Evaluation of Liver Stiffness-Spleen size-to-Platelet Count Ratio Score as a Risk Score for the Prediction of Oesophageal Varices in Compensated Cirrhotic Patients

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Key words:
Cirrhosis, Esophageal varices, Endoscopy

Background and study aims: The prevalence of gastro-esophageal varices (GOVs) in cirrhotic patients ranges from 40-80%.The most serious complication of cirrhosis is variceal hemorrhage since it has a mortality rate of 17-57%. Endoscopy is the standard test to detect GOVs. This study aimed at the evaluation of liver stiffness (LS)-spleen size-to-platelet count ratio score (LSPS) as a risk score for the prediction of esophageal varices (OVs) in patients with compensated liver cirrhosis.

Patients and Method: This study included 51 patients with compensated cirrhosis. Screening upper endoscopy was done for the detection of OVs. They were also evaluated by transient elastography and laboratory tests, then divided according to the presence or absence of OVs. We compared both groups based on LSPS and platelet count splenic diameter ratio (PSR).

Results: the LSPS ratio has sensitivity 87.88% and specificity 88.89% for prediction of OVs. Regarding Platelet count /Splenic diameter ratio the cut off value for the prediction of OV was 909.09 with sensitivity 87.9% and specificity 88.9%.

Conclusion: PSR and LSPS provided good diagnostic tool for the prediction of esophageal varices in compensated cirrhotic patients.

INTRODUCTION

The prevalence of gastro-esophageal varices (GOVs) in patients with cirrhosis ranges from 40 to 80%. In relation to the degree of liver injury, this prevalence increases steadily **[1]**. Upper gastrointestinal bleeding caused by the rupture of GOVs is the most fatal complication of portal hypertension, since it has a mortality rate of 17- 57% **[2].**

The hepatic venous pressure gradient (HVPG) measurement and esophagogastroduodenoscopy (EGD) that are invasive procedures are standard tests to determine the existence of esophageal varices **[3]**. There is a debate about the need for upper endoscopy screening for all compensated patients. This is due to the lower prevalence of clinically significant portal hypertension (CSPH) (60%), OVs (30-40 %) and high risk varicose varices (HRVs) (10-20%) in patients with compensated liver cirrhosis **[4, 5]**. The ideal method to predict OV should be simple, non-invasive, low-cost, accessible and with high sensitivity and specificity **[4]**.

The current Baveno VI consensus recommends combination of liver stiffness and platelet count to select patients who do not need endoscopic screening for OV. Screening endoscopy can be avoided in patients with compensated advanced chronic liver disease (cACLD) with liver stiffness less than 20 kPa and a platelet count more than than 150,000/μL **[6]**. In patients with compensated

cirrhosis, liver stiffness (LS)-spleen size-to-platelet ratio score (LSPS), which is a combination of 3 basic examination methods (LS, spleen size, and platelet count), was found to predict OV and HRVs **[4, 7]**. This study aimed at evaluation of liver stiffness-spleen size-to-platelet count (LSPS) ratio score as a risk score compared to platelet count (mm^3)/spleen diameter (mm) ratio (PSR) for the prediction of esophageal varices (OV) in patients with compensated cirrhosis.

PATIENTS AND METHODS

This prospective study was conducted in the Tropical Medicine Department, Zagazig University Hospitals, during the period from March 2019 to November 2019.

Patients:

The study included 51 patients with compensated liver cirrhosis who underwent screening for the presence of OVs.

Inclusion criteria: Compensated cirrhotic patients (Child - Pugh class A). Diagnosis was based on clinical, laboratory and imaging studies (US and fibroscan).

Exclusion criteria: Non-cirrhotic patients, decompensated cirrhosis (Child-Paugh class B and C), patients with other comorbidities like renal failure, heart failure or respiratory failure, and patients who underwent OV banding or injection.

Methods:

All patients in this study were subjected to:

Full medical history: age, sex, residence and special habits of medical importance. The history of HCV or HBV infection or other causes of liver diseases were reported.

Clinical examination: General examination and local abdominal examination looking for signs of portal hypertension.

Laboratory tests: Complete blood count (CBC), liver function tests, coagulation profile, kidney function tests.

Child - Pugh scoring.

Pelvi - abdominal ultrasound: To detect liver cirrhosis and to assess portal hypertension.

Transient elastography (Fibroscan):

Fibro Scan was done after 6 h of fasting and after ultrasound examination. The tip of the probe transducer was placed at the level of the right lobe of the liver on the skin between the rib bones. Results were calculated in Kilo Pascals (kPa) and equal the median of 10 validated measurements. TE > 15 Kpa is indicative of cirrhosis. TE > 20 - 25 Kpa is indicative of CSPH [8].

Calculation of platelet count (mm^3)/spleen diameter (mm) ratio (PSR): We measure spleen bipolar diameter for three times and calculate the mean value.

Calculation of liver stiffness (LS) - spleen size - to - platelet ratio risk score (LSPS): Formula was calculated as follows: LS value (kPa) × spleen diameter (cm)/ platelet count ($\times 10^3$ cell/μL) [9].

Upper gastrointestinal endoscopy (PENTAX VIDEO):

The patients were subjected to esphagogastroduodenoscopy. Endoscopy was performed using flexible end video endoscope (PENTAX VIDEO unit of endoscopy) by qualified endoscopist. The number of cords, grade of OV and risky signs were recorded. According to Westaby classification, OVs were classified into 3grades: **Grade 1** (small size OV): Varices looking as slight protrusion above the mucosal surface. **Grade 2** (moderate sized OV): Varices which occupy < 50% of the lumen. **Grade 3** (large sized OV): Varices that occupy > 50% of the lumen.

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for Windows (IBM Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Continuous quantitative variables were expressed as the mean ± SD or median (range), and categorical qualitative variables were expressed as absolute frequencies (number) or relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Independent samples Student's t-test was used to compare the two groups of normally distributed data while the Mann-Whitney U test was used for non-normally distributed data. Kruskal Wallis H test was used to compare a more than two groups of non-normally distributed data. Categorical data were compared using chi-square test or Fisher's exact

test when appropriate. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cut-off values of the ALBI score, and ALBI-PLT score with maximum sensitivity and specificity for the predication of OV. Area Under the Receiver operating characteristic curve (AUROC) was also calculated, criteria to qualify for AUC were as follows: 0.90 – 1 = excellent, 0.80–0.90 = good, 0.70–0.80 = fair; 0.60–0.70 = poor; and 0.50–0.6 = fail. The optimal cutoff point was established at point of maximum accuracy. All tests were two sided. p-value <0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered non-statistically significant (NS).

RESULTS

The study included 51 patients with compensated liver cirrhosis who underwent screening for the presence of OV in tropical medicine endoscopy unit. This study shows that the mean age of groups being studied is about 56 years and 66.7% of patients were males. The patients from rural areas were 76.5%. HCV was the cause of cirrhosis in all patients except one patient of unknown cause and 74.5% of studied patients were child score 5 (Table 1).

According to endoscopic findings, 33 (65%) patients had OVs, of them 12 (36.3%) patients have small-sized OVs, 6 (18.2%) patients have moderate-sized OVs and 15 (45.5%) patients have large sized OVs. High Risk Varices (HRVs) are present in 47% of all patients (Table 2).

Table (3) shows that liver stiffness and splenic diameter have a highly significant difference between patients with OV and patients without OV. Also, Liver size had a significant difference between the two groups.

The mean value of LSPS ratio in patients with OV was 7.19 with standard deviation 5.18 (Table 4). LSPS`s ratio has sensitivity 87.88% and specificity 88.89% for the prediction of OV in compensated cirrhotic patients (Table 5) (Figure 1). Regarding platelet count /splenic diameter ratio (PSP), the cutoff value for OV prediction in cirrhotic patient was 909.09 with sensitivity 87.9% and specificity 88.9% (Table 6) (Figure 2).

Table (1): Basic demographic and clinical data:

Basic charactertics	All patients (N=51)	
	No.	%
Sex		
Male	34	66.7%
Female	17	33.3%
Age (years)		
Mean ± SD	55.88 ± 7.95	
Median (Range)	58 (31 – 76)	
HCV Ab		
Negative	1	2%
Positive	50	98%
Residence		
Urban	12	23.49%
Rural	39	76.5%
HBs Ag		
Negative	51	100%
Positive	0	0%
Child score		
Score 5	38	74.5%
Score 6	13	25.5%
Median (Range)	5 (5 – 6)	

Table (2): Upper GIT Endoscopy findings:

Upper GIT Endoscopy findings	All patients (N=51)	
	No.	%
OV		
Absent	18	35.3%
Present	33	64.7%
Small	12	36.3%
Moderate	6	18.2%
Large	15	45.5%
HRV (N=33)		
Absent	9	27.3%
Present	24	72.7%
Fundal varices		
Absent	48	94.1%
Present	3	5.9%

Table (3): Comparison between patients with OV and without OV regarding pelvi-abdominal ultrasound findings and transient elastography

Pelviabdominal ultrasound findings	N	Without OV (N=18)		With OV (N=33)		Test	p-value (Sig.)
		No.	%	No.	%		
Liver size							
Average	47	14	29.8%	33	70.2%	9.235	0.010 (S)
Enlarged	4	4	100%	0	0%		
Splenic diameter (mm)							
Mean ± SD		139.44 ± 25.77		168 ± 25.62		-3.795	<0.001 (HS)
Median		132.50		160			
(Range)		(105 – 185)		(110 – 230)			
Liver stiffness (kPa)							
Mean ± SD		16 ± 5.84		30.72 ± 12.92		-5.582	<0.001 (HS)
Median		15		28			
(Range)		(6 – 26)		(9 – 55)			

Table (4): Value of LSPS ratio in all patients and patients with and without OV

OV	N	Mean	SD	Medium	Minimum	Maximum
Absent	18	1.548	0.89333	1.185	0.457	3.872
Present	33	7.191	5.184	5.6667	0.924	21.083
Total	51	5.199	4.989	3.346	0.457	21.083

Table (5): Diagnostic performance of LSPS ratio for the prediction of OV; ROC curve Analysis

Criterion	SN % (95% CI)	SP % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy (95% CI)	AUROC (95% CI)
>2.4	87.88% (71.8-96.6)	88.89% (65.3-98.6)	93.5% (79.6-98.2)	80% (61.1-91)	88.3% (69.5-97.3)	0.926 (0.797-0.972)

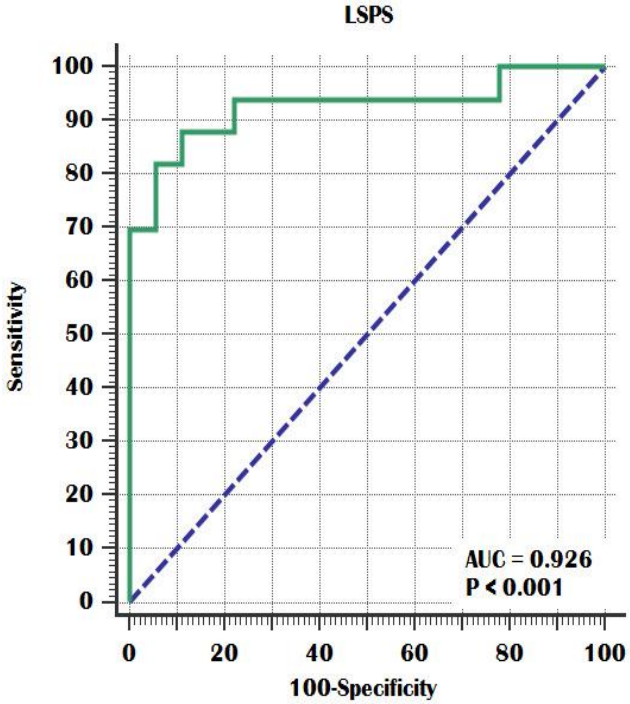

Figure (1): Receiver operating characteristic (ROC) curve of LSPS ratio for the prediction of OV.

Table (6): Diagnostic performance of Platelet/Splenic diameter ratio for the prediction of OV; ROC curve Analysis

Cut-off Values	SN % (95% CI)	SP % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy (95% CI)	AUROC (95% CI)
Ratio ≤909.09	87.9% (71.8-96.6)	88.9% (65.3-98.6)	93.5% (79.6-98.2)	80% (61.1-91)	88.3% (69.5-97.3)	0.911 (0.797-0.972)

*p-value (Sig.) <0.001 (HS)

ROC curve: Receiver Operating Characteristic curve; SN: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUROC: Area Under Receiver Operating Characteristic curve; 95%CI: 95% Confidence Interval; p< 0.05 is significant.

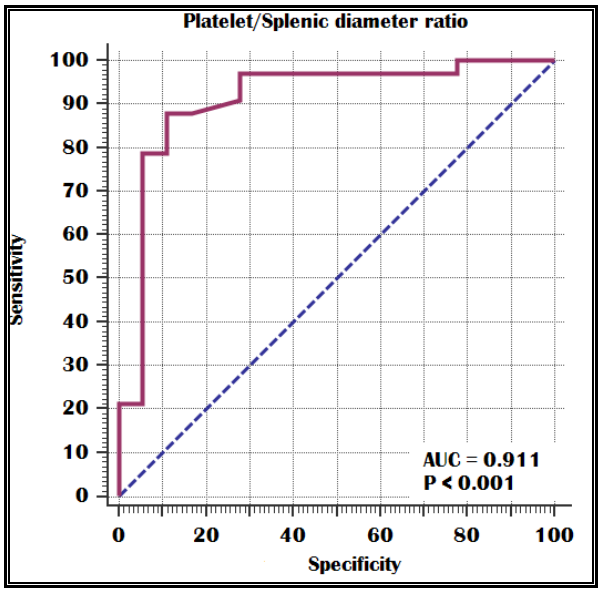

Figure (2): Receiver operating characteristic (ROC) curve of Platelet/Splenic diameter ratio for the prediction of OV.

DISCUSSION

Upper gastrointestinal bleeding, caused by the rupture of gastro-esophageal varices, is one of complications of portal hypertension with a mortality rate ranges between 17-57% **[2]**. So, early screening for varices is needed to improve the prognosis of liver cirrhosis **[10, 11]**. Upper endoscopy is the standard diagnostic method for the detection of varices. However, given the invasiveness and the relatively high cost of endoscopy and poor patient adherence, noninvasive diagnostic methods have been developed. So, searching for objective noninvasive parameters to expect the development of OVs in compensated cirrhotic patients is needed **[7]**.

The overall prevalence rates of OVs and HRVs in this study were 65% and 47%, respectively, which are higher than previously published rates. Previous studies reported that the prevalence of OV in compensated cirrhosis is about 30 - 40%, while up to 85% of decompensated patients may have OV **[12, 13]**. This may be due to past endemicity of *Bilharziasis* in Egypt, as most patients in this study from rural areas, which causes more mesenchymal decompensation and increase the incidence of clinically significant portal hypertension. Also nearly all patients have chronic hepatitis C infection which added to increase the incidence of cirrhosis and clinically significant portal hypertension, and this can explain the high prevalence of OV in our cohort of patients.

Many non-invasive tools were used to detect the presence of esophageal varices in cirrhotic patients **[14]**. Liver stiffness measurement is an important tool that can assess liver fibrosis, but the results in prediction of OV were less satisfactory. Recent studies have shown that LSPS is a strong risk predictive marker for presence of OV **[4]**.

The current Baveno VI consensus recommends combination of liver stiffness and platelet count to select patients who do not need endoscopic screening for OV. The screening endoscopy can be avoided in patients with compensated advanced chronic liver disease (cACLD) with liver stiffness less than 20 kPa and a platelet count more than 150,000/μL **[6]**. Baveno VI criteria have low saved endoscopy rate due to relatively low specificity **[15]**.

An ANTICIPATE study reported that the highest discriminatory value was shown by the LSPS for predicting OV, while LS and platelet count model were the second best model in terms of discriminative capacity **[16]**.

Manatsathit et al., showed that the combination of LS, spleen size, and platelet count (LS - spleen diameter to platelet ratio score [LSPS]) improved the OV detection efficiency **[17]**.

The present study confirmed the diagnostic accuracy of LSPS for detecting OVs in patients with CLD. The sensitivity of LSPS for identifying OV was 87.88 % and specificity 88.89%. These results are consistent with a similar study done by **Shibata et al.,** who reported that the sensitivity and specificity of LSPS for identifying OV were 61.5 % and 89%, respectively. The cut off value for prediction of OV was 0.7 **[18]**. According to study done by **Llop et al.,** patients with a cut-off < 3.5, avoided EGD safely with a negative predictive value (NPV) of 94.7%. On the other hand, patients with a cut-off > 5.5 have a positive predictive value of 94%.The results of this study were very close to results of our study **[19]**.

As reported by **Lee et al.,** the predictive value of LSPS was higher than those of LPS (P<0.001). In this study AUROC of LSPS was 0.92; 95% CI: 0.812-0.98. While AUROC of the LPS was (0.911; 95% CI: 0.797-0.972) (P<0.001) **[9]**. **Yan et al.; 2020,** also reported that LSPS at a cutoff value of 3.4 was a good predictor for the development of high risk varices (HRV) with an AUROC of 0.82 (95% CI, 0.75-0.89) **[20]**.

Also, in this study we evaluated platelet count/splenic diameter as a non-invasive test to predict OV in compensated cirrhotic patients. Low platelet count is the most common abnormal hematological parameter of portal hypertension; also splenomegaly is a common sign of PH **[21]**. Regarding Platelet count/Splenic diameter ratio (PSR), it is an excellent predictor of OV due to high specificity 90% and NPV 80% at cut-off value 909. These results agree with previous studies reported that for predicting varices, PSR of 899 has 92% sensitivity and specificity 72.2% and PSR of 831.5 for HGEVs (sensitivity 93.5% and specificity 90.9%) **[22, 23]**. A meta-analysis assessed the validity of PSR for the prediction of OV, at the cutoff value of 909, sensitivity was 92% and specificity was 87% **[24]**.

Another Meta-analysis included 49 studies was done by **Chen et al., 2017** reported that the sensitivity of PSR for any varices was 84% and high-risk varices 78%. The specificity of PSR for any varices was 78% and high-risk varices 67% at the cut off value 909 **[25]**.

Esmat et al., 2012 have conducted a study on *Egyptian* patients and concluded that the cut off value of 1326.58 for PSR had sensitivity 96.3% and specificity 83.3% **[26]**. Another study done on Egyptian patients stated that PSR at cut off value 939.7 the sensitivity was 100% and specificity 86.3% **[27]**.

This study showed that PSR and LSPS provided good diagnostic tool for the prediction of esophageal varices in compensated cirrhotic patients. The sensitivity of LSPS for predicting OV was 87.88 % and specificity 88.89%, while the sensitivity and specificity of PSR for prediction of OV were 87.9% and 88.9%.

CONCLUSION

Both non-invasive tests, PSR and LSPS, provided a good diagnostic tool in the prediction of OV. Both had a high NPV in excluding OV and reducing the number of unneeded screening endoscopies.

The combination of LS with PSR did not have a valuable increase in sensitivity or specificity for the prediction of OV in compensated cirrhotic patients. PSR is considered an easy cheap valuable method in the prediction of OV as well as it doesn't need special device (FIbroscan) that is usually not available in all hospitals.

Funding: none

Conflict of interest: none

Abbreviations:

GOVs; gastro-esophageal varices

HVPG; hepatic venous pressure gradient

EGD; esophago-gastro-duodenoscope

CSPH; clinical significant portal hypertension

HRVs; high risk varices

cACLD; compensated advanced chronic liver disease

LSPS; liver stiffness-spleen size-to-platelets count ratio score

PSR; platelets count/spleen diameter ratio

Ethical consideration: Informed consent was obtained from all patients and study protocol was approved by the ethical committee of the Faculty of Medicine, Zagazig University.

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