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Original Research Article

Non-invasive predictors of esophageal varices in patients with cirrhosis of liver

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Abstract

Background: Cirrhotic patients commonly undergo screening endoscopy for the existence of esophageal varices (EVs). Several studies have evaluated possible noninvasive markers of EVs to reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices. Aim of the present study was to identify and analyze clinical, biochemical, ultrasonographic predictors of EVs in cirrhotic patients and correlate these predictors with endoscopic findings.
Method: Total hundred newly diagnosed cirrhotic patients of aged ≥18 without prior history of gastrointestinal bleeding were subjected to clinical evaluation, biochemical workup, esophagogastroduodenoscopy, and ultrasonographic measurement of spleen bipolar diameter and ascites. Non-invasive parameters were assessed and platelet count (PC)/spleen diameter (SD) ratio was calculated for all patients.
Results: Out of 100 patients, 80 (80%) were found to have esophageal varices. The incidence of grade I (33%) and grade II (34%) varices predominate. Majority of patients belonged to Child-pugh class C (68%) followed by class B (28). Mean PC and SD among patients with varices was 115300±66077/cmm and 123±32.23mm while among those without varices was 158750±52711/cmm and 90±11.21mm respectively. The sensitivity of PC/SD ratio of <909 in predicting presence of esophageal varices was 74% with its positive predictive value (PPV) was 86%. The PC/SD cut off of <957 had a sensitivity of 78.75% and PPV of 95.92%.
Conclusion: The presence of thrombocytopenia and lower PC/SD ratio determine the incidence of higher grades of varices and can hence identify the subset of patients who require endoscopy for the prophylactic management of esophageal varices.

Keywords: Esophageal varices, Cirrhosis, Liver, Spleen, Diameter, Sensitivity, Thrombocytopenia, Endoscopy.

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1. Introduction

Liver cirrhosis (LC) is the final evaluative stage of any chronic liver disease, resulting in the formation of fibrous tissue, disorganization of liver architecture, and nodule formation, which interferes with liver function and results in portal hypertension [1,2].

The three primary complications of portal hypertension are gastroesophageal varices with potential rupture and hemorrhage, ascites, and hypersplenism [2]. Esophageal varices (EVs) develop in the context of increased portal blood pressure owing to increase portal vascular resistance. EVs are a dangerous clinical consequence of liver cirrhosis.

Despite significant improvements in early diagnosis and advancements made in the treatment modalities, the mortality rate of first variceal hemorrhage is still 20%. Numerous studies have demonstrated the significance of pharmacologic therapy for primary prevention of variceal bleeding; emphasizing the importance of screening endoscopy in all newly diagnosed cirrhotic patients for the presence of varices [3, 4]. But this test is not without its own limitations as it is invasive, high cost and poorly accepted by patients. Therefore, there is a particular need for the identification of noninvasive parameters that strongly predict the presence of esophageal varices as that might decreases the medical, public and economic burden of the disease.

Certain biochemical, clinical and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the risk of bleeding from varices. Several studies in the past have shown independent parameters like platelet count, splenomegaly, advanced child status, serum albumin, and high portal vein diameter at ultrasonography to be useful for this purpose [5-8]. According to Giannini, *et al* use of the platelet count/spleen diameter ratio would have avoided performing unnecessary endoscopies in all patients with a cut off >909 without running the risk of not diagnosing esophageal varices [9].

Non endoscopic assessment for presence and grades of varices from India are few. Thus, predicting the grade of varices by non-invasive methods at the time of registration is likely to predict the need for prophylactic β blockers or endoscopic variceal ligation in patients with cirrhosis and portal hypertension. Therefore, present study was undertaken to determine the appropriateness of the various clinical, biochemical and imaging parameters in predicting the existence and also the grade of esophageal varices in cirrhosis of the liver.

2. Materials and Methods

A total of 100 patients aged ≥18 years diagnosed to have cirrhosis of liver admitted in Medicine wards, in Department of Medicine at Tertiary Care Centre were enrolled in the study. The diagnosis of cirrhosis based on a combination of history, clinical findings, impaired liver function tests, deranged clotting profile and abdominal ultrasound. The written informed consent was obtained from all the patients. Patient with present or previous history of portal hypertensive bleeding, hepatocellular carcinoma, previous or current treatment with β blockers, diuretics or other vasoactive drugs, causes of non-cirrhotic portal hypertension, patients who have received endoscopic or surgical intervention for portal hypertension previously, patients having fever associated with thrombocytopenia in the past and history of fever in the past 15 days were excluded from the study.

A detailed clinical history and physical examination was done and findings were recorded. All patients in the study underwent a full clinical evaluation (complete haemogram including platelet count and routine investigations including RBS, Blood urea, serum creatinine, serum electrolytes, HBsAg), biochemical tests like liver function tests, CBC, renal function tests, prothrombin time. All patients underwent ultrasonographic examination of the upper abdomen to confirm the presence of cirrhosis and to record spleen biopolar diameter, portal vein size, ascites and presence of collaterals. It was done by the single radiologist. Child-Pugh score according to presence or absence of encephalopathy, ascites, levels of bilirubin, albumin and prothombin time was calculated for all patients. Upper GI endoscopy was done to confirm presence of varices and also grade them. All endoscopies were performed in a single endoscopy unit using a video endoscope. All the patients were divided in to those with EV and those without EV by endoscopic examination. The platelet count to spleen diameter ratio was calculated. The platelet count, spleen diameter and platelet count to spleen diameter ratio were compared between two groups of patients with and without EV.

2.1 Statistical analysis

Univariate analysis for determining the association of various clinical, laboratory and ultrasonographic variables with presence of varices was performed using Student t test for continuous variables and chi square tests for categorical variables. P value <0.05 was considered as statistically significant. All variables found significant were studied using logistic regression analysis to identify independent predictors for the presence of such varices.

3. Observations and Results

Out of 100 patients, 86 (86%) were males and 14(14%) were females. Incidence of cirrhosis was maximal in age group of 51-60 years followed by 31-40 years, (Table 1). The causes of cirrhosis were found to be alcoholism in 78%. In the study population 4 patients were showed viral markers positive for Hbs Ag.

Table 1: Age distribution of patients

Age in Years	No. of patients
<30	6
31-40	26
41-50	16
51-60	28
61-70	14
71-80	10

Majority of cases (86%) presented with abdominal distension, (Table 2). Presence of ascites was determined either clinically or radiologically by ultrasound and it was found in 88% of patients. Among 100 patients studied encephalopathy was present in 78 patients.

Table 2: Clinical signs and symptoms

Clinical Symptoms	No. of patients	Clinical Signs	No. of patients
Jaundice	60	Ascites	88
Swelling over feet	70	Edema feet	86
Abdominal distension	86	Distended veins	40
Abdominal pain	56	Hepatomegaly	20
Vomiting/nausea	32	Splenomegaly	48
Fatigue	68	Pallor	52
Weight loss/anorexia	48	Icterus	86
Decreased urine output	10	-	-
Symptoms of HE	18	-	-

Out of total cases, 80% were found to have esophageal varices. The incidence of grade I (33%) and grade II (34%) varices predominate and were almost similar. However, the incidence of grade III varices accounted for 13%. Majority of patients belonged to Child Pugh class C (68%) followed by class B (28%) and class A (4%). Most of the patients (30%) belonged to platelet count group between 50,000 and 1,00,000/mm^3 and the majority of patients (69%) belonged to category with splenic bipolar diameter between 100-200 mm, (Table 3).

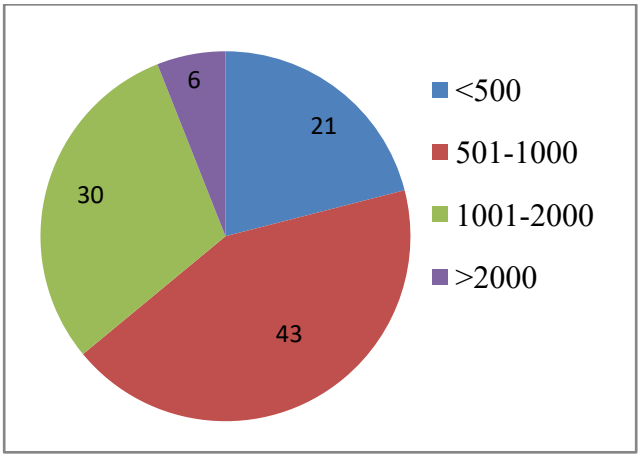
Mean PC and SD among patients with varices was 115300±66077/cmm and 123±32.23mm while among those without varices was 158750±52711/cmm and 90±11.21mm respectively.

Table 3: Distribution of cases based on platelet count and splenic bipolar diameter

Platelet count	No. of patients	Spleen bipolar diameter (mm)	No. of patients
<=50000	20	<100	31
50,001-1,00,000	30	100-200	69
1,00,001-1,50,000	23	>200	0
>150000	27	-	-

Most of the patients belonged to category of ratio between 501-1000 accounting to 43% followed by 1001-2000 constituting about 30%, (Figure 1).

Figure 1: Distribution of cases based on platelet count/spleen diameter ratio



On comparison of baseline characteristics of patients studied based on presence and absence of varices relationship between non-invasive parameters like age, serum bilirubin, serum albumin, child-pugh classification, platelet count, prothrombin time, spleen bipolar diameter, PC/SD ratio. Of these child-pugh classifications, platelet count, spleen bipolar diameter, PC/SD ratio had statistical significance, (Table4).

Table 4: Comparison of baseline characteristics based on presence and absence of varices

Baseline Characteristics		Varices		P value
		Present	Absent	
Age in years		48±18.22	50±14.09	0.6606
Child Pugh classification	Class A	4	5	0.0196
	Class B	23	5	
	Class C	53	10	
Hemoglobin		11±2.52	11±3.18	0.4420
Platelet count (n/cumm)		115300±66077	158750±52711	0.0066
Serum Bilirubin		10±11.13	7±9.16	0.2305
Direct Bilirubin		8±8.7	5±7.2	0.2199
SGOT		110±92.17	79±63.15	0.0695
SGPT		71±142.66	41±67.21	0.1453
ALK Phosphatase		139±75.50	138±58.24	0.9735
Total protein		7±0.90	6±1.08	0.052
Serum albumin		2±0.52	2±0.31	0.2983
PT		28±12.55	24±8.6	0.1498
INR		2±0.66	2±0.63	0.3731
Spleen Bipolar diameter (mm)		123±32.23	93±11.21	0.0001
Platelet count/ Spleenic diameter ratio		957±581.93	1724±592.10	<0.0001

The sensitivity of PC/SD ratio of <909 in predicting presence of esophageal varices was 74% with its positive predictive value was 86%. The PC/SD cut off of <957 had a sensitivity of 78.75% and positive predictive value (PPV) of 95.92%, (Table 5).

Table 5: Sensitivity, Specificity, Positive and Negative predictive values for the significant parameters

Parameters	Sensitivity	Specificity	PPV	NPV
CTP class B/C	95	75	93.83	78.95
Spleen diameter ≥160 mm	55.75	100	100	22.47
Platelet count ≤90,000/mm^3	53.75	85	93.48	31.48
Platelet count/spleen diameter ratio (909)	73.75	65	86	26
Platelet count/spleen diameter ratio (957)	78.75	90	95.92	35.29

4. Discussion

In the present study, incidence of cirrhosis was more in age group of 51-60 years and the main cause of cirrhosis was alcoholism seen in 78% of patients. The male patients outnumber the female. These findings were comparable with the study done by Legasto *et al* [10]. Hepatic encephalopathy was present in 22 patients which was correlated with other studies [5, 11,12]. Among the 100 patients, 80% patients were found to have varices and the incidence of grade I and grade II varices were more and found similar in each group. This finding is in accordance with the study done by Cherian *et al* [5].

Patients were grouped according to Child Pugh Classification of cirrhosis. Majority of patients belonged to Child Pugh class C followed by class B. Among class A patients, 44% had varices, among class B 82% had varices and among class C 84% had varices. Thus, varices were found to be more common among class B and class C. This finding is in agreement with the other studies [5, 9, 13]. The majority of our patients belonged to platelet count group between 50,000 and 1,00,000/mm^3 and most of the patients (69%) belonged to category with splenic bipolar diameter between 100-200 mm. There was no statistically significant difference for serum bilirubin and serum albumin levels among patients with and without varices. Also found no significant difference among patients with and without varices in regards to liver enzymes (SGOT, SGPT and alkaline phosphatase) and prothrombin time. All these finding was correlated with the previous studies [5,9,13-15].

In patients with chronic liver disease the presence of decreased platelet count may depends on multiple factors other than portal hypertension such as shortened platelet mean lifetime, decreased thrombopoietin production, or myelotoxic effects of alcohol or hepatitis viruses. On the other hand, the presence of splenomegaly in cirrhotic patients is likely the result of vascular disturbances that are mainly related to portal hypertension. With this in mind, the study used the PC/SD ratio as a parameter linking thrombocytopenia to spleen size in order to introduce a variable that takes into consideration the decrease in PC which most likely depends on hypersplenism caused by portal hypertension [9, 16].

The PC/SD cut off of <957 had a sensitivity of 78.75% and positive predictive value (PPV) of 95.92%., however it showed a low specificity and NPV and a ratio <957 indicated the presence of higher grades of varices showing the inverse correlation between the same. However, the parameters are not so significantly high as to replace the esophagogastroduodenoscopy (EGD) as a screening tool for the presence of esophageal varices. When a cut off value of PC/SD ratio of <909 was applied in order to take in to consideration the decrease in platelet count due to hypersplenism; it was found to be a good predictor of presence and grade of esophageal varices. The sensitivity of PC/SD ratio of <909 in predicting presence of esophageal varices was 74% with its PPV was 86%. Similar results were found in earlier studies [16-19]. Thus, the study found that the sensitivity was not acceptable enough to make this parameter as valid non-invasive screening tool for esophageal varices on its own. However, it has potential of prediction incorporating other clinical characteristics or varying PC/SD cut off and if used in conjunction with EGD, may help us prevent unnecessary screening EGDs. When compared with other non-invasive predictor tools, the PC/SD ratio is elegant, simple and inexpensive. With some minor modifications, it may become a helpful tool to limit the number of endoscopies in primary prophylaxis to be performed in patients with portal hypertension.

The present study demonstrated that the Child-pugh class B and C, low platelet count and spleen diameter are significant predictors for presence of esophageal varices. A higher grade of EV exists with lower platelet count and larger spleen size. PC/SD ratio of 909 is significant non-invasive measure of assessing EV in patients with compensated or decompensated liver cirrhosis but with suboptimal sensitivity and specificity. The use of PC/SD ratio would avoid unnecessary endoscopy in patients without significant risk of missing EV.

5. Limitations

1. Small sample size
2. Prospective studies were not done to validate the role of predictive parameters

6. Conclusion

The presence of thrombocytopenia and lower PC/SD ratio determine the incidence of higher grades of varices and can hence identify the subset of patients who require endoscopy for the prophylactic management of esophageal varices. Therefore, reduce the burden on the endoscopy units, avoiding unnecessary screening endoscopies and as well may reduce the cost of management of bleeding varices. Apart from being noninvasive, platelet count, spleen bipolar diameter and the PC/SD ratio is a relatively inexpensive test as platelet counts and abdominal ultrasounds would be obtained on all cirrhotic patients routinely as part of their clinical workup.

On the basis of present data, we hope that future studies will encourage other researchers to evaluate the reproducibility of the platelet count/spleen diameter ratio for the non-invasive diagnosis of EV in independent cohorts of patients with different clinical backgrounds.

Implication of study

These non-invasive predictors may be of help to the physicians practicing in rural areas where endoscopy facilities are not readily available, in helping them to initiate appropriate primary pharmacological prophylaxis in these patients.

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