Cytopenia As A Predictor Of Oesophageal Varices In Patients With Liver Cirrhosis

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Abstract: Introduction: Recent guidelines recommend that all cirrhotics undergo screening upper endoscopy to identify those patients at risk for bleeding from varices. However, referral for endoscopic screening of only patients at highest risk for varices may be most cost-effective. Therefore, there is a particular need for a noninvasive predictor for the presence of esophageal varices (EV) to ease the medical, social and economic burden of the disease. **The aim of this study** was to evaluate the role of leucopenia and thrombocytopenia as a noninvasive predictors of esophageal varices in cirrhotic patients. **Patients and Methods:** 120 patients with liver cirrhosis were enrolled in this study. Relevant clinical parameters assessed included Child-Pugh class, ascites and splenomegaly. Laboratory parameters like hemoglobin level, platelet count,WBC count, prothrombin time, serum bilirubin, albumin and ultrasonographic characteristics like splenic size, splenic vein size, portal vein diameter were assessed. Upper gastrointestinal endoscopy for assessment of esophageal and gastric varices. If EV were present, their size was graded as I-IV. **Results:** EV were found in 110 patients (91.7%). For the prediction of varices, the sensitivity and specificity of the platelet count($130x10^3$) were 80% and 90% respectively while WBC ($3.5x10^3$) was 80% sensitive and 52% specific. **Conclusion:** We concluded that thrombocytopenia and leucopenia can be used to stratify risk for occurrence of esophageal varices in cirrhotic patients and gastroscopy will have a high yield for varices when platelet count is ≤130,000/mm³ or total white is ≤3500/mm³. [Report and Opinion 2010;2(7):35-41]. (ISSN: 1553-9873).

Key words: Esophageal varices, leucopenia, non invasive predictor of varices, portal hypertension, thrombocytopenia

Introduction:

Esophageal variceal bleeding is a potentially deadly complication in patients with liver cirrhosis and portal hypertension. In patients with cirrhosis, the incidence of esophageal varices ranges from 35% to 80%. The risk of initial bleeding from varices is 25% to 35% in 2 years, with most first-bleeding episodes occurring within a year of detection of varices.[1]The reported mortality from a first episode of variceal bleeding ranges from 17% to 57%. Of patients who survive and do not receive active treatment (β-adrenergic blocking agents or endoscopy), two thirds will have another episode of bleeding within 6 months of the initial episode.[2] Therefore, early detection of EV in cirrhotic patients is crucial to minimize the complications. American College of Gastroenterology recommends screening all cirrhotic patients for the presence of esophageal varices and treating patients with large varices with β-adrenergic blocking agents to reduce the incidence of first variceal bleeding.[2] Other investigators recommend that screening should be performed every 2 years for cirrhotic patients without varices and that patients with known small varices undergo endoscopy every year.[3]However, screening all patients with endoscopy to guide therapy may significantly increase the cost. Therefore, there is a particular need for a noninvasive predictor for the presence of EV to ease the medical, social and economic burden of the disease. Platelet count, splenomegaly, platelet count/spleen diameter ratio(PC/SD), advanced Child-Pugh class, serum albumin, and high portal vein diameter may be useful non-invasive predictors of EV for patients with cirrhosis.[4,5] Several studies suggest that platelet count may predict the presence of EV in patients with cirrhosis.[6] However, the discriminating threshold for the presence of varices varies widely, ranging between 68,000 and 160,000/mm^3 .[7] The sensitivities for thrombocytopenia fluctuate from 62% to 100%, and the specificities range from 18% to 77%.[1] Predictors of varices and risk of bleeding may be expected to vary in different populations. Data on this aspect in Egyptian patients with liver cirrhosis, who usually have a higher proportion with hepatitis c viral and bilharzial etiology, remain unexplored.

Aim of the work: This prospective study was conducted to evaluate the role of leucopenia and thrombocytopenia as a noninvasive predictors of esophageal varices in cirrhotic patients .

Subjects & methods: 120 patients with liver

cirrhosis recruited from the hepatology clinic of Ain Shams University Hospitals were enrolled in this study. All patients were free of gastrointestinal tract complaints, including bleeding. None were taking nonsteroidal anti-inflammatory drugs, acid-suppressing drugs, or β-adrenergic blocking agents and nitrates. Patients with leucopenia, thrombocytopenia and anemia due to hematological causes, evidence of hepatocellular carcinoma , portal vein thrombosis, those who have received endoscopic or surgical intervention for portal hypertension previously were excluded from the study. All patients were subjected to the following:

1: Relevant history and physical characteristics including symptoms and signs of liver failure (spider angioma, palmar erythema etc.), hepatomegaly, spleenomegaly, and abdominal vein collaterals were recorded. Ascites was graded as none, mild (detectable only on ultrasound), moderate (visible moderate symmetrical abdominal distension) or severe (marked abdominal distension).[8] Hepatic encephalopathy was graded from grade 0 to IV. [9]Diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic findings.

2: Blood tests: Hematological and biochemical workup included measurement of hemoglobin, total leukocyte count, platelet count, prothrombin time, and serum concentrations of bilirubin (total and conjugated), protein, albumin, alanine aminotransferase and aspartate aminotransferase. For each patient, a modified Child-Pugh score was calculated.[10] All patients were tested for HBsAg and antibodies to hepatitis C virus to determine the cause of liver cirrhosis. Tests for other causes of cirrhosis (serum ceruloplasmin and slit lamp examination for Wilson's disease, tests for autoantibodies for autoimmune liver disease, iron studies for hemochromatosis) were carried out only if there was a suggestive clinical clue.

3: Ultrasound Doppler: All patients underwent ultrasonography after over night fast and the following details were recorded: Maximum vertical span of the liver; nodularity of liver surface; spleen size (length of its longest axis); diameter of the portal and splenic veins; presence of portal-systemic collaterals; and presence of ascites.

4: Endoscopic evaluation: All patients underwent upper gastrointestinal endoscopy for assessment of esophageal and gastric varices. If EV were present, their size was graded as I-IV, using the Paquet grading system.[11] Grade 0: No varices, grade I: Varices, disappearing with insufflation, grade II: Larger, clearly visible, usually straight varices, not disappearing with insufflation, grade III: More prominent varices, locally coil-shaped and partly occupying the lumen, grade IV: Tortuous, sometimes grape-like varices occupying the esophageal lumen. Further, patients were classified either as having large (risky)EV (grade III-IV) or as not having these (no varices or grade I-II).[11] Right hepatic lobe diameter/serum albumin ratio (Rt LLD/S.Alb) & platelet count/splenic size (PC/SD) ratio were calculated. Informed consent was obtained from all participants before enrollment in the study.

Statistical Analysis: All collected data were expressed as mean± SD and analyzed by using SPSS version 13 using the following tests: Student t test, Chi-square test, Wilcoxon Rank Sum test, Receiver operating curve (ROC) to detect area under curve (AUC), cut off value (COV) for best sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and efficacy. $P<0.05$ was considered significant and at $P<0.001$ was considered highly significant, while at $P>0.05$ was considered not significant.

Results: Of the 120 cirrhotic patients included in the study, 92(76.7%) were male and 28(23.3%) were females, with a mean age of 53.1 ± 12.2 years. EV were found in 110 patients (91.7%) 35 patients (29.2%) of them had risky varices. With advancing Child-Pugh class, the percentage of patients with varices increased: 6(50%) of 12 patients in Child-Pugh class A, 62(93.5%) of 66 in Child-Pugh class B, and 42(100%) of 42 in Child-Pugh class C had varices. Ascites was found in 74 (61.7%) (70 had EV and 4 had no EV). Hepatitis C infection was the most frequent cause of cirrhosis in 94 (78.3%), followed by hepatitis B infection in10 (8.3%), pure bilharzias in 4 (3.3%), six HCV infected patients were co-morbid with bilharziasis, 4 cases were due to autoimmune hepatitis (3.3%), Wilson disease in 2 patients(1.6%), Budd chiarri syndrome in 2(1.6%), Nash in 4 patients(3.3%) . By ultrasonography, 114 were found to have splenomegaly while 6 were found to have normal spleen dimensions. Patients with varices had lower platelet counts , lower PC/SD, larger Rt lobe / S albumin and lower serum albumin in comparison to those without varices (76.25±35.84 vs. 212.4±142 ; $P<0.05$), (443 vs. 1634 ; $p<0.05$), (5.58 vs. 4.4; $P<0.05$) and (2.5 vs. 3.3 $P<0.001$) respectively (Table 1).

Table 1: Comparison between patients with esophageal varices and those without varices

Variable	CLD with esophageal varices (110 patients)	CLD without esophageal varices (10patients)	P value
Age	52.85 ± 11.25	42.80 ± 12.53	>0.05
AST	77.22 ± 48.60	33.80 ± 15.38	>0.05
ALT	51.69 ± 32.33	34.20 ± 19.66	>0.05
Albumin	2.54 ± 0.48	3.32 ± 0.66	<0.01**
T.Bil	3.21 ± 4.13	1.76 ± 1.92	>0.05
WBC	4.66 ± 2.58	4.94 ± 1.82	>0.05
HB	9.86 ± 1.94	9.92 ± 2.64	>0.05
Platelet	76.25 ± 35.84	212.4 ± 142.7	<0.05*
INR	1.55 ± 0.42	1.21 ± 0.21	>0.05
RtLD/S. Alb	5.58 ± 1.18	4.40 ± 1.36	<0.05*
PC/SD	443 ± 242	1634 ± 1377	<0.05*

For prediction of esophageal varices, Receiver operating characteristic curve for platelet count $130x10^3$ and white blood cell count$3.5x10^3$ was performed. The sensitivity and specificity for the platelet count were 80% and 90% respectively while for WBC were 80% and 52% respectively as shown in (table 2 and figure1). 100 out of 104 viral cirrhosis patients had esophageal varices. For EV prediction in viral cirrhosis, the cutoff value of platelet count has been decreased to 76.000 with 63% specificity and 85% sensitivity ,with AUC of 0.817. However the same cutoff value of WBC (3.5) was 75% specific and 60% sensitive, with AUC of 0.721.

Table (2): Different predictors for presence of esophageal varices.

Variables	COV	Sensitivity	Specificity	PPV	NPV	Efficacy
Platelet	$130x10^3$	80%	90%	98.8%	29%	80%
WBC	$3.5x10^3$	80%	52%	94.8%	19.1%	77.6%
PC/SD	415	80%	60%	80%	60%	73.3%
Rt LLD/S.Alb	5.12	75%	65%	95.9%	19.11%	74.1%
Splenomegaly	-	94%	66%	98%	40%`	93%
Ascites	-	94.5%	13%	63.6%	60%	63.3%
Dilated portal vein	-	96.3%	100%	100%	71.4%	96.6%

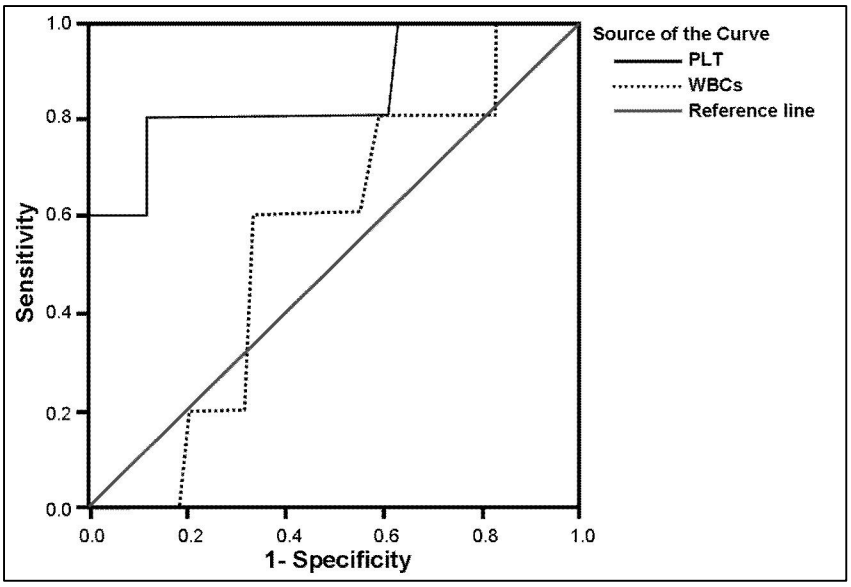

Figure (1) ROC curve of WBC and platelet count for prediction of varices

Cirrhotics were stratified into high risk (had EV grade III-IV) (35 patients) and low-risk groups (no varices or grade I-II) 75 patients. The platelet count and PC/SD were lower in high risk group (58.9 ± 26.88 vs. 101.9 ± 71.15 ; P <0.05and 312 ± 152 vs. 657 ± 624 ; P<0.05 respectively). The mean hemoglobin and serum albumin levels were lower and the prothrombin time ,AST were higher in the large(risky) varices group, indicating more advanced disease; however, these did not assume statistical significance (Table 3).

Table (3): Comparison between patients with large varices(35) and those with small or no varices(75) as regard different variables.

Variable	Patients with large(risky) varices (35)	Patients with small or no varices(75)	P value
Age	57.20 ± 6.59	49.42 ± 12.71	0.01*
AST	65.150 ± 51.64	60.22 ± 33.20	>0.05
ALT	43.95 ± 24.20	53.37 ± 34.74	>0.05
Albumin	2.56 ± 0.53	2.63 ± 0.55	>0.05
T.Bil	3.07 ± 3.89	3.10 ± 4.11	>0.05
WBC	3.20 ± 1.85	5.39 ± 3.08	>0.05
HB	9.46 ± 1.69	10.08 ± 2.10	>0.05
Platelet	58.9 ± 26.88	101.9 ± 71.15	<0.05*
INR	1.6 ± 0.36	1.52 ± 0.44	>0.05
Rt LLD/S. Alb	5.40 ± 1.28	5.53 ± 1.22	>0.05
PC/SD	312 ± 152	657 ± 624	<0.05*

The platelet count (63.000) found to be sensitive (75%) but less specific (65%), while WBC($3.1x10^{3)}$ was less sensitive (62.5%) and less specific (60%) for prediction of large varices (Table 4).

Table (4): Different predictors for large (risky)esophageal varices.

Variables	COV	Sensitivity	Specificity	PPV	NPV	Efficacy
Platelet	$63x10^3$	75%	65%	51.7%	83.8%	68.3%
WBC	$3.1x10^3$	62.5%	60%	34.4%	76.9%	60%
PC/SD	405	75%	55%	45.5%	81.4%	61.6%
Rt LLD/S.Alb	5.23	70%	60%	46.6%	80%	63.3%
Splenomegaly	-	100%	7.5%	35%	100%	38.3%
Ascites	-	95%	55%	51.5%	95.6%	68.3%
Dilated portal vein	-	100%	17.5%	37.7%	100%1	45%

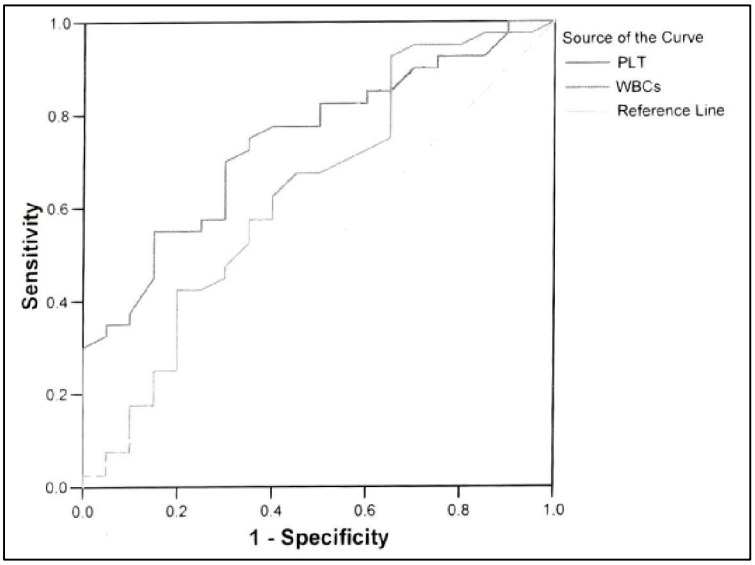

Figure (2) ROC curve of platelet count and WBC for prediction of large varices

Discussion:

We found that the platelet count was lower in patients with esophageal varices (mean 76.25 ± 35.84 x 10^3) than patient without varices (mean 212.40 ± 142.79 x 10^3). The best cut off value of platelet count as a predictor for presence of varices was 130 x 10^3 with 80% sensitivity and 90% specificity, this cutoff value has been decreased to 76 x 10^3 in patients with viral cirrhosis. ***Garcia- Tsao et al.***[12] (180 patients), ***Pilette et al.***[13] (116 patients) and ***Thomopoulos et*** al.[14] (184 patients) found that platelet count <118 x 10^3 was good predictor for presence of varices with sensitivity 95%, specificity 73 % and reported a low platelet count to be an independent risk factor for the presence of varices. ***Khuram et al.*** [15] (200 patients) found OV in 146 with 121 having thrombocytopenia (94.5%). In retrospective analysis of 143 patients with compensated cirrhosis, ***Schepis et al.***[16] reported OV in 63 patients (44%) with platelet count of <100,000 as predictor of OV. ***Zaman et al***.[6] reported that groups without varices had a higher mean platelet count (mean platelet count, 128500) than the group with small varices (mean platelet count, 107800) and platelet count of <90,000 increased the risk of having OV by nearly 2.5 fold. ***Zein et*** al.[17] reported (in chronic liver disease due to primary sclerosing cholangitis) platelet count of <150000 to be predictor of OV with sensitivity 88% and specificity 76%. **Madhotra et al.,**[18] found that the

platelet count in patients with esophageal varices ranged from (53 – 105 x 10^3) with median = 76 x 10^3 while in patients without varices was from (74 – 150 x 10^3) with median = 108 x 10^3. Their best cut off value was 68 x 10^3 where the sensitivity 71% and specificity 73%. ***Hong et al.***[19] stated that the discriminating threshold for the presence of varices varies widely ranging between 68,000 and 160,000/mm^3. These results could be explained by variation among studies regarding etiology and stage of liver cirrhosis.

Pathogenesis of thrombocytopenia includes productive, consumptive or distributional mechanisms.[20] The association of platelet count to the presence of varices is probably a reflection of the degree of portal hypertension and possibly other factors. Splenic sequestration or antibody-mediated destruction of platelets have been believed to be the cause of thrombocytopenia in patients with cirrhosis. However, recent studies have implicated reduced hepatic production of liver-derived thrombocytopoietic growth factor thrombopoietin or rapid degradation and suppressive effects of viruses on bone marrow may also add to thrombocytopenia.[3]

We found that PC/SD was lower in patients with esophageal varices (mean 443 ± 242) in comparison to patients without varices (mean 1634 ± 1377) P<0.01. Overall the PC/SD was a predictor for presence of varices with best cut off value 415 where the sensitivity was (80%) and the specificity was (60%).***Giannini et al.*** [21]study of 145 patients with cirrhosis found that the negative predictive value of platelet count/spleen diameter ratio 909 was 100% with sensitivity 100%, specificity 71% in prediction for presence of varices. ***Agha et al.***[22] studied 114 patients with compensated HCV related cirrhotics, 909 cut-off showed negative predictive value 100% and a positive predictive value of 93.8% for the diagnosis of EV. ***Baig et al.*** [23] reported a cut-off value of 1014, which gave positive and negative predictive values of 95.4% and 95.1%, respectively.

Regarding the WBC count, it was lower in patients with esophageal varices (mean 4.66 ± 2.58) in comparison patients without esophageal varices (mean 4.94 ± 1.82) P>0.05. With a cut-off value of 3.5 x 10^3, the WBC had a sensitivity of 80% and a specificity of 52% with an overall accuracy of 77.6% as a predictor for the presence of esophageal varices.

Gue et al.[24] found that leucopenia can be used to stratify the risk of occurrence of esophageal varices with diagnostic yield of 66.7% of WBC count 3.000 – 4.000 and this diagnostic yield increased to 94.8% of WBC count <3.000.

For EV prediction in viral cirrhosis, in spite lower cutoff value was found as regard the platelet count 76.000, the WBC had the same cutoff value.

The main cause of leucopenia is portal hypertension and hypersplensim, unlike thrombocytopenia which may occur due to multiple factors not just portal hypertension.[25]

Cirrhotics were stratified into high- and low-risk groups for the presence of large(risky) esophageal varices. Large esophageal varices was found in 35 patients (29.2%).

Platelet count less than 63.000 and WBC less 3.1x10^3 differentiated high from low-risk groups of cirrhosis with (sensitivity = 75%, 62.5%, specificity = 65%,60%, positive predictive value = 51.7%,34.4%, negative predictive value = 83.8%,76.9% and efficacy = 68.3%,60% respectively). The PC/SD was lower in patients with large varices (mean 312 + 152) in comparison to those with small or no variecs group (mean 657 + 624)P <0.05. Moreover, the use of platelet count/spleen diameter ratio showed a good result in discriminating small and large EVs with efficacy 61.6%.

The study findings suggest that thrombocytopenia and leucopenia are risk factors for the presence of not only large varices but also any varices in cirrhotic patients. These factors allow identification of a subgroup of cirrhotic patients who would benefit most from referral for endoscopic screening for varices. These results were in agreement with ***Limquiaco et al.***[26]who found a relationship between thrombocytopenia and occurrence of bleeding from esophageal varices, moreover, ***Chalasani et al*** [4] (346 patients) found that a platelet count <88,000 was an independent risk factor for the presence of large varices. However, ***Gue et al.***[24]found no relationship between WBC and bleeding from varices.

We concluded that thrombocytopenia and leucopenia can be used to stratify risk for occurrence of esophageal varices in cirrhotic patients and gastroscopy will have a high yield for varices when platelet count is < 130,000/mm^3 or total white is < 3500/mm^3.

Recommendations: All cirrhotic patients with thrombocytopenia below 130.000 and leucopenia below 3500 should undergo standardized programs for routine follow-up endoscopy, prophylactic band ligation and aggressive pharmacological therapy to decrease the risk of mortality from bleeding varices.

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