Brief Communication

Noninvasive Prediction of Large Esophageal Varices in Chronic Liver Disease Patients

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ABSTRACT

Background/Aim: Esophageal varices (EVs) are a serious consequence of portal hypertension in patients with liver diseases. Several studies have evaluated possible noninvasive markers of EVs to reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices. This prospective study was conducted to evaluate noninvasive predictors of large varices (LV). **Patients and Methods:** The study analyzed 106 patients with liver diseases from January 2007 to March 2008. Relevant clinical parameters assessed included Child-Pugh class, ascites and splenomegaly. Laboratory parameters like hemoglobin level, platelet count, prothrombin time, serum bilirubin, albumin and ultrasonographic characteristics like splenic size, splenic vein size, portal vein diameter were assessed. Univariate and multivariate analysis was done on the data for predictors of large EVs. **Results:** Incidence of large varices was seen in 41%. On multivariate analysis, independent predictors for the presence of LV were palpable spleen, low platelet count, spleen size >13.8 mm, portal vein >13 mm, splenic vein >11.5 mm. The receiver operating characteristic (ROC) curve showed 0.883 area under curve. Platelet spleen diameter ratio 909 had a sensitivity and specificity of 88.5%, 83% respectively. **Conclusion:** Thrombocytopenia, large spleen size, portal vein size and platelet spleen diameter ratio strongly predicts large number of EVs.

Key Words: Esophageal varices, non invasive predictor of varices, platelet spleen ratio

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Esophageal variceal bleeding is one of the most dreaded complications of cirrhosis because of its high mortality. The prevalence of varices in patients with cirrhosis is approximately 60-80% and the risk of bleeding is 25-35%. The incidence of esophageal varices (EVs) increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10 % per year.[1] Increasing size of varices is associated with an increase in variceal-wall tension to a critical level at which varices rupture and cause life-threatening bleeding. The mortality rate from variceal bleeding is about 20% when patients are treated optimally in hospital.[2] Incidence of first variceal hemorrhage ranges from 20 to 40% within two years. Recurrent bleeding occurs in 30 to 40% of patients within the next two to three days and in up to 60 % within one week. Thus, prevention of esophageal variceal bleeding remains at the forefront of long-term management of cirrhotic patients.

The American Association for the Study of Liver Disease and the Baveno IV Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of EVs when liver cirrhosis is diagnosed.[3] However, subjecting all patients with cirrhosis to screening endoscopy may not be cost effective. A more affordable approach for screening would be possible if patients at low or high risk of having EV could be identified from easily obtainable clinical variables. Investigators have attempted to identify characteristics that noninvasively predict the presence of varices. These studies have shown that biochemical, clinical and ultrasonographic parameters alone or together have good predictive power for noninvasively assessing the presence of EV.[7-16] Overall, the most common result of these studies is that parameters such as splenomegaly, thrombocytopenia, Childs score, ascites, portal flow patterns, and platelet count-splenic size ratio are predictors of EV. The study was conducted to identify clinical, biochemical and ultrasonographic parameters associated with the presence of large EVs in patients with portal hypertension.

PATIENTS AND METHODS

Newly diagnosed patients with liver diseases between August 2007 and December 2008 at our institution (Department of digestive health and diseases, Government peripheral hospital, Anna Nagar, Chennai) were included

in this prospective study. All patients underwent a detailed clinical evaluation at entry. 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.

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).[4] Hepatic encephalopathy was graded from grade 0 to IV, as per the Conn's grading.[5] Diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic findings.

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.[6] 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.

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.

Endoscopic evaluation

All patients underwent upper gastrointestinal endoscopy for assessment of esophageal and gastric varices within 2-3 days of admission. If EVs 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.[7] Further, patients were classified dichotomously either as having large EVs (grade III-IV) or as not having these (no varices or grade I-II). Presence of gastric varices, portal hypertensive gastropathy, duodenopathy and rectal varices were recorded wherever appropriate. All the clinical, laboratory, ultrasonographic and endoscopic assessments were completed in two weeks.

Statistical analysis

Univariate analysis for determining the association of various clinical, laboratory and ultrasonographic variables with presence of large varices was performed using 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 the presence of large EVs. All calculations were made using SPSS software (version 11 for windows; SPSS, Chicago, IL, USA).

RESULTS

One hundred and six patients belonging to southern India were enrolled in this study, with a median age of 45 years (range 18-74). There were 72 men at a male-female ratio of 2.1:1. Patient's symptom duration was 10-240 days with a median of 90 days. Clinically detectable ascites was present in 50 patients and 43 had pedal edema; 53 had jaundice at presentation. None had active bleeding at admission. EVs were detected in 77 of 106 patients (72.6%). Alcohol was the cause in 62 patients while the cause was hepatitis B in 23 patients. By ultrasonography, 42 were found to have splenomegaly while 64 were found to have normal spleen dimensions. Patients with large EVs had significantly lower platelet count as compared to those without. Spleen diameter was greater while platelet count/spleen diameter ratio was lower in patients with large EVs. Tables 1 show the clinical, laboratory and ultrasonographic parameters in the patients with small and large varices. Large varices were present in 41.1% of patients. The mean age, gender distribution, ascites, edema, jaundice and etiology were similar in the two groups. The mean hemoglobin and serum albumin levels were lower, and the prothrombin time, ascitic fluid albumin, SAAG, liver enzymes were higher in the large varices group, indicating more advanced disease; however, these did not assume statistical significance.

Patients in the large varices group had lower platelet counts in comparison to those in the small varices group (137725/mm^3 vs. 202781/mm^3; $P = 0.02$), larger splenic diameter (149 mm vs. 111 mm; $P = 0.001$) and Portal vein diameter (11.3 mm vs. 13.9 mm; $P = 0.001$). The frequency of radiologically detected ascites, collaterals, and liver size were similar in both groups [Table 1]. On multiple

logistic regression analysis, the independent predictors for the presence of large varices were platelet count <150,000/mm^3, clinically palpable spleen, splenic size >13.8 cm and portal vein size >13 mm. [Table 2]. A platelet spleen diameter ratio of less than 909 was statistically significant in predicting large varices (888.09 vs. 1669.97; $P = 0.000$). Receiver operating characteristic curve for platelet spleen diameter ratio 909 was performed. Area under curve was: 0.883 [95% CI (0.81-0.91)]. The sensitivity and specificity was 88.5% and 83% respectively [Figure 1].

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

Variables	Size of the esophageal varices		*P* value
	None (n = 29)/ small (n = 26)	Large (n = 51)	
Sex	35:16	37:18	0.77
Median age	43.3	42.5	0.72
Jaundice	24	29	-
Pedal edema	21	22	-
Palpable spleen	3	19	-
Ascites	14	36	-
Etiology			
Alcohol	32	29	-
HBV	15	8	-
HCV	1	1	-
AIH	3	4	-
Others	5	6	-
Hb	8.8 (4.6-12.8)	9.1 (4-13)	0.43
WBC count	8547 (6500-11200)	8198 (4500-9800)	0.18
Platelet count	202781 (70000-463000)	157725 (58000-472000)	0.02
Bilirubin	2.2 (0.8-7.1)	3.1 (0.7-16.1)	0.04
SGOT	93.6 (25-427)	62.6 (21-421)	0.08
SGPT	67.8 (23-285)	54 (12-500)	0.30
SAP	184.7 (59-403)	151.4 (56-356)	0. 27
Prothrombin time	2.5	4	0.838
S. albumin	2.7 (2-3.6)	2.7 (2.4-3.8)	0.478
Ascitic albumin	1.5 (0.6-2.5)	1.6 (1.2-2.9)	0.24
SAAG	1.18 (0.6-1.5)	1.1 (0.8-1.6)	0.66
CTP score	9 (5-13)	9 (5-13)	0.003
Liver size	11.7 (7-16)	12.1 (7-14)	0.362
Spleen size	11.17 (8.5-18)	14.9 (9.2-26)	0.0001
Portal vein size	11.3 (8-16)	13.9 (10-17)	0.001
Splenic vein size	7.8 (7-11)	9.2 (7-11)	0.06
Gastric varices	1	7	0.07
Portal hypertensive gastropathy	11	29	0.19

DISCUSSION

Severe upper gastrointestinal bleeding as a complication of portal hypertension develops in about 30-40% of patients with cirrhosis. Due to the increasing prevalence of chronic liver diseases, variceal hemorrhage is associated with significant morbidity, mortality, and health care costs. Numerous studies have demonstrated the efficacy of beta-blockers for primary prevention of variceal bleeding in patients with high-risk varices indicating the importance of screening for the presence of EVs. Therefore, there is a particular need for a noninvasive predictor for the presence of EVs to ease the medical, social and economic burden of the disease. Many previous studies have documented good predictive value of various non-endoscopic variables for the presence or absence of varices, but available data in our part of the country is limited. In our study, we considered only simple, commonly available, reproducible parameters, which have less interobserver variability.

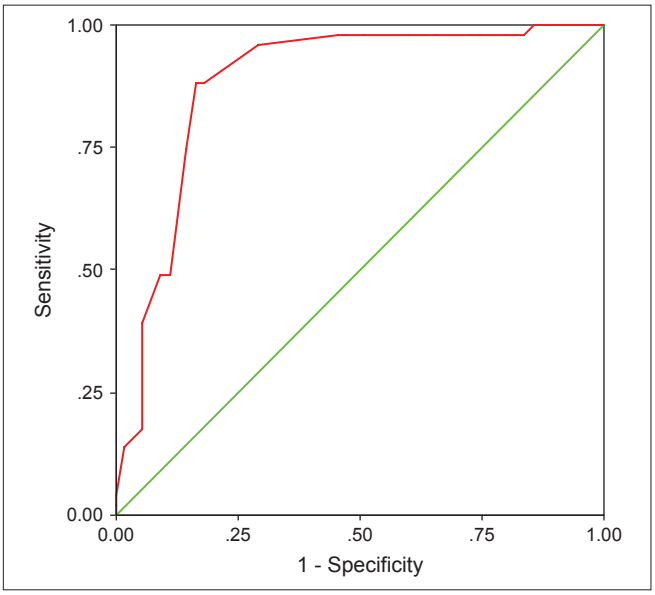

Figure 1: Receiver operating characteristic curve: Platelet spleen diameter ratio: Area under curve: 0.883 [95% CI (0.81-0.91)]

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

Predictor	Sensitivity	Specificity	Positive predictive value	Negative predictive value	*P* value
Bilirubin	-	-	-	-	0.08
Palpable spleen	76.3	70.5	78.3	80.5	0.02
Platelet count	72.5	75	63.8	70.5	0.001
Spleen size	88.5	83	83.3	70.5	0.003
Portal vein size	76.5	80	78	78.6	0.001
Splenic vein size	-	-	-	-	0.09
Platelet count/Spleen diameter ratio 909	88.5	83	83.3	90.5	0.001

Our study has demonstrated that platelet count, palpable spleen, splenic size, portal vein size, and a platelet spleen diameter ratio were found to be predictors of large EVs. 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.

Pathogenesis of thrombocytopenia includes productive, consumptive or distributional mechanisms.[8] It is commonly believed to be due to pooling and destruction of platelets in the spleen which may be mediated by platelet-associated IgG. Reduced levels of thrombopoeitin either due to impaired production or rapid degradation may also add to thrombocytopenia. Thus platelet count depends on multiple factors not just portal hypertension.[9] Garcia-Tsao *et al*.[10] (180 patients), Pilette *et al*.[11] (116 patients) and K. C. Thomopoulos *et al*.[12] (184 patients) reported a low platelet count to be an independent risk factor for the presence of varices. Mohammad Khuram *et al*.[13] (200 patients) found OV in 146 with 121 having thrombocytopenia (94.5%). We report that platelet count of <150,000/mm^3 is 72.5% sensitive and 75% specific predictor of OV with positive predictive value of 63.8% and negative predictive value of 70.5%. Chalasani *et al*.[14] (346 patients) found that a platelet count <88,000 was an independent risk factor for the presence of large varices. In retrospective analysis of 143 patients with compensated cirrhosis, Filippo Schepis *et al*.[15] reported OV in 63 patients (44%) with platelet count of <100,000 as predictor of OV.

Most of these studies did not have an etiologically uniform patient population. Zaman *et al*.[16] 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. The limitations of the study were retrospective analysis and inclusion of liver transplant patients only. Sarwar *et al*.[17] found platelet count of <88000 to be independent risk factor for the presence of large OV and Zein *et al*.[18] reported (in chronic liver disease due to primary sclerosing cholangitis) platelet count of <150000 to be predictor of OV.

The platelet count/spleen diameter ratio was deemed to be the appropriate parameter to be used as splenomegaly is implicated in thrombocytopenia of cirrhosis with spleen size being inversely correlated with platelet count. The use of this ratio normalizes platelet count to splenic sequestration since platelet count alone may be misleading and cannot be solely attributed to portal hypertension. We used the platelet count/spleen diameter ratio cut off determined by Giannini *et al*.[19] 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*.[20] 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*.[21] reported a cut-off value of 1014, which gave positive and negative predictive values of 95.4% and 95.1%, respectively. In our study this 909 cutoff had 88.5% sensitivity, 83.0% specificity, 83.5% positive predictive value and 90.5% negative predictive value for the diagnosis of large EV.

The measurement of the spleen bipolar diameter using ultrasonography is easily obtainable, reproducible and non-invasive and is routinely performed on patients with cirrhosis. Although this study had a small sample population, based on the inferred results, the use of platelet count/spleen diameter ratio showed a good result in discriminating small and large EVs. The use of platelet count/spleen diameter ratio would avoid unnecessary endoscopy in patients without significant risk of missing EVs. The use of this strategy of using non-invasive tests would necessarily lower the cost of management of cirrhotic patients since no additional expense would be entailed with the use of ultrasonography as cirrhotic patients usually undergo annual/biannual abdominal ultrasonography as part of the surveillance program for hepatocellular carcinoma. Based on the present study it was found that a simple non-invasive technique may be used as a reliable predictor for the presence of large EVs among cirrhotic patients.

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