ORIGINAL ARTICLE

Identification of Non-Endoscopic Predictors of Esophageal Varices in Cirrhosis

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ABSTRACT

Objective: To identify hematological, biochemical and ultrasonographic predictors of esophageal varices in patients of cirrhosis.
Design: Cross-sectional, analytical study.
Place and duration of study: Department of Gastroenterology, East Medical Ward, Mayo Hospital, Lahore, from September 2003 to March 2004.
Patients and methods: One hundred and fifty patients with established cirrhosis and no history of variceal bleed underwent physical examination, hematological, biochemical tests and abdominal ultrasound examination. Esophagogastroduodenoscopy (EGD) was carried out in all patients. Presence of varices on EGD was correlated with hematological, biochemical and ultrasonographic variables by regression analysis.
Results: Esophageal varices were seen in 96 patients while 54 patients had no varices. High grade varices were seen in 22 patients and 74 patients had low grade varices. Serum albumin less than 2.95g/dl, platelet count less than 88x103/µL and portal vein diameter more than 11mm were associated with presence of varices. High grade varices were predicted by serum albumin < 2.95g/dl and portal vein diameter more than 11mm.
Conclusion: Patients with serum albumin <2.95g/dl, platelet count < 88 x 103/µL and portal vein diameter > 11mm are more likely to have high grade varices.
Key words: Cirrhosis. Esophageal varices. Portal hypertension. Portal vein diameter. Serum albumin.

INTRODUCTION

Cirrhosis is the end result of hepatocellular injury that leads to both fibrosis and nodular regeneration throughout the liver. Cirrhosis is a serious and generally irreversible disease and is the 10th leading cause of death in United States. The clinical features result from hepatic cell dysfunction, portosystemic shunting and portal hypertension. The most common causes are chronic alcohol abuse, chronic hepatitis B and chronic hepatitis C infection, autoimmune diseases, metabolic disorders e.g. Wilson's disease, haemochromatosis etc. drugs e.g. amadiarone, methotrexate, methyldopa etc. and other causes e.g. hepatic vein thrombosis, bud chairi syndrome etc.

Its prevalence varies from 20-30% in patients with cirrhosis[3]. After varices have developed, one-third of all patients die of bleeding gastro-esophageal varices[4]. The risk of initial bleeding from varices is 25% to 35% within 2 years, with most first-bleeding episodes occurring within one year after detection of varices[5] The reported mortality from first episode of variceal bleeding in western studies ranges from 17% to 57%[6] as compared to 5-10% mortality reported in our population[7].

Recently, the Baveno III Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of esophageal varices when liver cirrhosis is diagnosed.[9] Repeat endoscopy is recommended at 2–3 years interval in patients without varices and at 1–2 years interval in patients with small varices to evaluate the development or progression of varices.[10] However, this approach has two major limitations.

Endoscopy is an invasive procedure and secondly the cost effectiveness of this approach is also questionable[11] as only 9-36% patients with cirrhosis are found to have varices on screening endoscopy. It may be more cost-effective to routinely screen patients at high risk for the presence of varices so as to reduce the increasing burden and procedure cost of endoscopy units. There are factors that predict risk for first variceal hemorrhage.[12] Certain biochemical, clinical and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the risk of bleeding from varices. However, the factors that

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predict the presence of varices are not as well defined. Identification of non-invasive predictors of esophageal varices will enable us to carry out upper gestrointestinal (GI) endoscopy in selected group of patients thus avoiding unnecessary intervention and at the same time not missing the patients at risk of bleeding.

PATIENTS AND METHODS

This cross-sectional analytical study carried out at Gastroenterology unit, East Medical Ward, Mayo Hospital, Lahore. One hundred & fifty patients with established cirrhosis and no history of variceal bleed underwent physical examination, hematological, biochemical tests and abdominal ultrasound examination. Esophagogastroduodenoscopy (EGD) carried out in all patients. All patients underwent upper GI endoscopy to evaluate for presence and degree of esophageal varices using an Olympus video endoscope GIF 160. Presence of varices on EGD correlated with hematological, biochemical and ultrasonographic variables by regression analysis. Mean values of different variables compared between patients with and those without varices.

Patients with cirrhosis of liver without past history of upper or lower gastrointestinal bleeding included. Diagnosis of cirrhosis was based on combination of physical findings present i.e. palmar erythema, spider nevi, gynaecomastia, splenomegaly or ascites, impaired liver function tests i.e. deranged clotting profile and low serum albumin and irregular liver surface detected on ultrasound and ratio of transverse caudate lobe to transverse right lobe width > 0.65.[13] All patients included in the study evaluated for clinical, hematological, biochemical and ultrasonographic parameters and classified according to Child-Pugh's criteria.[14,15] Patients who were not stable were not included in the study, nor those patients who had previously undergone sclerosis or band ligation of esophageal varices, transjugular intrahepatic porto-systemic shunt, or surgery for portal hypertension. Patients taking medicines for primary prophylaxis of variceal bleeding and patients with active (less than six months of alcohol abstinence) alcohol abuse were also excluded.

Esophageal varices classified into small and large varices, where small esophageal varices were defined as those which flatten with insufflation or minimally protrude into the esophageal lumen, whereas large esophageal varices were defined as those which protrude into the esophageal lumen and touch each other (presence of confluence), or fill at least 50% of the esophageal lumen.[16] This simple classification is considered the preferred classification.[17] In some cases, endoscopists use the grade (I-IV) classification, when grades I through IV are used. Grades I and II are reclassified as small and grades III and IV are reclassified as large for this study.

Statistical analysis performed using SPSS 17.0. Results were expressed as mean ± SD. Each continuous parameter between the two groups, patients with varices and patients without varices analyzed with two tailed un-paired student's t-test. Categorical data examined using the chisquarec2 test. Threshold of different variables for the best compromise sensitivity-specificity determined using ROC curve.[18] Data re-explored using these cutoff values, p-value of less than 0.05 considered significant. Multivariate analysis of variables with significant correlation carried out using stepwise logistic regression analysis.[19] The following cutoff points used for the linear logistic regression stepwise methods: p = .05 for entry into the model and p=.10 for removal from the model. Discriminant analysis used for developing combined predictability of variables. Ninety-five percent confidence intervals (CIs) used in all analyses. Analysis of variance (ANOVA) used for prediction of grade of varices.

RESULTS

The total number of patients in the study were 150. Male to female ratio was 1.14: 1 (80/70). Mean age of patients was 53 (± 11.11) years. On clinical examination 14 patients had palpable liver and palpable spleen below left costal margin was noted in 26 patients. Based on physical examination, hematological and biochemical parameters, 22 patients were of Child class A, 73 class B and 55 patients were in Child Pugh class C. Mild ascites was noted in 42 patients, moderate in 75 patients and tense ascites was found in 6 patients while 30 patients had no ascites. All patients underwent EGD, esophageal varices were seen in 97 patients. High grade varices were seen in 22 patients while 75 had low grade varices. Nine patients with high grade varices were treated with band ligation due to signs of impending bleed. 25 patients had gastric varices, 22 gastroesophageal and 6 isolated gastric varices and 5 patients were also given treatment for gastric varices. Mean values of different variables were compared between patients with and those without varices as given in Table I.

Linear correlation revealed significant correlation between presence of varices and gynaecomastia (p-0.028), platelet count (p-0.045), serum potassium (p-0.026), serum albumin (p- 0.007) and portal vein diameter (p-0.023). Grade of esophageal varices had significant association with gynaecomastia (p-0.048), platelet count (p-0.169), serum potassium (p-0.142)

portal vein diameter (p-0.012) and serum albumin (p-0.023). Cutoff values of 88 x 103/µL for platelet count, 2.95g/dl for serum albumin and 11mm for portal vein diameter were identified using ROC curve. Variables with significant correlation with presence of varices were checked for sensitivity, specificity, positive predictive value, negative predictive value, OR (odds ratio) and area under ROC (receiver operating characteristic) curve as shown in Table II.

Platelet count < 88 x 103/µL, serum potassium, serum albumin, and portal vein diameter were checked for predictability of grade of varices by applying analysis of variance (ANOVA). Serum albumin < 2.95g/dl (p-0.028) and portal vein diameter > 11mm (p-0.043) were found to have significant predictive value for high grade varices. (CI > 95%). These variables were then checked for prediction of esophageal varices using stepwise logistic regression analysis. Serum albumin (p-value 0.013) and portal vein diameter (p-value 0.038) had strong prediction value as compared to not so strong correlation of platelet count (0.156) in multivariate analysis.

Presence of any of three predictors could determine presence of varices with 100% sensitivity and 11% specificity, while presence of all three variables had 23% sensitivity and 89% specificity for presence of varices. Predictability of different combinations of these variables is shown in Table III.

Table I: Comparison of variables in patients with and without varices

	Patients with varices Mean±SD (Total patients: 97)	**Patients without varices Mean ± SD (Total patients: 53)**	**p-value**
Platelet count (× 10^3/µL	99 ± (73.08)	109±(69.24)	0.046
Prothrombin time (sec)	18.50 ±(6.02)	21.49 ± (19.20)	0.319
Serum potassium (mEq/dl	3.99 ± (0.82)	4.40 ± (0.83)	0.027
Serum albumin (g/dl)	2.74 ± (0.08)	3.26 ± (0.62)	0.007
Cholesterol (mg/dl)	103.86± (148.65)	160.6 ± (27.98)	0.340
Child score	8.49 ± (1.87)	8.65 ± (1.95)	0.706
Portal vein diameter (mm)	12.95 ± (2.07)	10.37 ± (2.68)	0.023
Size of spleen (mm)	14.50 ± (2.28)	14.73 ± (2.55)	0.669
Age (years)	51.52 ±(10.83)	54.23 ± (11.57)	0.245
SD-Standard deviation			

Table II: Values of variables in predicting presence of varices

Variables	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**OR**	**Area under ROC**
Serum albumin < 2.95gms/dl	62	66.8	76	51	3.34	0.66
Platelet count < 88 10^3 / µL	58.5	62.7	72.4	47.7	0.42	0.338
Portal vein diameter > 11mm	91	25.6	67.54	64.23	3.74	0.582
PPV-Positive predictive value; NPV-Negative predictive value; OR-Odds ratio: ROC-Receiver operating characteristic						

Table III: Combined predictability of three significant predictors for esophageal varices

Predictors present	**%age of original grouped cases correctly classified**
Albumin < 2.95g/dl	64
Portal vein diameter > 11mm	67
Platelet count < 88,000/µ L	60.2
Albumin < 2.95g/dl and PV diameter > 11mm	62.8
Albumin < 2.95 g/dl and platelet count < 88,000/ µ L	65.5
PV diameter > 11mm and platelet count < 88,000/ µL	61.4
Albumin <2.95 g/dl, Platelet count <88,000/ µL and PV diameter >11mm	63.7

DISCUSSION

Most of the studies concerning the non-invasive diagnosis of esophageal varices were performed on a particular subgroup of patients i.e. those going to be placed on a liver transplantation waiting list. Some of the studies lacked uniformity in esophageal varices classification or adequate statistical analysis.22-25 Factors previously identified as noninvasive predictors of esophageal varices were less reproducible in clinical practice26, were subject to interobserver variability27, and were assessed in different ways even within the same study. In this study, only simple, commonly available and reproducible parameters were considered. Multiple studies have been performed to evaluate clinical, laboratory, and imaging factors that are strongly associated with the presence of varices. Cales et al.28 reported that of 84 patients, 16 were without varices (19%) and 35 had small varices (42%), developed large varices during 16-month follow-up. In their study, multivariate analysis revealed that initial size of varices and interval worsening of the Child-Pugh score predicted the development of varices. Chalasani et al.22 found that of 346 patients, presence of splenomegaly on physical examination and platelet count less than 88 x 103/µL were independent risk factors for the presence of large varices. In a study by Pilette et al.24 low platelet count, high prothrombin time, and the presence of spider angiomata were independent risk factors for the presence of varices. Schepis, et al. found prothrombin activity less than 70%, portal vein diameter more than 13 mm and platelet count less than 100,000/mm3, significantly associated with presence of esophageal varices.29 Low albumin level and platelet count less than 150 x 103/µL were associated with presence of esophageal varices in study by Zein et al. In this study three factors were identified, which have independent correlation with presence of varices. Serum albumin less than 2.95g/dl, platelet count < 88 x 103/µL and portal vein diameter > 11mm, were only significant predictors after multivariate analysis for the presence and grade of esophageal varices. Low serum albumin is indicator of deranged hepatic function. The degree of hepatic dysfunction likely affects the development of portal hypertension via humoral factors and, thus the development of varices. Portal vein diameter of > 11mm had significant correlation with high grade varices with sensitivity and specificity of 91% and 25.7% respectively. Width of portal vein on ultrasonographic examination is indirect indicator of portal pressure which is responsible for development of varices. Low platelet count is implicated in many recent studies to be associated with esophageal varices.22,24,27,29,30 Splenic sequestration and antibody-mediated destruction of platelets has been thought to be the cause of thrombocytopenia in patients with cirrhosis.32 It was found that platelet count less than 88 x 103/µL to be independent predictor for presence of varices. But low area under ROC and low odds ratio (OR) is suggestive of weak association. Weak correlation of platelet count was probably due to factors independent of portal hypertension which can result in thrombocytopenia, like bone marrow suppression in patient with cirrhosis. The combined predictability model of these three variables showed that patients with none of these three variables do not have varices. But performing surveillance EGD, only in patients with two or three predictors will achieve accuracy of 60-65%. In other words, one-third of patients with esophageal varices will not undergo EGD and will be deprived of primary prophylactic treatment of varices. Considering the significant morbidity and mortality associated with variceal bleed, it will be safe to have few endoscopies of patients without varices rather than missing patients with varices and potential to bleed. Our recommendation is to perform surveillance endoscopy in patients with any of three predictors identified, thus not missing any patient with esophageal varices, at the same time reducing number of patients with no gastroesophageal varices undergoing surveillance endoscopies. Finally these predictors should be used only to supplement and not to supplant clinical judgment.

CONCLUSION

Platelet count less than 88 x 103/µL, serum albumin less than 2.95gm/dl and portal vein diameter more than 11mm on ultrasonography are independently associated with presence of varices. Patients with established cirrhosis and no past history of upper GI bleed, should have surveillance endoscopy if any of these predictors is identified.

REFERENCES

1. Gupta TK, Chen L, Groszmann RJ. Pathophysiology of portal hypertension. Clin Liver Dis 1997; **1**: 1-12.
2. De Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. Clin Liver Dis 2001; **5**:645–63.
3. Wasty WH, Yousuf M, Mirza MR. Frequency of esophageal varices among patients undergoing GI endoscopy. Pak J Med Sci 2005; **21**: 164-7.
4. Rigo GP, Merighi A, Chalen NJ, Mastronardi M, Codeluppi PL, Ferrari A, et al. A prospective study of the ability of three endoscopic classifications to predict hemorrhage from esophageal varices. Gastrointest Endosc 1992; **38**: 425-9.

5. The Northern Italian Endoscopic Club for the study and treatment of esophageal varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. N Engl J Med 1988; **319**: 983-9. 6. Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology 2002; **122**: 1620–30.
6. Farooqi RJ, Farooqi JI, Rehman M, Ahmad H, Ahmad F, Gul S. Outcome after injection sclerotherapy for esophageal variceal bleeding in patients with liver cirrhosis and COPD. J Postgrad Med Inst 2005; **19**: 76-80.
7. Grace ND, Groszmann RJ, Garcia-Tsao G. Portal hypertension and variceal bleeding: an AASLD single topic symposium. Hepatology 1998; **28**: 868–80.
8. D'Amico G, Garcia-Tsao G, Calés P. Diagnosis of portal hypertension: how and when. In: De Franchis R, (edi).
9. Proceedings of the third Baveno International Consensus Workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science 2001; 36–63. 10. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995; **22**:332–54.
10. Brennan MRS, Targownik L, Gareth SD, Hetal AK, Ian MG. Endoscopic screening for esophageal varices in cirrhosis: Is it ever cost effective? Hepatology 2003; **37**: 366-77.
11. Zoli M, Merkel C, Donatella M, Marchesini G, Gatta A, Pisi E.Evaluation of a new endoscopic index to predict first bleeding from the upper gastrointestinal tract in patients with cirrhosis. Hepatology 1996; **24**: 1047-52.
12. Harbin WP, Robert NJ, Ferrucci JT Jr. Diagnosis of cirrhosis based on regional changes in hepatic morphology: a radiological and pathological analysis. Radiology 1980; **135**: 273-83.
13. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, (edi). The liver and portal hypertension. Philadelphia: WB Saunders, 1964: 50-64.
14. Pugh RNH, Murray-Lyon IM, Dawson JL. Transection of the esophagus in bleeding esophageal varices. Br J Surg 1973; **60**: 648-52.
15. de Franchis R, Pascal JP, Ancona E, Burrough AK, Henderson M, Flerg W, et al. Definitions, methodology and therapeutic strategies in portal hypertension. A consensus development workshop, Baveno, Lake Maggiore. Italy: J Hepatol, 1992; **15**: 256–61.
16. de Franchis R. Portal hypertension II: proceedings of the second Baveno International Consensus Workshop on definitions, methodology, and therapeutic strategies. Cambridge. Mass: Blackwell Science; 1996.
17. Metz CE. Basic principles of ROC analysis. Semin Nucl Med 1978; **8**: 283-98.
18. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 1989.
19. Metcalf M, Brown N, Peterson S, Feld A, Gale F, Kirk J, et al. Health care costs associated with chronic hepatitis B. Am J Health Syst Pharm 1999; **56**: 232–6.
20. Wong JB, McQuillan GM, McHutchinson JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the US. Am J Publ Health 2000; **90**:1562–9.
21. Chalasani N, Imperiale TF, Ismail A, Sood G, Carey M, Wilcox CM, et al. Predictors of large esophageal varices in patients with cirrhosis. Am J Gastroenterol 1999; **94**: 3285–91.
22. Zaman A, Hapke R, Flora K, Rosen HR, Benner K. Factors predicting the presence of esophageal varices or gastric varices in patients with advanced liver disease. Am J Gastroenterol 1999; **94**: 3292–6.
23. Pilette C, Oberti F, Aubé C, Rousselet MC, Bedossa P, Gallois Y, et al. Non-invasive diagnosis of esophageal varices in chronic liver disease. J Hepatol 1999; **31**: 867–73.
24. Ng FH, Wong SY, Loo CK, Lam KM, Lai CW, Cheng CS, et al. Prediction of oesophagogastric varices in patients with cirrhosis. J Gastroenterol Hepatol 1999; **14**: 785–90.