, 14% of the patients were unable to quantify their splenic stiffness; however, according to the inclusion criteria, these patients were not included in the analysis. As in other published investigations, SSM has also been demonstrated in this study to be superior to other non-invasive markers, such as liver stiffness measurement, spleen diameter to platelet ratio score, and platelet count to spleen diameter ratio.[7,8] HVPG, the spleen diameter to platelet ratio score, the liver stiffness measurement, and the platelet count to spleen diameter ratio all exhibited strong correlations with splenic stiffness. Similar findings were made by, who demonstrated a strong association between splenic and hepatic stiffness and demonstrated that adding measures of both LSM and SSM raised the diagnostic precision of EV to 90%.[1,2,18]

The assessment of splenic stiffness has the disadvantage that 14% of patients do not have an accurate measurement, which is primarily caused by a small spleen and a high body mass index. In this investigation, we did not discover any relationship between splenic stiffness and BMI. Splenic stiffness could be evaluated in some patients in earlier research, and it could, be used to diagnose OV in patients but did not distinguish between different grades of OV.[7,8] However, in our study, we were able to distinguish between patients with small vs. large varices and even between bleeders and non-bleeders. Another concern is that different cutoff values for splenic stiffness may be required for the prediction of EV in different causes of PHTN, similar to how liver stiffness levels change with the etiology of liver illness for predicting fibrosis and cirrhosis.[18] Because other SSM cutoffs have been used in earlier research.[1,7,8,10] However, when we divided the patients into two groups-alcoholic and nonalcoholic-we found no discernible difference in the splenic stiffness patients with varices. We should think about monitoring splenic stiffness in all PHTN patients in light of the effectiveness of splenic stiffness in predicting the EV and EV bleed in patients with cirrhosis and extrahepatic portal venous blockage.

This study's advantages include a sizable patient cohort that had endoscopy, ultrasonography, blood tests, and TE. Numerous members of the cohort showed both small and large varices. Additionally, a sizable percentage of patients had variceal hemorrhage. Because HVPG, the gold standard for measuring PHTN in patients with cirrhosis, was not tested in all patients, there was no way to compare the diagnostic accuracy of other tests with that of HVPG in this investigation. Possible inter observer variations in endoscopic findings on the size of the EV could not be ruled out, and some patients in our

study did not have measures taken for their liver and spleen stiffness. In conclusion, given the requirement to screen patients with cirrhosis, non-invasive tests, such as splenic stiffness, may aid in the detection of people at risk of having EV, particularly large EV, as well as those who are in danger of bleeding.

However, it's important to note that while this research is promising, it might not be a definitive predictor on its own. Esophageal varices are influenced by multiple factors, and their prediction and management often involve a combination of clinical, radiological, and endoscopic assessments. Additionally, the field of medical research is ever evolving, and the conclusions drawn may vary based on the specifics of the study, patient population, and methodology used.

CONCLUSION

Given the need to screen patients with cirrhosis for esophageal varices, the authors of the current study conclude that non-invasive measurements, such as splenic stiffness, may serve to identify those at risk of having esophageal varices, especially large ones, and those at risk of bleeding. Such studies in large numbers across the globe are required to decide on non-invasive approaches of predicting cirrhosis by splenic stiffness.

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