Original Article

Correlation of Spleen Stiffness by Transient Elastrography with Parameters of Indicated Portal Hypertension and the Presence of Esophageal Varices

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Background: Portal hypertension is a complication of cirrhosis, which causes esophageal varices [EV], splenomegaly, ascites and hepatic encephalopathy. The gold standard for diagnosis of portal hypertension is hepatic venous pressure gradient [HVPG] measurement, which is not routinely performed in every hospital. There is evidence that the spleen stiffness value correlates with the HVPG.

Objective: To study the relationship between spleen stiffness and parameters of indicated portal hypertension and study the relationship between spleen stiffness and the presence of EV.

Materials and Methods: Thirty-eight patients with clinical signs or any indicators of cirrhotic portal hypertension were evaluated by measuring splenic diameter and portal vein diameter by ultrasound. The authors measured liver and spleen stiffness using transient elastrography and upper endoscopy for the diagnosis of EV.

Results: Spleen stiffness showed no significant correlation between groups indicated portal hypertension. Sixteen patients, in a group which had the highest median value of spleen stiffness, had EV (75%). The present study found 81.5% of all patients had EV; EV group tend to have higher median spleen stiffness values than those without EV, although this is not statistically significant (54.2 vs. 49.6 kPa, $p = 0.38$). Integrating liver stiffness value, splenic diameter and platelet count in terms of LSPS score, showed that LSPS score was significantly higher in the EV group (6.89 vs. 1.72, $p = 0.011$).

Conclusion: LSPS score, but not spleen stiffness was a good non-invasive measurement for predicting portal hypertension in terms of the presence of esophageal varices.

Keywords: Esophageal varices, Portal hypertension, Spleen stiffness

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Portal hypertension is a major complication of cirrhosis. This condition causes esophageal varices [EV], ascites, splenomegaly, and affects quality of life and patient survival. EV in particular have been reported in up to 50% of cirrhotic patients and the mortality rate approaches 30%. The gold standard for the diagnosis of portal hypertension is a hepatic venous pressure gradient [HVPG] measurement greater than 10 mmHg. HVPG greater than 12 mmHg was associated with the occurrence of EV[1-3]. Although HVPG measurement is the gold standard, it cannot routinely be performed in every hospital due to the invasiveness of the procedure. A portal vein diameter greater than 13 mm has a 40% sensitivity for the diagnosis of portal hypertension[4]. Spleen diameter ranging from 12 to 14.5 cm has been correlated with clinically significant portal hypertension[5]. Platelet count less than $100x10^9$/L was associated with the presence of EV[6]. Therefore, the authors attempted different measurements to diagnose portal hypertension.The primary objective of the present study is to evaluate spleen stiffness measurement and correlate values with parameters of

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indicated portal hypertension. The secondary objective is to study the relationship between SS and the presence of EV.

Materials and Methods

Study population

The study was performed in the liver clinic at Vajira Hospital, Navamindradhiraj University during December 2015 to December 2016. A total of 38 patients were enrolled. All were diagnosed with cirrhosis with at least one parameter for indicated portal hypertension. Clinical signs of portal hypertension include splenomegaly greater than 13 cm, platelet count less than$100x10^9$/L and the presence of EV. Patients who had body mass index greater than 30 kg/m^2, tense ascites, narrow ribs, and pregnancy were excluded. Each patient was studied for 2 days. On the first day all patients had blood tests composed of blood chemistry and underwent ultrasound measurement of the splenic diameter and portal vein diameter. The authors measured liver stiffness and spleen stiffness with transient elastrography. On the second day, upper endoscopy was performed.

Measurement of spleen stiffness and liver stiffness

Liver stiffnesswas assessed by transient elastrography after patient fasting for at least 6 hours. The transient elastrography device consists of a 3.5-MHz ultrasound transducer with a medium probe mounted on the axis of a vibrator. Mild amplitude and low-frequency vibrations (50 Hz) are transmitted to the liver tissue, inducing an elastic shear wave that propagates through the underlying tissue. The M probe can measure liver stiffness at a depth of 25 to 65 mm from the skin. liver stiffness values were accepted if the success rate was greater than 60% and the interquartile range [IQR] less than 30% of the individual value. After liver stiffness measurement, spleen stiffness values were obtained using the transient elastrography with the same probe under ultrasound guidance, with adjustments due to individual anatomical spleen characteristics. The patient lay in a supine position with abduction of the left arm. The probe was applied to an intercostal space where the spleen was correctly visualized by ultrasound. The authors accepted the success rate and the interquartile range [IQR] as the same value of liver stiffness. The median value of liver stiffness and spleen stiffness were expressed in kilopascals [kPa]. Use of the transient elastrography for patients with a splenic parenchymal thickness less than 4 cm under the probe proved unfeasible and those patients were therefore excluded. Patients who had limitations to measurement due to ascites, obesity, and intercostal spaces too narrow for use of the M-probe were excluded. Assessing the reproducibility of spleen stiffness, the authors accepted intraobserver and interobserver reproducibility of 96 and 94%, respectively.

Measurement of portal vein diameter

Portal vein diameter was measured by using ultrasound during suspended respiration in a supine position. This assessment was conducted over the long axis of the portal vein. A portal vein diameter greater than 13 mm indicated that a patient might have portal hypertension.

Measurement of splenic diameter

Patients were examined at various stages of inspiration to maximize splenic area. Splenic diameter measured by using ultrasound along the length of the spleen from the top to bottom edge with patients in a supine position. A previous study of chronic hepatitis C cirrhosis showed that the median value of splenic diameter in portal hypertension was 12 to 14.5 cm[5].

Upper endoscopy

All patients underwent upper endoscopy. The endoscopic findings were recorded as the presence of EV and/or portal hypertensive gastropathy [PHG].

Other non-invasive assessment

The liver stiffness-spleen diameter to platelet ratio score [LSPS] was assessed by calculated this according to the formula: liver stiffness x spleen diameter/platelet count, and the platelet count/spleen diameter ratio (Plt/Spl ratio).

Statistical analysis

Patient characteristics and parameters of suspected portal hypertension were categorized as qualitative data (percentages) and quantitative data as median (range). For comparison of spleen stiffness with number of parameters indicated portal hypertension, the authors divided patients into 4 groups. The data were shown as free distribution; the Kruskal-Wallis test was used for statistical analysis. The performance of spleen stiffness was used to determine the presence EV. Receiver operating characteristics [ROC] were calculated and area under the curve [AUC] was computed and represented in terms of sensitivity, specificity, accuracy, positive predictive value and

negative predictive value and the areas under ROC curves with a 95% confidence interval were calculated. The comparison between LSPS, Plt/Spl ratio and the presence of EV in cirrhotic patients was calculated by use of Fisher's exact test. All analyses were performed with SPSS for Windows version 22.0. The level of statistical significance was set at 0.05.

Results

A total of 38 patients were enrolled into the study. The mean age was 54.6±10.2 years. Thirty-one of 38 patients (81.6%) were male. The mean weight was 66.3±11.7 kg, the mean height was 163.6±8.9 cm and the mean body mass index was 24.7±3.3 kg/m^2. The causes of cirrhosis were attributed to alcohol (60.5%), chronic hepatitis B (31.6%), chronic hepatitis C (23.7%) and non-alcoholic fatty liver disease (10.5%). All patients had a median platelet count of 109x10^9/L and median spleen diameter was 12 cm. Splenic stiffness value of all patients ranged from 12.6 to 75 kPa and a median value of 52.3 kPa. The value of liver stiffness in the present study ranged from 13 to 75 kPa (Table 1).

The characteristics of the patients were assessed by blood tests, ultrasound and upper endoscopy to collect parameters of indicated portal hypertension. Of all patients, 47.4% had a platelet count less than 100x10^9/L, 10.5% had a portal vein diameter greater than 13 mm, and 21.1% had a spleen diameter greater than 13 cm. Furthermore, 89.5% had EV or PHG (Table 2).

The number of parameters for indicated portal hypertension in each patient was divided into 4 groups to compare median values for spleen stiffness. The results show that the median values of splenic stiffness were 69.6 (IQR 41.7 to 75), 51.4 (IQR 46 to 73.5), 61.6 (IQR 49.6 to 73.5) and 53.5 kPa (IQR 32 to 75) in groups 1,2,3 and 4, respectively. There was no significant difference between groups in number of parameters for indicated portal hypertension and splenic stiffness (p = 0.91), as shown in Table 3.

There were 16 patients in the group who had only one parameter for portal hypertension. However, this group had the highest median value of spleen stiffness (Table 3). Furthermore, 12 of the patients in this same group (75%) had EV. Only 1 patient in this group (7.1%) had a portal vein diameter greater than 13 mm and 1 patient (7.1%) had splenic diameter greater than 13 cm. This result shows the relationship between the presence of EV and high spleen stiffness values.

Spleen stiffness measurements were performed by ROC curve for assessing the presence of EV. Spleen stiffness can predict the presence of EV with an AUC value of 0.606 (Figure 1). To determine the utility of spleen stiffness in the presence of EV, the authors studied different cut-off values and found that a cut-off value of 46 had a sensitivity of 74.2%, specificity of 28.6% and had a good positive predictive value of 82.1%. A cut-off value of 46 was more accurate than another cut-out off, as shown in Table 4.

EV were detected in 31 patients (81.5%) using upper endoscopy. All patients in whom PHG was detected also had EV. The authors compared spleen stiffness between patients with and without EV and found that the median value of spleen stiffness in patients with EV was higher than the group without EV,

Table 1. Baseline characteristics of cirrhotic patients with and without EV (n = 38)

Characteristics	Results
Age (years)	54.58±10.15
Weight (kg)	66.3±11.7
Height (cm)	163.6±8.9
Body mass index (kg/m□)	24.7±3.3
Sex,n (%)	
Male	31 (81.6)
Female	7 (18.4)
Cause of cirrhosis	
Alcohol, n (%)	23 (60.5)
Chronic hepatitis B, n (%)	12 (31.6)
Chronic hepatitis C, n (%)	9 (23.7)
Non-alcoholic fatty liver disease, n (%)	4 (10.5)
Platelet count (x10^9/L)*	109 (37 to 279)
Spleen diameter (cm)*	12 (8.7 to 18.9)
Spleen stiffness (kPa)*	52.3 (12.6 to 75)
Liver stiffness (kPa)*	35.8 (13 to 75)

Data are presented as mean ± standard deviation or number (%).
* Data are presented as median (range)

Table 2. Parameters as indicators of portal hypertension (n = 38)

Parameters	n	%
EV and/or PHG	34	89.5
Portal vein diameter >13 mm	4	10.5
Spleen diameter >13 cm	8	21.1
Platelet count <100x10^9/L	18	47.4

EV = esophageal varices; PHG = portal hypertensive gastropathy

Table 3. Comparison of spleen stiffness and parameters as indicators of portal hypertension (n = 38)

Number of parameters for indicated portal hypertension*	Participants		Spleen stiffness		*p*-value
	N	%	Median	IQR	
1	16	42.1	69.6	(41.70 to 75.0)	0.91
2	18	47.4	51.4	(46.00 to 73.5)	
3	2	5.3	61.6	(49.60 to 73.5)	
4	2	5.3	53.5	(32.00 to 75.0)	

* Number of parameters: each patient had 1 or more of the criteria; esophageal varices or portal hypertensive gastropathy, portal vein diameter >13 mm, splenic diameter >13 cm and platelet count <100x10^9/L according to the Table 2.

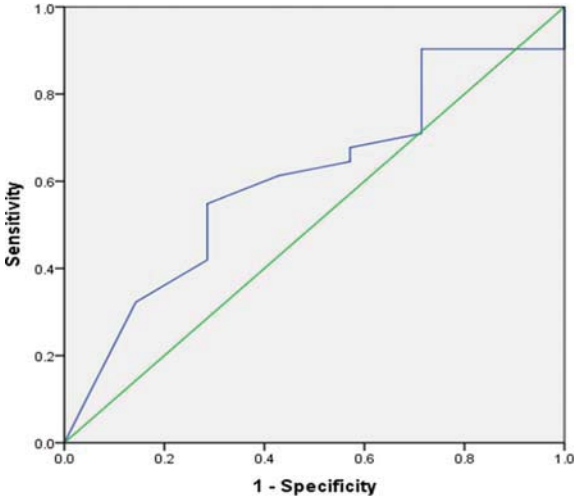

Figure 1. Receiver operating characteristic for spleen stiffness for predicting the presence of esophagealvarices (EV).

though not statistically significant (54.2 vs. 49.6 kPa, $p = 0.38$).

The authors tried to apply any data from non-invasive tests to predict EV by the use of liver stiffness value, splenic diameter and platelet count in terms of LSPS score. The median value of LSPS score in patients with EV was significantly higher than those without EV (6.89±4.16 vs. 1.72±0.77, $p = 0.011$), as shown in Table 5. When the authors used a ratio of LSPS above 5.5, as in a previous paper[7], the results still differed significantly between groups.

The present study found that the median values of platelet count/splenic diameter ratio in patients withEV were lower than patients without EV but not statistically significant (815.99±331.88 vs. 1,364.5±730.91, $p = 0.108$) as shown in Table 5.

Discussion

Portal hypertension is a major complication of cirrhosis, and the main cause of EV, ascites and splenomegaly, and affects quality of life and patient survival. The gold standard for diagnosis of portal hypertension is HVPG measurement and a value over 12 mmHg was associated with the presence of EV[1-3]. Although HVPG measurement is the gold standard, it cannot routinely be performed in every hospital due to the invasiveness of the procedure. From the knowledge that portal hypertension can be suspected when the portal vein diameter is greater than 13 mm, thrombocytopenia or splenomegaly are present. Therefore, the authors tried to measure in a different way to diagnose portal hypertension.

The present study found that only 10.5% of cirrhotic patients had portal vein diameter greater than 13 mm. The size of portal vein alone may not be a reliable indicator for diagnosis of portal hypertension because previous studies have shown that a portal vein diameter of greater than 13 mm has a sensitivity for diagnosing portal hypertension of only 40%[4]. Moreover, the present study did not include measuring the changes in portal vein parameters such as disappearance of caliper variation during respiration, or decrease in portal velocity and reversed portal vein flow (hepatofugal flow).

Splenomegaly represents a common finding in cirrhotic patients with portal hypertension. Splenomegaly in portal hypertension results from tissue hyperplasia and passive splenic congestion. Splenic size varies from 12 to 14.5 cm in diagnoses of portal hypertension measured by HVPG[5]. The authors used a cut-off of greater than 13 mm. The present study found spleen sizes ranging from 8.7 to 18.9 cm. Only 21.1% of patients had a spleen diameter greater than 13 cm, corresponding with previous knowledge that the

Table 4. Spleen stiffness for predicting the presence of esophageal varices

Cut off	AUC	Sensitivity	Specificity	LR+	LR-	PPV	NPV	Accuracy
≥46.0	0.514	74.2%	28.6%	1.04	0.90	82.1%	20.0%	65.8%
≥46.8	0.553	67.7%	42.9%	1.19	0.75	84.0%	23.1%	63.2%
≥50.0	0.592	61.3%	57.1%	1.43	0.68	86.4%	25.0%	60.5%

AUC = area under the curve; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value

Table 5. Liver stiffness value, splenic diameter and platelet count score (LSPS) and platelet count/splenic diameter of patients with and without esophageal varices (EV) (n = 38)

Variables	EV (n = 31)	No EV (n = 7)	*p*-value
LSPS	6.9±4.2	1.7±0.8	0.010
platelet count/ splenic diameter	816.0±331.9	1364.5±730.9	0.108

absence of splenomegaly does not exclude this condition.

A low platelet count has been suggested as an indicator of suspected portal hypertension. A total 47.4% of all patients had platelet counts lower than $100x10^9$/L. The authors used this cut off value based on a previous study that associated this level with portal hypertension and the presence of esophageal varices[6]. However, in some patients mild portal hypertension may also be present when the platelet count was higher than $100x10^9$/L. Elevated portal pressure plays a major role in the development of EV. Patients with suspected portal hypertension had an 89.5% detection rate of EV or PHG.

Splenic stiffness is a noninvasive assessment which has been reported in many published papers. A study by Colecchia et al[5] reported a correlation between spleen stiffness measurement and prevalence of portal hypertension. By measuring HVPG they found that spleen stiffness value was higher in the group with clinically significant portal hypertension than in the pre-clinical portal hypertension group by a statistically significant margin (56 vs. 37 kPa). There is a good correlation between spleen stiffness and the HVPG value, a correlation that is still seen even with raised HVPG and conclude that spleen stiffness increases in parallel with the later stages of portal hypertension[1,5]. The present study showed that spleen stiffness values of all patients ranged from 23.7 to 75 kPa with a median value of 52.3 kPa. Due to unsatisfactory results using each parameter alone for suspected portal hypertension, the authors integrated the data by combining these parameters and categorizing them into 4 groups. Each patient with suspected portal hypertension was compared with the value of spleen stiffness. The results showed that median values of spleen stiffness were indifferent between groups which had 1, 2, 3 or 4 parameters. There was no significant difference between the respective parameter groups in instances of either portal hypertension and spleen stiffness.

The authors observed that 16 patients within a group who had the highest median value for spleen stiffness and 12 patients in the same group (75%) also had EV. These results reflect the relationship between the presence of EV and a high spleen stiffness value, as supported by a previous study showing that spleen stiffness measurement can be used for noninvasive assessment and detection of EV in chronic hepatitis C patients with cirrhosis[5]. The authors could not include enough patients in the third and fourth group because these groups were associated with the presence of ascites, which are a limitation to measuring spleen stiffness. Therefore, mean value of spleen stiffness in these groups may not represent the actual value. More participants will be required in any future analysis.

The authors detected EV in 31 patients (81.5%) using upper endoscopy. The comparison of spleen stiffness between patients with EV and those without EV showed that the median value of spleen stiffness was higher in patients with EV than those without it, but not statistically significant (54.2 vs. 49.6 kPa). The authors need more participants to have an impact on the results. Moreover, the present study showed that the spleen stiffness could predict the presence of EV with an AUC value of 0.606. To determine the utility of spleen stiffness in the presence of EV, the authors studied different cut-off values and found that a cut-off value of 46 had a sensitivity and specificity of 74.2% and 28.6%, respectively, and a good positive

predictive value of 82.1% with moderate accuracy. A cut-off value of 46, was more accurate than cut-off value of 46.8 and 50.The low specificity of the spleen stiffness cut-off value in the present study was due to a smaller number of patients in the non-EV group. Some previous studies suggested a different cut-off value of spleen stiffness for the presence of EV. In Western populations, an spleen stiffness value of higher than 55 kPa has a sensitivity and specificity of 71.7% and 95.7%, respectively in predicting the presence of EV and the degree of portal hypertension measured by HVPG[5]. Secondly, a previous study of Thai patients reported that an spleen stiffness value of higher than 36.3 could predict the presence of EV significantly with a sensitivity of 100%[7]. Looking to future research, the authors need more data for a universal cut-off value of spleen stiffness for the presence of EV.

Liver stiffness is a noninvasive parameter of liver fibrosis that reflects an increase in intrahepatic resistance, which occurs primarily in portal hypertension. A previous author study showed that a cut-off value for liver stiffness of 13 kPa gave an AUROC of 0.924 for diagnosis of cirrhosis[8]. In previous study, liver stiffness value greater than 21 kPa can very accurately predict clinically significant portal hypertension with an AUROC of 0.945[9]. Liver stiffness values in the present study ranged from 13 to 75 kPa. Liver stiffness-spleen diameter to platelet ratio score [LSPS] is related to the presence of EV. A previous study of chronic hepatitis B cirrhosis reported that patients with an LSPS greater than 5.5 should undergo endoscopic variceal screening[3,10]. Result of the present study show that LSPS was significantly higher in the EV group than those without EV (6.89 vs.1.72) supporting the combination of liver elastrogram and morphological/biochemical parameters give a good non-invasive assessment of portal hypertension in the presence of EV. The Baveno 6 consensus workshop stratified risk for portal hypertension by the use of platelet count, spleen size, and signs of portal hypertension, as measured by doppler ultrasound, as a screening. They combined this with liver and spleen stiffness measurements to determine whether patients have clinically significant portal hypertension and to determine which patients require variceal screening[11].

The authors looked at other biochemical and morphological parameters, such as the Plt/Spl ratio, for determining the presence of EV and found that the median value was lower in the EV group than among those without EV, but not statistically significant (815.99 vs. 1,364.5). Previous data has shown that a Plt/Spl cut-off value of 909 had a 100% negative predictive value for the presence of EV[12,13]. However, the present study had 11 patients (35.4%) in the EV group who had a value greater than 909. This may be explained by the present result showing that only 21.1% of all patients had splenomegaly. Another previous author study of 164 Thai cirrhotic patients found that platelet count/ spleen area ratio had a higher specificity than Plt/Spl ratio in predicting the presence of EV[14].

Limitations of the present study was the exclusion of patients with ascites due to being unable to measure spleen stiffness. From knowledge that ascites is a condition that reflects hyperdynamic circulation and is found in the later stages of portal hypertension. Therefore, the authors cannot estimate the spleen stiffness value in this group, which is expected to have high spleen stiffness values.

Conclusion

The value of spleen stiffness is not superior to liver stiffness-spleen diameter to platelet ratio score for predicting portal hypertension in terms of the presence of EV but it may have benefit for clinician where upper endoscopy cannot be done.

What is already known on this topic?

Spleen stiffness value of all cirrhotic patients ranged from 12.6 -75 kPa and a median value of 52.3 kPa.

What this study adds?

A cut point of spleen stiffness alone has low specificity for predicting the presence of EV. Liver stiffness-spleen diameter to platelet ratio score gives a better non-invasive assessment of portal hypertension in the presence of EV than spleen stiffness.

Potential conflicts of interest

None.

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