ORIGINAL

Non-invasive assessment of large esophageal varices with liver cirrhosis ; a study conducted in Pakistan

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Abstract : The assessment of non-invasive parameters for the prediction of large esophageal varices among patients with liver cirrhosisis is of utmost importance. In this study, non-invasive parameters for prediction of large esophageal varices were retrospectively evaluated. The presence of esophageal varices grade III and IV was classified as large esophageal varices positive while no varices or grade I and II were classified as large esophageal varices negative. There were 473 (90.09%) patients with ascites [mild 38 (8.03%), moderate 257 (54.33%) and severe 178 (37.63%)]. Frequency of esophageal varices was found to be higher (n=415, 79.04%). Whereas, large esophageal varices were found in 251 (47.81%) patients. The sensitivity, specificity, positive predicted value, negative predicted value and test accuracy of thrombocytopenia in predicting large esophageal varices were found to be 88.05%, 59.85%, 66.77%, 84.54% and 73.33% respectively. A significant association for large esophageal varices was observed for low platelet counts (AOR : 0.98, 95% CI : 0.97-0.99), high bilirubin level (AOR : 1.22, 95% CI : 1.07-1.39), ascites (AOR : 1.98, CI : 1.02-3.85) and Child score A (AOR : 0.26, 95% CI : 0.09-0.75) and Child Score B (AOR : 0.42, 95% CI : 0.28-0.61). In conclusion, low platelet count, high bilirubin level and ascites are found to be non-invasive predictive factor for large esophageal varices. J. Med. Invest. 66 : 248-251, August, 2019

Keywords **:** *Large esophageal varices (LEVx), Platelet, Bilirubin, Liver cirrhosis*

INTRODUCTION

Esophageal varices are a big challenge in managing cirrhotic patients and suggest its early detection with either invasive or non-invasive methods. (1)

Various studies have evaluated the non-invasive predicting markers for large esophageal varices (LEVx) (2-5). Advanced Child-Pugh score, platelet count, serum albumin level, splenomegaly and increase portal vein diameter at ultrasonography are reported by several studies as the possible useful markers (6-8).It is stated that due to the disparities in the etiology and severity of liver cirrhosis and because of the nutritional status differences, these non-invasive prognostic factors showed variations when studied in different populations (8). Frequent hospitalizations due to the complications including the variceal bleeding are owing to late presentation of cirrhotics in our country (9).

American Association for the Study of Liver Disease (AASLD) and American College of Gastroenterology (ACG) practice guidelines have stated that upper GI endoscopy should be performed in all patients with liver cirrhosis to rule out LEVx. If the patient is found positive for having LEVx, treatment with β-adrenergic receptor antagonists should be started (10). Though long-term administration of β-adrenergic receptor antagonists in patients with LEVx reduces the incidence of first variceal bleeding, adverse effects are largely reported from its prolonged administration (11). In addition, its use is not recommended in patients with small esophageal varices (11, 12).

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Consequently, LEVx screening not only generates a huge burden on endoscopic units but is also a financial constraint on liver cirrhotics. Keeping the social, financial, and healthcare resource burdens implicated by these recommendations, recent studies have focused on the utility of non-invasive approaches to identify patients with LEVx, thereby, preventing the endoscopy of patients with lower risk (3-5, 8).

METHODOLOGY

A retrospective study at Civil Hospital Karachi (CHK) was conducted from 2012 to 2016 after taking ethical approval (IRB-878/DUHS/2017/78) from Dow University of Health Sciences (DUHS).

Diagnosis

Cirrhosis was confirmed on clinical (stigmata of chronic liver disease), biochemical and radiological (abdominal ultrasound or computerized tomography) parameters. Radiological features demonstrated small shrunken liver and intra-abdominal varices with or without enlarged spleen. Cirrhosis was also confirmed on a histopathological basis, wherever required (13).

Gastroesophageal varices were defined and classified in accordance to Dagradi classification (14). Varices with blue or red in color and brought out by compression of the esophageal wall with the tip of the oesophagoscope were defined as grade 1. Grade 1 varices are usually linear, maybe sigmoid shaped having less than 2 mm in diameter. Grade 2 varices were defined as bluish, mildly tortuous or straight, and were elevated above the surface or the relaxed esophagus having 2-3 mm in diameter. Grade 3 were vividly elevated bluish veins either straight or tortuous having 3-4 mm in diameter. Tortuous bluish varices having > 4 mm in diameter, which completely occupies the esophageal lumen closely packed around the wall and may or may not have

a good mucosal cover defined as Grade 4. Varices grape-like in appearance, obstructing the lumen of the approaching oesophagoscope with presence of small, cherry-red varices overlying the large, slightly deeper lying, slate blue-grey varices (also known as 'varices over varices') were defined as grade 5.

Those patients with the presence of hepatocellular carcinoma (HCC), portal hypertension surgery, history of esophageal variceal bleeding, on primary prophylaxis treatment for variceal bleeding, sclerotherapy and/or portal vein thrombosis (PVT) were excluded to control the factors affecting the platelet count.

Data collection

A detailed demographic and clinical information including age, gender, hematological and biochemical findings, liver disease severity, and ascites were recorded. The severity of the liver disease was noted on the basis of Child-Pugh Score whereas ascites was graded as none, mild, moderate and severe. Laboratory findings were evaluated using hemoglobin (Hb) count, platelet count, total leukocyte count (TLC), serum concentration of albumin, bilirubin, alkaline phosphate (ALP), and alanine aminotransferase (ALT). The seropositivity of hepatitis B and C virus were also evaluated with patient's history of alcohol intake and intravenous drug abuse.

Abdominal ultrasonography with high-resolution real-time ultrasound machines was performed in all patients using GE Voluson S8 and Xario 100, Toshiba using 3.5-MHz convex transducer. Endoscopy of the upper gastrointestinal system was performed using one endoscopic unit (Olympus Corporation, Tokyo, Japan).

The presence of esophageal varices grade III & IV was classified as LEVx positive while no varices or grade I & II were classified as LEVx negative.

Statistical analysis

The mean and standard deviation for quantitative variables like age, Hb level, platelets count, TLC, Albumin, Bilirubin, ALP, and ALT was calculated while frequency and percentages for quantitative variables like gender, ascites, and the Child-Pugh score were calculated. Differences in the mean values of quantitative variables were explored using independent t-test while to check the relationship in between LEVx and quantitative variables, chi-square test was applied. P-value < 0.05 was considered significant.

The significant association between various independent variables and outcome variable (LEVx) were also explored using univariate binary logistic regression. All significant variables in univariate analysis were selected for multiple logistic regressions to calculate adjusted odds ratio (AOR).

Diagnostic accuracy was calculated using the standard thrombocytopenia level (150,000) as cut-off point of platelets counts.

RESULTS

Initially, 600 patients were included. However, 75 patients were excluded because of the presence of HCC and/or history of esophageal variceal bleeding and portal vein thrombosis. Thus, in the final analysis, 525 cases were selected. The mean age was reported as 46.44 ± 14.43 years. Majority of the patients (n = 279, 53.14%) were males. HCV virus was the predominant hepatic cirrhosis etiology reported in 396 (75.42%) patients, whereas HBV virus was found in 57 (10.85%), Cryptogenic 41 (7.81%), Wilson's Disease 14 (2.67%), autoimmune hepatitis 9 (1.71%), alcoholism 5 (0.95%), and both HBV and HCV were found in 3 (0.57%) patients. There were 473 (90.09%) patients with ascites. Among these, mild ascites was observed in 38 (8.03%), moderate in 257 (54.33%) and severe in 178 (37.63%) patients.

The endoscopic finding showed that esophageal varices were found in 415 (79.04%) patients. Out of these 415 esophageal varices positive patients, "grade I" esophageal varices were observed in 48 (11.56%) patients, "grade II" in 116 (27.97%), "grade III" in 202 (48.67%), and "grade IV" in 49 (11.81%) patients. There were 251 (47.81%) patients with LEVx (grade III & IV) whereas 274 (52.19%) patients with no LEVx.

The Child-Pugh score C was found in the majority (n = 328, 62.47%) of the patients followed by Child-Pugh Score B in 178 (33.90%) and Child-Pugh score A in 19 (3.62%) patients.

Thrombocytopenia (platelet count below 150,000) was observed in 331 (63.04%) patients whereas 194 (36.95%) patients were presented with normal platelet count (platelet count above 150,000). A significant difference of esophageal varices was observed among patients with and without thrombocytopenia (p-value < 0.001). LEVx was found significantly higher (n = 221, 66.8%) among patients with thrombocytopenia as compared to normal platelet count (n = 30, 15.5%) (p-value < 0.001). (Figure 1) The sensitivity, specificity, PPV, NPV and test accuracy of thrombocytopenia in predicting LEVx was found to be 88.05%, 59.85%, 66.77%, 84.54% and 73.33% respectively. (Table I)

The difference in majority of the variables were insignificant among patients with and without LEVx including age (p-value 0.092), gender (p-value 0.442), Hb (p-value 0.175), TLC (p-value 0.159), ALP (p-value 0.202), and ALT (p-value0.075). While, the platelet count (p-value < 0.001), Bilirubin (p-value < 0.001), presence of ascites (p-value 0.045) and Child-Pugh Score (p-value < 0.001) were the only variables found significantly related with LEVx. (Table II)

The univariate analysis revealed that platelet counts (OR : 0.98, 95% CI : 0.97-0.99),Child score A (OR : 0.28, 95% CI : 0.98-0.79) and Child Score B (OR : 0.42, 95% CI : 0.29-0.61)

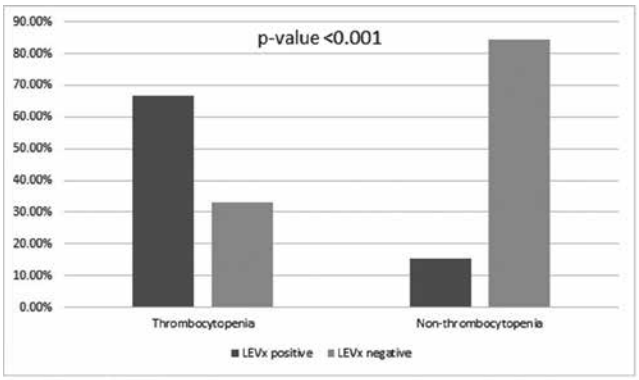

Figure 1 : Difference between occurrence of large size esophageal varices versus no large size esophageal varices in thrombocytopenic and non-thrombocytopenic patients (n = 525)

Table I : Diagnostic accuracy of thrombocytopenia in predicting large esophageal varices (n = 525)

Thrombocytopenia	Large scale esophageal varices		
	Yes	No	Total
Yes	221	110	331
No	30	164	194
Total	251	274	525
Sensitivity : 88.05%			
Specificity : 59.85%			
Positive Predicted Value (PPV) : 66.77%			
Negative Predicted Value (NPV) : 84.54%			
Test Accuracy : 73.33%			

were less likely whereas bilirubin level (OR : 1.18, 95% CI : 1.06-1.31) and presence of ascites (OR : 1.83, 95% CI : 1.01-3.34) were more likely to have LEVx. Similarly, on multivariate analysis (adjusted for platelet counts, bilirubin, ascites and Child-Pugh score), platelet counts (AOR : 0.98, 95% CI : 0.97-0.99),Child score A (AOR : 0.26, 95% CI : 0.09-0.75) and Child Score B (AOR : 0.42, 95% CI : 0.28-0.61) were less likely whereas bilirubin level (AOR : 1.22, 95% CI : 1.07-1.39) and presence of ascites (AOR : 1.87, 95% CI : 1.02-3.49) were more likely to have LEVx. (Table III)

Table II : Comparison of Large esophageal varices with predictor variables (n = 525)

Variables	Large esophageal varices (LEVx)		
	Positive (n=251)	Negative (n=274)	p-value
	n (%)	n (%)	
Age (years)	45.33 ±14.37	47.46 ±14.43	0.092†
Gender			
Male	150 (53.8)	129 (46.2)	0.442‡
Female	124 (50.4)	122 (49.6)	
Hematological and biochemical findings			
Hb (g/dl)	7.05 ±0.83	7.14 ±0.73	0.175†
TLC (x 1000/µL)	7.17 ±5.32	7.92 ±6.73	0.159†
Platelets (x 1000/µL)	67.07 ±35.47	183.57 ±158.78	<0.001†**
Albumin (mg/dL)	2.77 ±0.45	2.69 ±0.46	0.056†
Bilirubin (mg/dL)	2.23 ±2.07	1.73 ±1.35	<0.001†**
ALP (IU/L)	71.47 ±42.57	67.01 ±37.43	0.202†
ALT (IU/L	225.76 ±109.99	206.89 ±130.52	0.075†
Ascites			
Yes	233 (49.3)	240 (50.7)	0.045‡*
No	18 (34.6)	34 (65.4)	
Child-Pugh Score			
A	5 (26.3)	14 (73.7)	<0.001‡**
B	62 (34.8)	116 (65.2)	
C	184 (56.1)	144 (43.9)	

†Independent t-test applied, ‡Chi-square test applied, *p-value < 0.05, **p-value < 0.001
ALP : Alkaline Phosphate, ALT : Alanine Transaminase, TLC : Total Leukocyte Count, Hb : Hemoglobin

Table III : Regression analysis of factors associated with large esophageal varices (n = 525)

	OR (95% CI)	p-value	AOR (95% CI)	p-value
Age (years)	0.99 (0.97-1.01)	0.092	-	
Gender				
Male	0.874 (0.62-1.23)	0.442	-	
Female	1			
Hematological and biochemical findings				
Hb (g/dl)	0.85 (0.69-1.07)	0.175	-	
TLC (x 1000/µL)	0.98 (0.95-1.01)	0.159	-	
Platelets (x 1000/µL)	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Albumin (mg/dL)	1.44 (0.98-2.09)	0.057	-	
Bilirubin (mg/dL)	1.18 (1.06-1.31)	<0.001	1.22 (1.07-1.39)	0.003
ALP (IU/L)	1.01 (0.99-1.02)	0.202	-	
ALT (IU/L)	0.99 (0.99-1.01)	0.120	-	
Ascites				
Yes	1.83 (1.01-3.34)	0.047	1.87 (1.02-3.49)	0.040
No	1		1	
Child-Pugh Score				
A	0.28 (0.98-0.79)	0.017	0.26 (0.09-0.75)	0.0.12
B	0.42 (0.29-0.61)	<0.001	0.42 (0.28-0.61)	<0.001
C	1		1	

CI : Confidence Interval, OR : Odds ratio, AOR : Adjusted Odds Ratio, ALP : Alkaline Phosphate, ALT : Alanine Transaminase, TLC : Total Leukocyte Count, Hb : Hemoglobin

DISCUSSION

This study has shown a higher proportion of patients with liver cirrhosis having LEVx. Low platelet counts, high bilirubin level, presence of ascites, severity of cirrhosis (CTP-A, and CTP-B) were found to have predictive ability on univariate analysis. Earlier studies (2, 4, 15-17) have also shown an independent predictive ability of low platelet count in liver cirrhosis patients to predict LEVx.

A palpable or enlarged spleen is reported to be an important predictor in most of the studies (2, 6, 18-20). Various studies have recommended "platelet count/spleen diameter" (PC/SD) ratio as the most viable non-invasive tool in the prediction of the varices (4, 19-23). However, as this study is retrospective PC/SD ratio of our patients was not calculated. Though mostly earlier studies have shown PC/SD ratio as an effective non-invasive parameter for prediction of LEVx, but one local study in Pakistan has shown contrary findings (24) where PC/SD ratio could not reliably predict the esophageal varices in cirrhotic patients. Furthermore, above referred study (24) have also reported an insignificant association of low platelet count with esophageal varices.

Low platelet count and ascites are widely reported as a noninvasive predictor of esophageal varices by earlier published studies (25-31) which is in agreement to this study. Prior studies (32, 33) have validated both clinical and sonologically determined ascites as an independent predictor for LEVx.

High level of serum bilirubin has shown a significant predictor for LEVx in this study which is in accordance to an earlier study (29). Schwarzenberger *et al*. in their study reported various parameters like ascites, splenomegaly, serum albumin concentration, Child score, and portal vein diameter as predictive variables for LEVx (30). Recently, Chen et al evaluated the combined effect of "albumin bilirubin grade and platelet count" to predict risk of large varices and variceal haemorrhage (5). Due to the diversity of liver diseases and variations in the characteristics among different populations earlier studies have shown different parameters to predict large esophageal varices. In fact, a highly accurate non-invasive predictive model for LEVx is still awaited (4).

Findings of this study could be ascertained in the light of the limitations that due to retrospective nature of the study, spleen diameter values of our patients were not collected. Thus, PC/SD ratio of our patients was not evaluated which if determined would have a more statistical impact. However, to the best of our knowledge, this is the first study from Pakistan reporting the predicting factor for LEVx from such a larger population.

CONCLUSION

Low platelet count, high bilirubin level and presence of ascites can be used as independent non-invasive predictive factors for LEVx among patients with liver cirrhosis. Further validation of these non invasive parameters through large prospective studies in resource-limited areas like Pakistan where endoscopy is not available everywhere,would definitely provide a non invasive alternative to endoscopy with substantial reduction in financial burden.

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