Prediction of Oesophageal Varices in Compensated Cirrhotic Patients

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ABSTRACT

Background: The prevalence of gastro-esophageal varices in patients with cirrhosis ranges from 40 to 80%.The most lethal complication of cirrhosis is Upper GIT Bleeding (UBG) caused by rupture of oesphageal and gastric varices, with a mortality rate of 17 to 57 percent.We aimed at evaluation of platelet count splenic diameter ratio (PSR) and Liver stiffness, spleen size to platelet count ratio risk score (LSPS) for prediction of oesophageal varices.

Patients and methods: this study included 51 patients with compensated cirrhosis. Screening upper endoscopy was done for detection of OV. They also evaluated by transient elastography, laboratory tests and divided according to the presence of OV. We compared both groups based onLSPS,ALBI-PLT score and PSR.

Results:LSPS ratio had sensitivity 87.88% and specificity 88.89% for prediction of OV.Regarding Platelet count /Splenic diameter ratio the cut off value for prediction of OV was 909.09 with sensitivity 87.9% and specificity 88.9%.ALBI-PLT scorehad sensitivity 75.8%and specificity72.2%.

Conclusion: ALBI-PLT score, PSR and LSPS provided good diagnostic toolfor prediction of oesophagealvarices. The combination of LS with PSR did not have valuable increase in sensitivity or specificity.

Keywords: Oesophageal Varices; ALBI-PLT score; Cirrhotic Patient

Introduction:

Portal hypertension isthe most common complication of cirrhosis. The prevalence of gastro-esophageal varices in patients with cirrhosis ranges from 40 to 80%. In relation to the degree of liver injury, this prevalence increases steadily **(1).** The most lethal complication of cirrhosis is Upper GIT Bleeding (UBG) caused by rupture of oesphageal and gastric varices, with a mortality rate of 17 to 57 percent **(2).**

Hepatic venous pressure gradient (HVPG) measurement and esophago-gastroduodenoscopy (EGD) which are invasive procedures are standard tests to determine the existence of oesophageal 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%), OV (30 %-40 %) and high-risk varicose veins (HRV) (10 % -20%) in patients with compensated liver cirrhosis**(4).** The

ideal method to predict OVshould be simple, non-invasive, low-cost, accessible and with high sensitivity and specificity (**5**).

The Baveno VI consensus recommends combination of the 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 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 EV and high risk EV(**7**). One research suggested the use of the extended Baveno VI criteria (LS <25 kPa and platelet count >110 × 10^9 cells/L) due to the low saved endoscopy rate with these criteria (**8**). A previous study suggested that the LS-spleen diameter to platelet ratio score (LSPS) was a valid non-invasive tool for predicting the existence of OV (**7**).

Therefore, the aim of the present study was to evaluate of platelet count splenic diameter ratio (PSR) and Liver stiffness, spleen size to platelet count ratio risk score (LSPS) for prediction of oesophageal varices.

Patients and Methods:
This prospective study was conducted in Tropical Medicine Department, Zagazig University Hospitals, during the period from March 2019 to November 2019. The study included 51 patients with compensated liver cirrhosis who underwent screening for presence of OV.

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

Exclusion criteria:
- Non-cirrhotic patients.
- Decompensated cirrhosis (Child-Paugh class B and C).
- Other comorbidities like renal failure, heart failure or respiratory failure.
- Patients who undergone OV banding or injection.

Methods:
All Participants in this study were subjected to:

(1) **Full medical history** including: age, sex, residence and special habits of medical importance.History of HCV or HBV infection or other causes of liver diseases.

(2) **Clinical examination** include general examination, local abdominal examination looking for signs of portal hypertension.

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

(4) **Child - Pugh scoring:** Child A score (5 -6)**,** Child B score(7-9) **and** Child 12 score (10-15).

(5) **Pelvi-abdominal ultrasound:** To detect liver cirrhosis and to assess of portal hypertension.

(6) **Transient elastography (Fibroscan):**Fibro Scan is done after 6 hours of fasting and after ultrasound examination. It is done in supine position with the right arm behind the head for easy access to the right upper quadrant of the abdomen. 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 for cirrhosis. TE >20-25 Kpa is indicative of CSPH **(9).**

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 (×10 3 cell/μL) **(10).**

Calculation of ALBI-PLT score: ALBI-PLT score was calculated by adding the ALBI grade and platelet count. The cut-off value for the platelet count was 150,000/mm3. One point was given if the platelet count was >150,000/mm3, and 2 points were given if ≤150,000 /mm3. The ALBI-PLT score was defined as the sum of ALBI grade and the point of platelet count, which ranged from 2 to 5 **(11).**

Upper gastrointestinal endoscopy (PENTAX VIDEO):

1. The patients were subjected to oesphagogastroduodenoscopy.
2. Endoscopywas performed using flexible end videoendoscope (PENTAX VIDEO unit of endoscopy) by qualified endoscopist.
3. Number of cords, grade of OV and risky signs was recorded.

According to Westaby classification OV were classified into 3grades:

♦ Grade 1 (small sized OV):Varices looking as slight protrusion above mucosal surface, which can disappear with insufflations.

♦ Grade 2 (moderate sized OV): Varices which occupy <50% of the lumen.

♦ Grade 3 (large sized OV): Varices which occupy >50% of the lumen.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.(Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard

deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

Results:

The demographic and clinical data of all studied patients; the mean age was about 56 year, 66.7% were male. The patients from rural areas were 76.5%. HCV was the commonest cause of cirrhosis (98%) and 74.5% of studied patients were child score 5 **(Table 1)**.

According to endoscopic findings, only (35%) of studied patients had no OV. Small OV are present in (36.36%) of those patients, (18.2%) had moderate sized OV and (45.5%) had large OV. HRV were present in (73%) in patients with OV and in 47% in all studied patients. Fundal varices are present only in 3% of patients **(Table 2)**. TE and splenic diameter had highly significant difference between the two groups alsoLiver size had significant difference between two groups **(Table 3)**.The mean value of LSPS ratio in patients with OV is 7.19 with standerd deviation 5.18 **(Table 4)**.

Regarding Diagnostic performance of LSPS ratio for prediction of OV; ROC curve Analysis, LSPS ratio had sensitivity 87.88% and specificity 88.89% **(Figure 1)**. Regarding Platelet count /Splenic diameter ratio the cut off value for prediction of OV was 909.09 with sensitivity 87.9% and specificity 88.9% **(Table 5)**. Diagnostic performance of ALBI score, Platelet/Splenic diameter ratio and ALBI-PLT score for prediction of OV; ROC curve Analysis showed PLT count / Splenic diameter ratio and ALBI-PLT score were the best for prediction of OV **(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%
HBVs Ag		
Negative	51	100%
Positive	0	0%
Child sore		
Score 5	38	74.5%
Score 6	13	25.5%
Mean ± SD	5.25 ± 0.44	
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	36.36%
Moderate	6	18.18%
Large	15	45.45%
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.

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)		

‡ Chi-square test, * Independent samples Student's t-test, p< 0.05 is significant, Sig.: Significance.

Table (4): LSPS ratio among the studied patients

LSPS

OV	N	Mean	Std. Deviation	Median	Minimum	Maximum
Absent	18	1.54866	.893342	1.18575	.457	3.872
Present	33	7.19122	5.184454	5.66670	.924	21.083
Total	51	5.19973	4.989001	3.43640	.457	21.083

Mann-Whitney Test

Test Statistics[a]

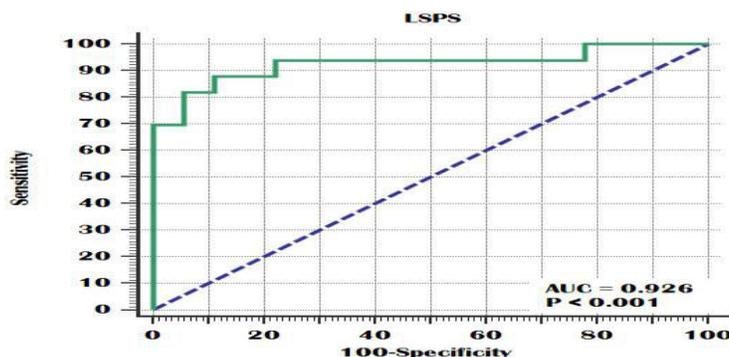|	LSPS
Mann-Whitney U	44.000
Wilcoxon W	215.000
Z	-4.987
Asymp. Sig. (2-tailed)	<0.001

a. Grouping Variable: OV

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

Table (5): Diagnostic performance of Platelet/Splenic diameter ratio for 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
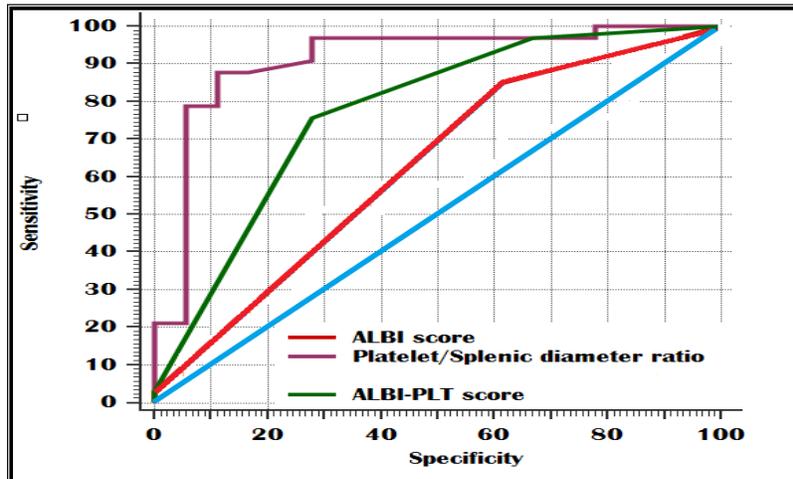
significant.

Figure (3): Receiver operating characteristic (ROC) curve of ALBI score, Platelet/Spleenic diameter ratio, RT lobe diameter/ Albuminratio and ALBI-PLT score for prediction of OV.

Discussion:

Upper gastrointestinal bleeding, caused by rupture of gastro-esphagealvarices, is the most serious complications of portal hypertension with a mortality rate ranges between 17% and 57% **(2).** So, early diagnosis and screening of varices is needed to improve the prognosis of liver cirrhosis **(12).** Upper endoscopy is the gold standard diagnostic method for detection of varices. However, given the invasiveness and the relatively high cost of the endoscopy and poor patient adherence, non-invasive diagnostic methods have been developed. So, searching for objective non-invasive parameters to expect the development of OV in compensated cirrhotic patients is needed **(7).**

The overall prevalence rates of OV and HRV in this study were 65% and 47% respectively, which are higher than previously published rates by **Pagliaro et al., (13) and Kovalak et al., (14)** who reported that the prevalence of OV in compensated cirrhosis is about 30-40%, while up to 85% of decompensated patients may have OV. This may be due to past endemicity of Bilharziasis in Egypt 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 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 oesophagealvarices in cirrhotic patients **(15).** 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 **(5).**

The current Baveno VI consensus recommends combination of the 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 150,000/μL **(6).** Baveno VI criteria has low saved endoscopy rate due relative low specificity **(8).**

An anticipate study reported that the highest discriminatory value was shown by the LSPS for predicting OV while LS and platelet count model was the second bestmodel in terms of discriminative capacity **(3).**

A meta-analysis studydoneby **Manatsathit et al., (16)** illustrated that the combination of LS, spleen size, and platelet count (LS-spleen diameter to platelet ratio score [LSPS]) was shown to further enhance EV detection efficiency.Yet there is discrepancy between studies mainly due to differences in the study population. This study confirmed the diagnostic accuracy of LSPS for detecting EV in patients with CLD.The sensitivity of LSPS for identifying EV was 87.88 % and specificity 88.89%.

These results are consistent with similar study done by **Shibata et al., (17)** who reported that the sensitivity and specificity of LSPS for identifyingEV were 61.5 % and 89% respectively. The cut off value for prediction of OV was 0.7.

According to study done by **Llop et al., (2018)** patients with a cut-off < 3.5, gastroscopy could be avoided with a negative predictive value (NPV) of 94.7%. On the other hand, patients with a cut-off > 5.5 has a positive predictive value of 94%.The results of this study were very close to results of our study.

As reported by **Lee et al., (10)** the AUROC ofLSPS for the prediction of OV was (0.797; 95% CI: 0.774-0.820). It was higher than those of LPS (0.780; 95% CI: 0.749-0.811) (P < 0.001). In this study AUROC of LSPS was 0.92; 95% CI: 0.812-0.98.WhileAUROC of the LPS was (0.911;95% CI:0.797-0.972)(P < 0.001).

Yan et al., (19) also repoted that LSPS was good predictor for high risk varices(HRV). Cutoffvalue of LSPS for predicting HREVwas 3.4.The value of AUROC for LSPS was 0.82 (95% CI, 0.75-0.89).

Also, this study evaluatedplatelet count/splenic diameter as a non-invasive test to predict OV in compensated cirrhotic patients. Low platelets is the most common laboratory indicator of portal hypertension, also splenomegaly is sensitive but non-specific sign of PH **(20).**

Regarding Platelet count/Splenic diameter ratio (PSR), it is an excellent predictor for OV due to high specificity 90% and NPV 80% at cut off value 909. These results agree with previous studies; **Ambulge et al.; (21) and De Franchis et al. (6)** who reported that for predicting varices, PSR of 899 has 92% sensitivity and specificity 72.2% and PSR 831.5 for HGEVs (sensitivity 93.5% and specificity 90.9%).A meta-analysis assessed the validity of PSR for prediction of OV, at cutoff value 909, sensitivity was 92% and specificity was 87% **(22).**

Another meta-analysis included 49 studies was done by **Chen et al., (23)** reported that the sensitivity of PSR for any varices was 84%and high-risk varices78%. The specificity of PSR for any varices 78% and high-risk varices 67% at the cut off value for presence of OV is 909.

Esmat et al., (24) 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%. Another study done on Egyptian patients stated that PSR at cut off value 939.7 the sensitivity was 100% and specificity 86.3% **(25).**

From the previous studies it was obvious that addition of liver stiffness to platelet count splenic diameter did not add any advantage regarding sensitivity and specificity.

Among these non-invasive tests, Albumin bilirubin-platelets score, which was initially introduced as a tool to predict HRV among patients with hepatocellular carcinoma who have compensated liver function. ALBI-PLT score is composed of albumin and bilirubin as indicators of synthetic liver function and platelets as an indicator of portal hypertension **(23).** In such way, it is obvious that ALBI-PLT score is consistent with Baveno VI consensus. It was reported that compensated cirrhotic patients with platelets >150,000 and transient elastography of liver <20 KPa, are less likely to have OV and can avoid unnecessary endoscopy **(26).**

It is obvious from our results that ALBI-PLT score can predict the presence of esophageal varices in compensated cirrhotic patients and hence can be used as a simple and non-invasive tool to detect patients at low risk for development of OV to avoid unnecessary screening endoscopy. In our study, the number of patients with ALBI-PLT score ≥3 was 44 (86%) patients, 32 (73%) patients out of them have OV, while those with ALBI-PLT score <3 were 7 patients, only one of them has OV. This study reported that ALBI grade >1 alone has very low specificity 38.9% and negative predictive value (58.3%) for prediction of OV, while after addition of platelet to this score specificity increased to 72% and negative predictive value increased to 62% with cut value score>3. These results are near to what was observed by similar studies applied on compensated cirrhotic patients with HCC. **Chen., et al (23)** who reported that negative predictive value

is 97% if the patients had ALBI-PLT score=2**.** But the discrepancy may be due to small number of our cohort which needed to be increased in next studies.

Conclusion:

PSR andLSPS provided good diagnostic tool in terms of ARUOCfor prediction of OV.Because LSPS had a highNPV in excluding OV, it might have a role inreducing the number of unnecessary screening endoscopies.

The combination of LS with PSR did not have valuable increase in sensitivity or specificity. PSR and ALBI-PLT scoreare considered easy cheap valuble method in prediction of OV with high sensitivity and specificity in prediction of OV.

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