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RESEARCH ARTICLE

NON INVASIVE PREDICTORS FOR PRESENCE OF ESOPHAGEAL VARICES IN PATIENT OF LIVER CIRRHOSIS-A CROSS SECTIONAL ANALYTIC STUDY

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ABSTRACT

Objective: Objective of this study was to identify non invasive predictors for the presence of Esophageal varices in patients of liver cirrhosis without prior history of upper Gastrointestinal bleeding.

Methodology: This cross sectional analytic study was conducted from August 2011 to July 2016 in the Department of Gastroenterology at Liaquat National Hospital Karachi and Aga Khan University Hospital, Karachi. Patients diagnosed to have liver cirrhosis without prior history of upper GI (gastrointestinal) bleeding secondary to varices either visiting the outpatient department or admitted in hospital were included. Informed consent was taken from all patients. Screening Esophagogastroduodenoscopy (EGD) was performed in all patients to detect varices once the diagnosis of liver cirrhosis was confirmed. Patients of both gender and age more than 16 years were included in the study. Statistical package of social science (SPSS) were used to analyze data.

Results: Hundred patients of liver cirrhosis who fulfilled the selection criteria were included in the study. Average age of the patients was found to be 48.71±12.38, out of 100 patients 46% were male and 56% were female. Esophageal varices were seen in 76/100 (76%) patients, significant large varices (Grade III and IV) seen only in 9.2 % of patients. 37(47.7%) Patients with Varices were male and 39(51.3%) were female. Univariate and multivariate analysis of variables was performed between patients with and without varices. Serum albumin, bilirubin, portal vein diameter were significantly associated with presence of esophageal varices whereas platelets counts, prothrombin time and splenic size were not significant in univaiate analysis. Multivariate analysis show low platelets, decreased albumin, increased prothrombin time, increased serum bilirubin and increased portal vein diameter were significant independent predictors of presence of esophageal varices.

Conclusion: Incidence of esophageal varices in patients with liver cirrhosis without a history of upper GI bleeding was significantly high our study. The statistically substantial predictors of presence of esophageal varices were, platelets count<150,000/cmm, serum albumin <2.8gms /dl, serum bilirubin>1.2mg /dl , prothrombin time >2 seconds of control value , portal vein diameter >11mm.

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INTRODUCTION

Liver cirrhosis is the end result of hepatocellular injury that leads to both fibrosis and nodular regeneration throughout the liver. Portal hypertension is one of the major complication of liver cirrhosis which is directly responsible for two of its most common and lethal complication that are ascites and variceal development and bleeding. Gastroesophagealvarices are present in approximately50% of patients with cirrhosis. Their presence correlateswith the severity of liver disease, while only 40% of Child A patients has varices, they are present in 85%of Child C patients (Pagliaro *et al*., 1994). Patients without varices develop them at a rate of 8% per year (Groszmann *et al*., 2005; Merli *et al*., 2003) Patients with small varices develop large varicesat a rate of 8% per year. Decompensated cirrhosis (Child B/C), alcoholic cirrhosis, and presence of red wale marks (defined as longitudinal dilated venules resembling whip marks on the variceal surface) at the time of baseline endoscopy are the main factors associated with the progression from small to large varices (Merli *et al*.,

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2003). Despite significant improvement in the early diagnosis of varices, morbidity and mortality rate of first variceal hemorrhage remain high. Because of the high mortality and substantial utilization of resources associated with occurrence of variceal hemorrhage in patients with cirrhosis, Strategy for early identification and prevention of bleeding from esophageal varices is important. The American Association for the Study of Liver Disease and the Baveno Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of EV when liver cirrhosis is diagnosed (Grace *et al*., 1998; D'Amico *et al*., 2001). Screening endoscopy on one hand is an invasive procedure and on other hand would require a great deal of health care cost, in terms of cost and manpower. Various studies has proven that only one third of cirrhotic patients have clinical significant esophageal varices on screening endoscopy. To reduce the number of unnecessary endoscopies there are number of studies have been conducted so far at various levels to identify the variable that can predict the presence of esophageal varices noninvasively. The conclusion from most of these studies is that by selecting patients for endoscopic screening for varices based on laboratory and or imaging variables, an appreciable number of unnecessary endoscopies may be avoided, while keeping the rate of undiagnosed varices, which are at risk of bleeding, acceptably low. Many of these predictors either singly or in combinations have good prognostic value. However the accuracy of these variables is still uncertain and none of them has been recommended for use in clinical practice so far.

In low Socio economical underdeveloped countries where health care cost is a significant problem while knowing the fact that not all the patient with cirrhosis will have clinically significant varices on screening endoscopy, subjecting all cirrhotic patients to screening EGD may not be a wise decision or cost effective particularly in our setup. The rationale of this study is to identify the non endoscopic predictors of presence of esophageal varices in cirrhotic patients, which will guide us to carryout screening endoscopy in selected group of patients and avoiding unnecessary intervention. Identification of those predictors will provide relief in medicals economic cost which is one of the most important aspects of patient management in our country.

METHODOLOGY

This cross sectional analytic study was conducted from August 2011 to July 2016 in the Department of Gastroenterology at Liaquat National Hospital Karachi and Aga Khan University Hospital, Karachi. Hundred Patients diagnosed with liver cirrhosis without prior history of upper GI bleeding were included in the study. Informed consent was taken from all patients. Detailed history and examination was performed, and relevant needed laboratory and imaging studies were carried out where needed. Screening Esophagogastroduodenoscopy (EGD) was performed in all patients to detect varices once the diagnosis of liver cirrhosis was confirmed. Grading of esophagealvarices was done according toPaqet.[6]Grade-Iwas classified as Small varices without luminal prolapsedGrade-II as Moderate-sized varices showing luminalprolapsed with minimal obscuring of the Gastro esophageal junctionGrade-III as large varices showingluminal prolapsed substantially obscuring the gastro esophageal Junction and Grade –IV as Very large varices completely obscuring the Gastro-esophageal junction.

Grade I and II were considered as Small varices and Grade III and IV were considered as large varices.Patients of both gender and age more than 16 years having Cirrhosis of any etiologywere included in the study. Patients with prior history of upper GI bleeding of portal hypertensive origin and patient of non-cirrhotic portal hypertension, and patient who had any intervention related to portal hypertension like TIPs were excluded from the study. Statistical package of social science, SPSSversion 21 was used toanalyze data. Frequency and percentage were computed for qualitative variables like gender, ascites and grade of varices. Mean and standard deviations were computed for continuous variables that were platelets count, prothrombin time, serum albumin, bilirubin, size of spleen and portal vein diameter. Student t- test was used to check mean difference of continuous variables in patient with and without varices. Chi square test was applied to assess the difference of ascites for the presence or absence of ascites, with 0.05 level of significance. Logistic regression analysis was used to predict the presence of esophageal varices with independent variables.Sensitivity, specificity, positive predictive value and negative predictive values were determined for hematological test, biochemical test, and ultrasonographic examination with EGD.

RESULTS

One hundred patients of liver cirrhosis were enrolled through selection criteria. The average age of the patients was 48.71± 12.38 (ranging from 21 to 85) years. Out of 100 patients there were 46 males and 56% females in this study. Female to male ratio was 1.2:1.Ascites was present in 36 (36%) of patients, In patients who had esophageal varices minimal ascites was present in 19 patients while 14 patients had mild to moderate ascites, 2 patients with minimal ascites and 1 patient with mild to moderate ascites had no esophageal varices. All the patients underwent EGD; (Esophagogastroduodenoscopy) esophageal varices were seen in 76(76%) patients. Grade 1 varices were seen in 31(41%) patients while 38(50%) had grade II varices. (Figure 1)To identify predictors of the presence of esophageal varices, Univariate and multivariate analyses were performed. Univariate comparison of the variables between patients with and without esophageal varices showed**,** Serum albumin, Serum bilirubin, Portal vein diameter were significantly associated with the presence of esophageal varices whereas Platelets count, Prothrombin time and spleen size were not significant in Univariate analysis (Table 1)

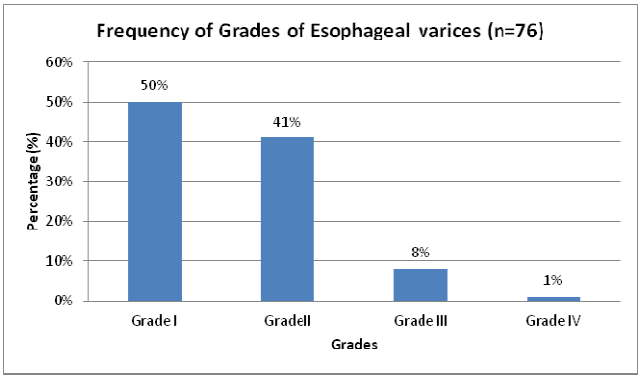

Figure 1. Showing the grading of esophageal varices

Multivariate analysis showed the significant independent predictors of presence of esophageal varices, in decreasing order of significance:

Table 1. Comparision of variables between patients with and without varices

Variables	PATIENTS WITH VARICES n= 24	PATIENTS WITHOUT VARICES N=24	P-Values
Platelets count (cmm)	107876.3 ±54541.4	120916.6 ± 58205.7	0.32
Prothrombin time (sec)	6.3±4.00	6.5±9.48	0.90
Serum albumin (mg/dl)	2.7 ±0.66	3.18 ± 0.57	0.004*
Serum bilirubin (mg/dl)	2.1 ±1.63	1.3 ±0.65	0.03*
Portal vein diameter (mm)	1.3 ±0.29	1.1 ±0.17	0.0001*
Spleen size (cm)	14.2±1.74	13.5 ±2.07	0.11
Age (years)	46.75 ±11.48	49.33±12.66	0.37
Ascites No (%)	33(43.42%)	3 (12.5%)	0.02*

Table 2. Value of variables according to cut off in predicting of esophageal varices

Variables	Cut off	Sensitivity	Specificity	PPV	NPV
Platelets count (cmm)	<150,000 cmm	84.2%	37.5%	81.0%	42.9%
Prothrombin time (Sec)	>3 sec	65.8%	58.3%	83.3%	35.0%
Serum albumin (mg/dl)l	≤ 3.5 mg/dl	90.8%	37.5%	82.1%	56.3%
Serum Bilirubin (mg/dl)	>1.2 mg/dl	50.0%	91.7%	95%	36.7%
Portal vein diameter (mm)	≥11 mm	82.9%	54.2%	85.1%	50.0%
Spleen size (cm)	>13 cm	85.5%	29.2%	79.3%	38.9%

Platelets count <100,000/cmm (Odd ratio {OR}:4.93;95% CI 1.95-25.74),Platelet count between 100,000 to 150,000(OR: 7.2;95% CI 1.2-42.5),and Prothrombin time 2-4 sec (OR:5.6;95%CI1.35-23.5), PT 4-6sec(OR:23.7,95%CI2.6-27.1), PT>6sec(OR:4.3:95%CI 1.3-14.15) and serum albumin<2.8 gm/dl (OR: 12.6; 95% CI 3.3-48.6) and serum bilirubin 1.2-3.0 mg/dl(OR: 5.7;95% CI 1.8-11.5),Serum bilirubin >3 mg/dl(OR :4.9 95% CI 1.03-23.3).Portal vein Diameter ≥ 11 mm (OR: 5.73 95% CI 2.11-15.58). Spleen size and ascites was not significant predictor of presence of esophageal varices by multivariate analysis. Sensitivity, Specificity according to cut off value for independent predictors were calculated, Platelets count <150,000/cmm sensitivity and specificity is 84.2% and 37.5% respectively, Serum albumin <3.5 gm/dl sensitivity and specificity is 90.8% and 37.5% respectively, Portal vein diameter >11 mm, sensitivity and specificity is 82.9% and 54.2% respectively and Spleen size >13 cm sensitivity and specificity is 85.5% and 29.2% respectively .Serum bilirubin >1.2 mg was found to give 91.7% specificity and 50% sensitivity (Table 2).

DISCUSSION

Development of esophageal and varices and variceal bleeding is one of the serious consequences of portal hypertension in patients of liver cirrhosis, and it is associated with significant morbidity, mortality and health care cost. Thus the primary prevention is the most important strategy. Endoscopy is the gold standard test for detection of esophageal varices so far.An alternate to screening endoscopy is empiric pharmacological therapy with nonselective beta-blocker for prevention of variceal hemorrhage in cirrhotic patients. Prevention of varicealbleeding is further complicated by uncertainty about whether non selective betablockers can prevent the development of esophageal varices or the progression of small varices to large varices that may bleed; this approach is not supported in studies as well (Spiegel *et al*., 2003). The possibilityofidentifying cirrhotic patients with esophageal varices without history of upper GI bleeding by non invasive measure is attractive, because it will allow and guide us for performing screening endoscopy in patients who have high risk of having varices. Various studies have been performed to identify characteristics that noninvasively predict thepresence of varices. These studies have shown that biochemical, clinical and Ultrasonographic parameters aloneor together have good predictive value for predicting the presence of EV (Gorka *et al*., 1997; Chalasani *et al*., 1999; Zaman *et al*., 1999; Pilette *et al*., 1999; Ng *et al*., 1999; Schepis *et al*., 2001; Zaman *et al*., 2001; Madhotra *et al*., 2002). In our study 76(76%) patients had esophageal varices, which is near to a local study by sarwar et[16] al and other study of prihatini *et al*. (2015). Grade 1 varices were seen in 31(41%) patients while 38(50%) had grade II varices, Grade III varices were seen in 8% patients and Grade IV in 1%, so practically speaking only few patients needed therapeutic intervention for varices as majority had grade I and II varices. In a study by schepis *et al*. (2001) found that prothrombin activity less than 70%, PV diameter more than 13mm and platelets count lessthen 100,000/cmm, were significantly associated with presence of esophageal varices, which is more or less comparable to pour study. In another study esophageal varices were found in58% of patients with cirrhosis; splenomegaly and thrombocytopenia were independent predictors of presence of esophageal varices. Platelet count of less than 68000/cmm had highest discriminative value for large varices with a sensitivity 71 % and specificity 73% as observed byMadhotra *et al*. (2002). In our study five factors were identified, which have independent correlation with presence of esophageal varices. Platelets count lessthen 100,000/cmm, prothrombin time more than 2 seconds of control value, serum albumin < 2.8gms /dl , serum Bilirubin > 1.2mg /dl and PV diameter > 11mm were only significant predictors after multivariate analysis for the presence of esophageal varices. These results were further supported by above mentioned studies.

Thrombocytopenia is implicated in many recent studies to be associated with esophageal varices, splenic sequestration, antibody mediated destruction of platelets and bone marrow suppression has been thought to cause of thrombocytopenia. Raised prothrombin time reflect defective synthesis of coagulation factor by liver. In our study the mean value of prothrombin time in patients with varices is 6.3 seconds above the control value. Prothrombin time > 2 seconds of control value had significant P value and is associated with esophageal varices. Low serum albumin is one of the indicators of poor hepatic synthetic function. The degree of hepatic dysfunction likely affects the development of portal hypertension and thus the development of varices. Mean albumin level in patients with varices is 2.7gms /dl, below this level is associated with risk of developing varices, increase serum bilirubin could well

be explained by the severity of liver disease as this get worse as much as portal hypertension increased so as the development of esophageal varices. The mean serum bilirubin was 2.1 m/dl in patients with varices. Portal vein diameter of >11mm had significant correlation with esophageal varices with sensitivity and specificity of 82.9% and 54 % respectively. Width of portal vein on Ultrasonographic examination is indirect indicator of portal pressure which is responsible for development of varices. Insignificant of ascites might be due to it multifactorial pathogenesis.

Conclusion

Incidence of esophageal varices in patients with liver cirrhosis without a history of upper GI bleeding was significantly high our study. The statistically substantial predictors of presence of esophageal varices were, platelets count<150,000/cmm, serum albumin <2.8gms /dl, serum bilirubin>1.2mg /dl , prothrombin time >2 seconds of control value , portal vein diameter >11mm.

Recommendations

On the basis of predictors, patients can be stratified in to low risk and high risk group for the presence of esophageal varices to avoid the unnecessary endoscopies, while keeping the rate of undiagnosed varices, which are at risk of bleeding, acceptably low.Considering high morbidity and mortality associated with variceal bleeding these predictors should be used to supplement clinical judgment.

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