"Comparative study of the accuracy of Platelet count/ spleen diameter ratio with other non-invasive parameters in predicting large esophageal varices in patients with chronic liver disease"

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Abstract

Introduction: Bleeding from esophageal varices causes significant mortality and morbidity in patients with chronic liver disease. With upper GI endoscopy not available in many centers and in rural India, certain non-invasive methods can help to aid in the prediction of the presence of large esophageal varices. Early identification of large varices helps in prophylaxis to prevent bleeding until definitive management is done. Here in this study, we are using platelet count/spleen diameter ratio in predicting the large esophageal varices and comparing its sensitivity and specificity with non-invasive parameters.

Study: This is a cross-sectional study (Prospective study) in a tertiary hospital.

Methods: Patients admitted to SSIMS & RC, DAVANAGERE between January 2021 and June 2021 with a diagnosis of chronic liver disease were included in the study. Patients were assessed for ascites, splenomegaly, ultrasonographic measurements like splenic size and portal vein diameter, and laboratory parameters like hemoglobin, platelet count, total bilirubin, prothrombin time and serum albumin. The ratio of platelet count with spleen diameter was calculated. Univariate and multivariate analyses were done.

Results: Incidence of large varices were seen in 44%. By ultrasonography, 22 were found to have splenomegaly while 28 were found to have normal spleen dimensions. Patients with large esophageal varices had significantly lower platelet counts as compared to those without. Spleen diameter was greater while platelet count/spleen diameter ratio was lower in patients with large esophageal varices. On multivariate analysis, independent predictors for the presence of large varices were palpable spleen, low platelet count, spleen size >13.8 mm, portal vein >13 mm and splenic vein >11.5 mm. The platelet count/ spleen diameter ratio had a sensitivity and specificity of 87 % and 85% respectively which was more than other parameters. Hence platelet count/ spleen diameter ratio can be a reliable indicator for predicting the presence of large esophageal varices than other non-invasive parameters.

Conclusion: Platelet count/ spleen diameter ratio is more accurate and a strong predictor of large esophageal varices than any other non-invasive parameters in patients with chronic liver disease which warrant the need for prophylaxis and early intervention to prevent life-threatening hemorrhage.

Keywords: Esophageal varices, noninvasive predictors, portal hypertension, cirrhosis

Introduction

Bleeding esophageal varices is one of the major causes of death in chronic liver disease patients due to life-threatening hemorrhage. Approximately 60-80 % of cirrhotic liver patients will have esophageal varices among which 20-25 % have the risk of bleeding. Esophageal varices are portosystemic collaterals and they form as a consequence of portal hypertension (a progressive complication of cirrhosis), preferentially in the submucosa of the lower esophagus. Rupture and bleeding from esophageal varices are major complications of

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portal hypertension and are associated with a high mortality rate. Variceal bleeding accounts for 10-30% of all cases of upper gastrointestinal bleeding. Most cirrhotic patients develop esophageal varices over their lifetime (5 to 15% / year) and the annual rate of esophageal hemorrhage is 5 to 15% [1]. The frequency of esophageal varices varies from 30% to 70% in patients with cirrhosis and 9-36% of patients have what is known as high-risk varices. Esophageal varices develop in patients with cirrhosis at an annual rate of 5- 8% but the varices are large enough to pose a risk of bleeding in only 1-2% of cases[2]. The progression from small to large varices is 8% per year. Approximately 30% of patients with esophageal varices will bleed within the first year after diagnosis. Despite improved diagnosis and treatment for variceal hemorrhage, the mortality rate still remains high (20%-35%). Recurrent bleeding occurs in 30 to 40% of patients within the next two to three-day sand in up to 60 % within one week. Thus, the prevention of esophageal variceal bleeding remains at the forefront of the long-term management of cirrhotic patients.

All cirrhotic patients should be screened for the presence of esophageal varices when liver cirrhosis is diagnosed[3]. However, upper GI endoscopy for screening is not available in rural India and in small towns, also it may not be cost-effective in poor socioeconomic patients. Hence more affordable approach for screening would be possible if patients at low or high risk of having esophageal varices could be identified from easily obtainable clinical variables. Studies have shown that certain clinical, biochemical and ultrasonographic parameters can accurately predict the presence of esophageal varices in cirrhosis patients. Parameters such as splenomegaly, thrombocytopenia, Child's Pugh score, ascites, portal flow patterns, and platelet count-splenic size ratio are predictors of esophageal varices[4]. This study is to compare the accuracy of platelet count/ spleen diameter ratio with other non-invasive parameters in predicting large esophageal varices in patients with chronic liver disease.

Materials and Methods

Patients admitted to SSIMS & RC, Davangere between January 2021 and June 2021 with a diagnosis of chronic liver disease were included in the study. This was a cross-sectional prospective study.

Sample Size Calculation:

$N= (Z\alpha/2)^2 * p * (1-p)/ E^2$

Zα/2 is the critical value of the Normal distribution at α/2- 1.28 (at 80% confidence level)

E is the margin of error- 0.029

p is the sample proportion- 3.3% (from the article by Arul Prakash Sarangapani et al)

N is the population size. Substituting the above values in the formula, the sample size obtained is 50.

Inclusion Criteria: Patients with a diagnosis of chronic liver disease. Diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic findings.

Exclusion Criteria: Patients with evidence of hepatocellular carcinoma on ultrasonography, or previous or current treatment with beta-blockers, nitrates and diuretics were excluded from the study. Patients who have received endoscopic or surgical intervention for portal hypertension previously were also excluded from the study.

A detailed clinical evaluation was done for all patients during admission. Relevant clinical history and physical examination were done. Symptoms and signs of liver failure (spider angioma, palmar erythema, etc.), hepatomegaly, splenomegaly, 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) [5]. Hepatic encephalopathy was graded from grade 0 to IV, as per Conn's grading [6]

Hematological and biochemical workup was done, which included hemoglobin, total leukocyte count, platelet count, prothrombin time, and serum concentrations of bilirubin (total and conjugated), protein, albumin, alanine aminotransferase and aspartate aminotransferase. A modified Child-Pugh score was calculated for all patients [7]. All patients were tested for HBsAg and antibodies to the 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.

Ultrasonography was done and the following details were recorded for all patients: Maximum vertical span of the liver; nodularity of liver surface; spleen size (length of its longest axis); diameter of the portal and splenic veins; the presence of portal-systemic collaterals; and presence of ascites. Upper gastrointestinal endoscopy for assessment of esophageal and gastric varices was conducted for all the patients. If esophageal varices were present, their size was graded as I-IV, using the Paquet grading system. 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.[8] patients were classified dichotomously either as having large varices (grade III-IV) or as having small varices (no varices or grade I-II). The Presence of gastric varices, portal hypertensive gastropathy, duodenopathy and rectal varices were recorded wherever appropriate. All the clinical, laboratory, ultrasonographic and endoscopic assessments were done.

Statistics: Univariate analysis for determining the association of various clinical, laboratory and ultrasonographic variables with the presence of large varices was performed using the Student t-test for continuous variables and chi-square tests for categorical variables. Differences were considered statistically significant if the two-tailed p-value was less than 0.05. All variables found significant were studied using logistic regression analysis to identify independent predictors for the presence of such varices. Receiver operating characteristic curves (ROC) analysis was performed on the available data set for the parameter that had the best predictive value of large esophageal varices. All calculations were made using SPSS software (version 11 for windows; SPSS, Chicago, IL, USA).

Results

Table 1: Relationship of various parameters with the presence or absence of large esophageal varices on univariate analysis

Variables	Small varices group N = 28	Large varices group = 22	p- value
Sex	20:8	17:5	
Median age	48 (17- 72)	50 (26 - 73)	
Jaundice	21	29	
Ascites	28	22	0.001
Platelet count	200000 (42000-442000)	90,100 (28000-245000)	0.001
Hb	8.8 (4.8 - 12.8)	9 (4.1 - 12.0)	
Serum bilirubin	1.2 (0.4-19.4)	2.8(0.2 - 10.2)	0.001
Prothrombin time	2 (0.4 -13)	3.6 (0.8 - 12)	0.004
Serum albumin	3.7 (2.2 - 4.8)	2.2 (1.6 - 3.9)	0.001
SGOT	90.5 (27 - 416)	68 (28 - 398)	0.08
SGPT	63 (29 - 234)	45 (32 - 305)	0.30
Portal vein diameter	12 (8.0 -15.2)	15.6 (10.8 - 22.4)	0.001
Spleen size	142 (92 - 218)	182.5(140 - 258)	0.001
Platelet count/ spleen diameter ratio	1477 (300 - 4804)	454 (144 - 1601)	0.001
ETIOLOGY			0.531
Alcohol	7	12	
HBV	5	2	
HCV	2	1	
Alcohol +HBV	3	2	
Alcohol +HCV	2	1	
Others	9	4	

A total of 50 patients were included in this study. Alcoholic liver disease was the major cause of cirrhosis in this study. The relationship of various parameters with the presence or absence of large esophageal varices is tabulated [**Table 1**]. Out of 50 total patients, 28 had small varices and 22 had large varices.

In the small varices group, the median age was 48 (17 -72), in the large varices group median age was 50 (26-73). In the small varices group, 20 patients were male and 8 patients were female. In the large varices group, 17 patients were male and 5 patients were female. Alcohol was the most common etiology and out of 19 patients, 12 had large varices.

Large varices were associated with increasing grade of ascites, p-value<0.001 median platelet count in the large varices group was 90,100. The median platelet count in small varices group was 2 lakh. With a p-value <0.001, low platelet count was significantly associated with large varices.

Large varices were significantly correlated with increasing bilirubin levels and a median value of 2.8 mg/dl (p-value: 0.001). Large varices were significantly correlated with low albumin levels and a median value of 2.2 mg/dl (p-value 0.001).

Large varices were significantly correlated with elevated prothrombin time, a median value of 3.6 sec prolonged (p-value: 0.004). Large varices were significantly correlated with increasing portal vein diameter with a median value of 15.6 mm (p-value 0.001). Large varices were significantly correlated with increasing spleen size with a median value of 182.5 mm (p-value 0.001). Large varices were significantly correlated with lower values of platelet count/spleen diameter ratio with a median value of 454.1(p-value 0.001).

Table 2: Multivariate logistic regression analysis for predictors of the presence of large esophageal varices

Predictors	Sensitivity	Specificity	Positive predictive value	Negative predictive value	p-value
Bilirubin	-	-	-	-	0.08
Serum albumin	72	70.5	68	80.5	0.001
Prothrombin time	73.5	71.5	80	71.5	0.004
Platelet count	72.5	75	63.8	70.5	0.001
Spleen size	86.5	83	83.5	70.5	0.001
Portal vein size	76.5	80	78	78.5	0.001
Platelet count/spleen diameter ratio	87	85	83	90.5	0.001

On Multiple logistic regression analysis, the independent predictors for the presence of large varices were platelet count <150,000/mm3, clinically palpable spleen, splenic size >13.8 cm and portal vein size >13 mm [**Table 2**].

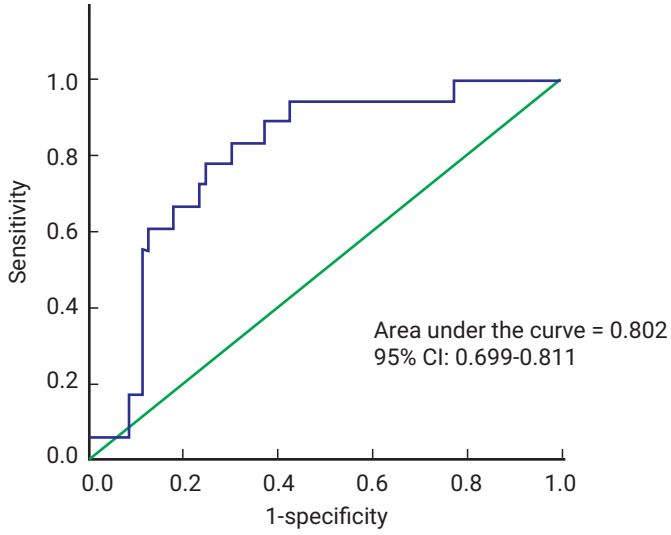

Figure 1: Receiver operating characteristic curve: Platelet spleen diameter ratio: Area under the curve: 0.802 [95% CI (0.699-0.811)]

A platelet count/ spleen diameter ratio of less than 909 was statistically significant in predicting large varices (888.09 vs. 1669.97; P = 0.000). The Receiver operating characteristic curve for platelet spleen diameter ratio 909 was performed [**Figure 1**]. Area under curve was 0.801[95% CI (0.699-0.81)]. The sensitivity and specificity were 87% and 85% respectively

Discussion

In roughly 30-40% of individuals with cirrhosis, severe upper gastrointestinal bleeding arises as a consequence of portal hypertension. Variceal hemorrhage is related to high morbidity, mortality, and healthcare costs because of the rising prevalence of chronic liver disorders. The efficacy of beta-blockers for the primary prevention of variceal bleeding in patients with high-risk varices has been proven in numerous studies, highlighting the need for screening for the presence of esophageal varices. As a result, a noninvasive predictor for the existence of esophageal varices is urgently needed to reduce the disease's medical, social, and economic costs. Many earlier research has shown that many non-endoscopic characteristics have a high predictive value for the presence or absence of varices, but data is limited. We exclusively used simple, widely available, and repeatable factors in our research since they had lower interobserver variability. Our study has demonstrated that platelet count, splenic size, portal vein size, and a platelet spleen diameter ratio were found to be predictors of large esophageal varices. A platelet cutoff of 909, platelet count 150,000/mm^3, splenic diameter of 138 mm and a portal vein size of 13 mm were chosen because they represented the median values and offered the best discrimination.

The pathogenesis of thrombocytopenia comprises mechanisms that are consumptive, or distributional [9]. It's thought to be caused by platelet pooling and destruction in the spleen, which could be mediated by platelet-associated IgG. Thrombopoietin levels that are low due to defective synthesis or quick breakdown can also contribute to thrombocytopenia. Platelet count is thus influenced by a number of factors other than portal hypertension.

Thus platelet count depends on multiple factors, not just portal hypertension. Garcia- Tsao et al [10]. (180 patients) and K. C. Thomopoulos et al [11]. (184 patients) reported a low platelet count to be an independent risk factor for the presence of varices. Mohammad Khuramet al [12]. (200 patients) found OV in 146 with 121 having thrombocytopenia (94.5%). We report that a platelet count of <150,000/mm3 is 72.5% sensitive and 75% specific predictor of esophageal varices with a positive predictive value of 63.8% and a negative predictive value of 70.5%. Chalasaniet al [13]. (346 patients) found that a platelet count <88,000 was an independent risk factor for the presence of

large varices.

In most of these studies, etiology is not uniform in the study population. 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 esophageal varices by nearly 2.5 fold. The limitations of the study were retrospective analysis and inclusion of liver transplant patients only. Sarwar et al [14]. found platelet count of <88000 to be an independent risk factor for the presence of large esophageal varices and Zein et al[15] reported (in chronic liver disease due to primary sclerosing cholangitis) platelet count of <150000 to be a predictor of esophageal varices.

The platelet count/spleen diameter ratio was chosen as the relevant parameter, since splenomegaly has been linked to thrombocytopenia in cirrhosis patients, and spleen size is negatively associated with platelet count[1]. Because platelet count alone might be misleading and cannot be attributed purely to portal hypertension, this ratio is used to adjust platelet count to splenic sequestration.

We used the platelet count/spleen diameter ratio cut-off determined by Giannini et al [16]. in predicting large varices. Giannini et al. study of 145 patients with cirrhosis found that the negative predictive value of platelet count/spleen diameter ratio 909 was 100%. Agha A et al [17] studied 114 patients with compensated HCV-related cirrhotics, 909 cut-offs showed a negative predictive value of 100% and a positive predictive value of 93.8% for the diagnosis of esophageal varices. Baiget al reported a cut-off value of 1014, which gave positive and negative predictive values of 95.4% and 95.1%, respectively. [18] In our study, this 909 cut-off had 87% sensitivity, 85.0% specificity, 83% positive predictive value and 90.5% negative predictive value for the diagnosis of large esophageal varices.

Ultrasonography is used to determine the bipolar diameter of the spleen, which is a simple, repeatable, and noninvasive procedure that is regularly performed on cirrhotic patients [19]. Despite the short sample size, the use of the platelet count/spleen diameter ratio was found to be effective in distinguishing between small and large esophageal varices based on the inferred results. In individuals with a low risk of missing esophageal varices, the platelet count/ spleen diameter ratio could be used to avoid needless endoscopy [20].

Conclusion

Cirrhotic patients usually undergo annual/biannual abdominal ultrasonography as part of the surveillance program for hepatocellular carcinoma, using this strategy of using non-invasive tests would necessarily lower the cost of management of cirrhotic patients because there would be no additional expense with the use of ultrasonography.

According to the findings of this study non-invasive approach can be used to reliably predict the existence of large esophageal varices in cirrhotic patients. Among all the non-invasive methods of predicting the presence of large esophageal varices, platelet count/ spleen diameter ratio has got more accuracy than other parameters. Hence platelet count/spleen diameter ratio can be used as a reliable predictor for large varices which helps in initiating the prophylactic measures or treatment to prevent hemorrhage from varices and thereby helps in reducing the mortality in cirrhotic patients.

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