Non-Invasive Predictors of Gastro-Oesophageal Varices

Subash Bhattarai,[1] Khus Raj Dewan,[1] Gaurav Shrestha,[1] Bhanumati Saikia Patowary[1]
[1]Department of Medical Gastroenterology, College of Medical Sciences, Chitwan, Nepal.

ABSTRACT

Introduction: The worldwide accepted tool for screening and monitoring gastro-oesophageal varices in patients with liver cirrhosis is upper gastrointestinal endoscopy. Endoscopy needs clinical expertise and has got its own procedure related complications. Repeated endoscopies may be expensive and patients tend to develop poor compliance. This study was undertaken to establish the role of non-invasive parameters in predicting gastro-esophageal varices.

Methods: Two hundred patients with clinical features, laboratory and sonological findings suggestive of cirrhosis of liver and endoscopic evidence of portal hypertension were included in the study. Blood parameters like serum albumin, international normalized ratio (INR), platelets count and ultrasonography assessments of portal vein diameter and spleen size were compared with presence of gastro-oesophageal varices.

Results: At cutoff point of 2.55g/dl, serum albumin had high specificity of 99% whereas platelets count <1,44,000/mm^3 had 87.9% sensitivity for presence of oesophageal varices. Sensitivities of 92.72% and 94.5% while specificities of 90% and 75% were detected for presence of oesophageal varices when the cutoff values for portal vein diameter and spleen size were 12.25 mm and 13.9 cm respectively.

Conclusions: Measurements of serum albumin, platelets count, portal vein diameter and spleen size by ultrasonography can be recommended as a non-invasive predictor for gastro-oesophageal varices in cirrhosis of liver. All these non-invasive parameters could be useful to patients with liver cirrhosis with portal hypertension in predicting presence of varices as well as in long-term clinical monitoring and management.

Keywords: cirrhosis of liver; endoscopy; gastro-oesophageal varices; non-invasive predictors.

INTRODUCTION

Cirrhosis of liver is a progressive, diffuse, fibrosing, nodular condition of liver that disrupts its entire normal architecture.[1] Portal hypertension leads to dilatation of portal vein, splenomegaly, ascites and formation of portal systemic collaterals including gastro-oesophageal varices. Variceal bleeding is a life-threatening complication of cirrhosis.[2-4]

Liver cirrhosis is a common disease in Nepal. Patients usually present late in decompensated state with myriad of complications. Upper Gastro-intestinal endoscopy is considered the best screening tool for detection of varices in cirrhotic patients.[5,6] Despite its advantages, it is an invasive method and expertise not readily available. Patients' compliance tends to decrease as they have to be subjected to repeated endoscopies for surveillance, screening and follow ups.

This study was undertaken to establish the role of some

Correspondence: Dr. Subash Bhattarai, Department of Medical Gastroenterology, College of Medical Sciences, Chitwan, Nepal. Email: kiwisubash@yahoo.com, Phone: +977-9815293117.

non invasive parameters like serum albumin, platelets count, international normalized ratio, portal vein diameter and spleen size measurement by ultrasonography in predicting gastro-oesophageal varices.

METHODS

This observational, cross-sectional, hospital based study was carried out in the department of medical gastroenterology at College of Medical Sciences Teaching Hospital, Nepal from January 2015 to December 2016. Informed consent was taken from patients or/and patient relatives. Ethical approval was taken from Institutional Review Committee of College of Medical Sciences. All cases attending the department of medical gastroenterology as outdoor and/or admitted in ward with clinical features, laboratory and sonological findings suggestive of cirrhosis of liver and assessed according to Child-Turcotte-Pugh (CTP) score along with sonological and/ or endoscopic evidence of portal hypertension were included in the study. The following cases with portal hypertension were excluded from the study: 1. Cirrhosis with hepatic encephalopathy III / IV. 2. Critically ill patients, cirrhotic patients with end stage renal failure, hepatocellular carcinoma and those who fail to give consent. 3. Other cases with portal hypertension, i.e., non-cirrhotic portal hypertension, Budd-Chiari syndrome, extra hepatic portal venous obstruction.

A detailed history, general physical examination and clinical examination of the abdomen were done. Patients were classified under CTP classes. Basic blood investigations like complete blood count, platelets count, liver function test, prothrombin time / international normalized ratio (PT/INR), coagulation profile and others were done as necessary.

After an overnight fast, patients underwent Ultrasonography (USG) of the abdomen and Upper gastro-intestinal (UGI) endoscopy in the morning. A complete study of liver, spleen, portal, and splanchnic veins by Doppler ultrasonography (TOSHIBA XARIO model SSA-660A ultrasound system) capable of B-mode imaging using a 3.5 MHz curved array transducer was performed by consultant radiologist. Spleen size and portal vein diameter (PVD) were measured by placing the patient in supine position during full inspiration. The spleen can be more echogenic when it enlarges. A maximum cephalo-caudal measurement of more than 13 cm indicates enlargement. In normal individuals, the PVD does not exceed 13 mm in quiet respiration and is measured where the portal vein crosses anterior to the IVC.[3] Each patient underwent endoscopic investigation by standard flexible gastroduodenal endoscope (PENTAX EPK 700, PENTAX JAPAN Inc) and diagnostic findings were documented. Varices were classified as small (≤5 mm diameter) or large (>5 mm diameter) when assessed with full insufflations.[5]

Data were collected on a structured proforma covering the relevant subjects of the study and entry was done in Statistical Packages for the Social Sciences (SPSS) version 20. All categorical data were expressed in percent and absolute number. All numerical continuous data were expressed in mean ±SD. The data analysis was done using SPSS version 20. Chi squared test was used to test for significant difference of proportions (categorical data). Additionally, Receiver Operating Characteristic (ROC) curves for albumin, platelets, INR, portal vein diameter and spleen size to predict the presence of varices were constructed. Further analyses were performed to estimate the best cut off points for all these non-invasive parameters with sensitivities and specificities at those points. All tests were analyzed with a 95% confidence interval and a P value of <0.05 was considered significant.

RESULTS

A total of 200 patients with cirrhosis of liver; 154 (77%) male and 46 (23%) female were enrolled in the study. Mean age of the study group was 54.3 years (range of 27 to 85 years). Alcoholic cirrhosis accounted 170 (85 %) patients of total cases. Twenty (10%) cases were diagnosed with chronic hepatitis B. Five (2.5%) cases were of chronic hepatitis C and rest 5 (2.5%) were classified as cryptogenic. One hundred and forty (70 %) patients had esophageal varices at presentation. No sex difference was noted in cirrhotic subjects with varices. No cases of cirrhosis were detected with class A. Cirrhotic subjects without varices were almost equally distributed between class B and C. Majority of cases with varices were of Class C. Significant association was observed between CTP classes and presence of varices (Chi sq. test statistic = 9.99; df = 1;P = 0.002). Risk of varices being present increases with CTP class and varices being present in Class C individuals was found to be 1.43 times that in Class B (Table 1).

Table 1. Distribution of subjects according to CTP classes.

Particulars		CTP		Total
		Class B	Class C	
Esophageal Varices	No Varix	28	32	60
	Varices	30	110	140
Total		56	144	200

Chi sq. test statistic = 9.99; df = 1; P = 0.002 Risk Ratio of presence of varices in Class C vs. Class B = 1.43

Average values of all the non-invasive parameters of both variceal and non variceal groups were calculated. Average value of serum albumin of patients without gastro-oesophageal varices was 3.10 ± 0.41 gm/dl, while it was 2.68 ± 0.51 gm/dl in patients with varices. This difference was statistically significant (P < 0.001). Average platelets count of patients without varices was 176570 ± 7510/mm^3 and with varices was 111890 ± 3584/ mm^3. This difference was statistically significant (P < 0.001). Average value of INR of patients without gastro-oesophageal varices was 1.63 ± 0.56, while it was 1.96 ± 1.25 in patients with varices. However, no significant difference was observed (P = 0.051; P was > 0.005). Average portal vein diameter (PVD) of patients without gastro-oesophageal varices was 10.82 ± 1.18 mm, while it was 13.69 ± 1.10 mm in patients with varices. This difference was statistically significant (P < 0.001). Average spleen size of patients without varices was 12.66 ± 2.15 cm. and with varices was 15.50 ± 1.01 cm. This difference was statistically significant (P < 0.001) (Table 2).

Table 2. Comparisons of non-invasive parameters between non variceal and variceal groups.

Parameters	Non-variceal group n = 60	Variceal group n = 140	Significance (P value)
Albumin	3.10 ± 0.41	2.68 ± 0.51	< 0.001
Platelets (x 1000)	176.57 ± 75.1	111.89 ± 35.84	< 0.001
INR	1.63 ± 0.56	1.96 ± 1.25	0.051
Portal vein diameter (PVD; mm)	10.82 ± 1.18	13.69 ± 1.10	< 0.001
Spleen size (cm)	12.66 ± 2.15	15.50 ± 1.01	< 0.001

Receiver operating characteristic (ROC) curve of PVD and spleen size when plotted showed that both were significant predictors for the presence of varices. The ROC curve of INR on the other hand showed that it was a poor predictor for the presence of varices when compared with ROC curves of both PVD and spleen size (Figure 1). The portal vein diameter was stronger predictor (AUC – PVD = 0.948; P < 0.001 vs. AUC – spleen size = 0.895; P < 0.001 vs. AUC –INR = 0.571; p = 0.109) (Table 3).

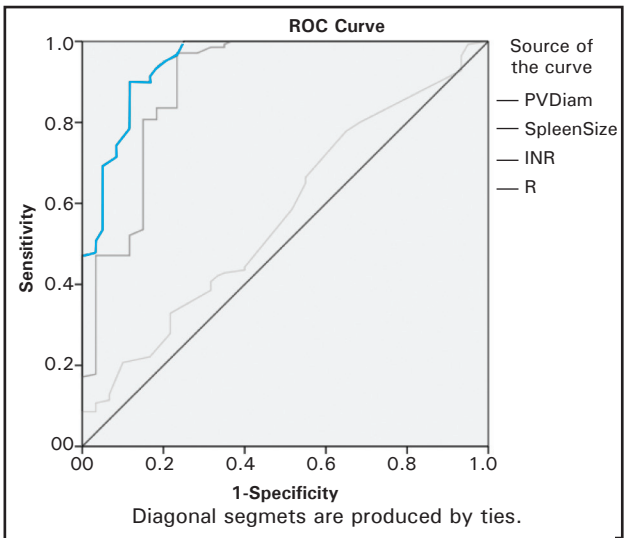

Figure 1. ROC curve for sensitivity and specificity of portal vein diameter, spleen size and INR for the prediction of varices.

Table 3. Statistical correlation between various non-invasive parameters.

Area Under the Curve					
Test Result Variable (s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Albumin	0.716	0.037	< 0.001	0.643	0.788
Platelets Count	0.766	0.038	< 0.001	0.691	0.841
INR	0.571	0.044	0.109	0.486	0.657
Portal Vein Diameter (mm)	0.948	0.017	< 0.001	0.914	0.982
Spleen Size	0.895	0.029	< 0.001	0.840	0.951

Receiver operating characteristic (ROC) curve of platelets count and serum albumin level when plotted showed that both were significant predictors for the presence of varices (Figure 2). The reduced platelets count was relatively a better predictor compared to reduced serum albumin level (AUC – platelets count = 0.766; P < 0.001 vs. AUC – serum albumin level = 0.716 vs.; P < 0.001) (Table 3).

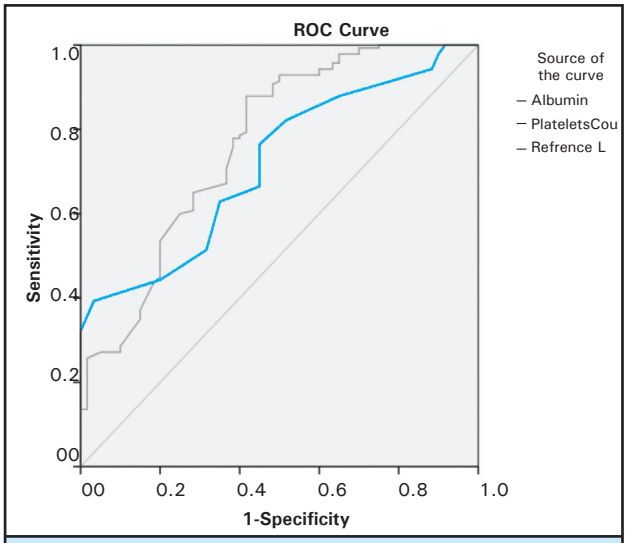

Figure 2. ROC curve for sensitivity and specificity of albumin and platelets count for the prediction of varices.

Best cutoff points for predictors of presence of gastro-oesophageal varices were detected by ROC curve analysis. There was 90% sensitivity and 88.3% specificity for prediction of presence of oesophageal varices when the cutoff value (by ROC curve analysis) for portal vein diameter was 12.25 mm. There was 97.1% sensitivity and 76.7 % specificity for prediction of presence of oesophageal varices when the cutoff value (by ROC curve analysis) for spleen size was 13.9 cm. There was low sensitivity of 39.3% but high specificity of 99% for prediction of presence of oesophageal varices when the cutoff value (by ROC curve analysis) for albumin was <2.55 gm/dl. There was 87.9% sensitivity but low specificity of 41.7% for prediction of presence of oesophageal varices when the cutoff value (by ROC curve analysis) for platelets count <1,44,000/mm^3 (Table 4).

Table 4. Sensitivities and specificities of various parameters with their best cutoff points.

Parameters	Best Cut-off point	Sensitivity (%)	Specificity (%)
Albumin	2.55	39.3	99
Platelets Count	144000	87.9	41.7
Portal Vein Diameter(mm)	12.25	90.0	88.3
Spleen Size	13.9	97.1	76.7

DISCUSSION

Two hundred forty patients of cirrhosis of liver with gastro-oesophageal varices were taken up for the study. But 12 patients were taken away to home or elsewhere by patient relatives against medical advice despite initial management and few days of admission and 18 were excluded because of inadequate data. Finally, a total of 200 patients with cirrhosis of liver were enrolled in the study.

Upper GI endoscopy is considered the best screening tool for varices in cirrhotic patients and to diagnose those at risk of bleeding. Presence of large varices, cherry red spots etc on endoscopy are some signs associated with high risk of bleeding.[5,6] Repeated endoscopic examinations and surveillance are recommended in cirrhotic patients with and without gastro-oesophageal varices. Despite the advantages of endoscopy, it is still expensive, invasive method and has poor compliance among patients. Various non-invasive tools have been described in literatures which could be used as indirect predictors for presence of gastro-oesophageal varices.
Two hundred cirrhotic patients (male 77%; female 23%) with mean age of 54.3 years (median age of 54 years; range of 27 to 85 years) were enrolled in the study. Similar pattern of male dominance of 69.3% has been reported by Mandal et al,[7] and 86.1% by Sharma and Aggarwal[8] in their series. However median age of our patients was more (54 years) than those reported by them as 40 years and 45 years respectively.

Etiology of cirrhosis in our series was chronic alcohol consumption (85%) followed by chronic hepatitis B (5%), chronic hepatitis C (2.5%) and cryptogenic (2.5%). Esophageal varices were detected in 70 % of cirrhotics at presentation. Mandal et al,[7] reported 75.6% of cirrhotics with varices. Risk of varices was found to increase with CTP class. Individuals with CTP class C were found to have 1.43 times more varices than those in Class B.

Average value of serum albumin of patients without gastro-oesophageal varices was 3.10± 0.41 gm/dl, while it was 2.68±0.51 gm/dl in patients with varices. This difference was statistically significant (P <0.001). There was low sensitivity of 39.3% but high specificity of 99% for prediction of presence of oesophageal varices when the cutoff value (by ROC curve analysis) for albumin was <2.55g/dl. Mandal et al,[7] reported serum albumin of 3.484±0.402 in patients without varices and 2.52±0.421 in patients with varices (P>0.10). Shanker et al,[9] reported that serum albumin was lower (2.3±0.5 gm/dl) in patients with varices than in patients without varices (3.2±0.4 gm/dl; P<0.01). Sarwar et al,[10] also described low serum albumin to be an independent factor associated with presence of oesophageal varices, however another study by Cherian et al,[11] described insignificant correlation between serum albumin and oesophageal varices. This could be due to variation in sample sizes etiology, duration of

illness, stages of liver cirrhosis and their complications at presentation and many other factors.

Average platelets count of patients without varices was 176570 ± 7510/mm^3 and with varices was 111890 ± 3584/mm^3 (P < 0.001). Mandal et al,[7] reported average platelets count of 2,15,000 ± 5,500/ mm^3 in patients without varices and 1,11,000 ± 2,840/ mm^3 in patients with varices (P > 0.10). Our study had sensitivity of 87.9 % and specificity of 41.7% for cutoff platelets count of < 144,000/ mm^3. Shanker et al,[9] reported platelet count of < 120,000/mm^3 to be 90% sensitive and 50% specific in predicting oesophageal varices. Thomopoulos et al,[12] mentioned platelet count of < 118,000/mm^3 to be a good predictor for presence of varices with sensitivity of 95% and specificity of 73 %. Average value of INR of patients without gastro-oesophageal varices was1.63 ± 0.56, while it was 1.96 ± 1.25 in patients with varices and no significant difference was observed (P = 0.051; P was > 0.005).

This study showed that patients without varices had average PVD 10.800 ± 1.1402 mm, while it was 13.731 ± 1.061mm in patients with varices. This difference was statistically significant (P < 0.01). In an Indian study, Mandal et al,[7] mentioned average PVD of patients without gastro-oesophageal varices was 11.545 ± 1.514 mm (P < 0.05) and with varices was 13.998 ± 1.123 mm. Shanker et al,[9] reported the average PVD 11.78 ± 1.58 mm in non-variceal group and 14.05 ± 2.26 mm in variceal group (P < 0.01). Portal vein diameter of 10.5 ± 2.6 mm among patients without esophageal varices and PVD of 11. 5 ± 2.4 mm among patients with varices were reported by Ng et al.[13]

The best cutoff of PVD for prediction of oesophageal varices in our study population was > 12.25 mm (Sensitivity = 90%, Specificity = 88.3%). Shanker et al,[9] in India, reported PVD > 12.20 mm, value similar to ours, as a predictor of esophageal varices (sensitivity 80%, specificity = 80%). Prihatini et al[14] and Cherian et al[11] mentioned PVD of 15 mm and 13 mm respectively to be predictive for variceal detection in cirrhotic patients. Portal vein diameter mentioned for development of gastro-esophageal varices was 13.5 mm by Thomopoulos et al,[12] 13 mm by Schepis et al,[15] and 11 mm by Sarwar et al.[10]

In the present study, average spleen size of patients without varices was 12.66 ± 2.15 cm. and with varices was 15.50 ± .01 cm. This difference was statistically significant (P < 0.001). Mandal et al,[7] mentioned average spleen size for patients without gastro-oesophageal varices as 13.13 ± 1.1c m and with varices as 14.99 ± 1.92 cm. Shanker et al,[9] reported that average size of spleen in variceal group (14.69 ± 1.08 cm) was larger than in non-variceal group (12.45 ± 0.65 cm) (P < 0.01).

In this study, there was 97.1 % sensitivity and 76.7 % specificity for prediction for oesophageal varices being present when the cutoff value (by ROC curve analysis) of spleen size was > 13.9 cm. Shanker et al,[9] reported 90% sensitivity and 80% specificity for prediction for presence of oesophageal varices when the cutoff value of spleen size was > 13.5 cm which is in consistency with our results. Spleen size of more than 13.5 cm (values almost similar to ours) and more than 13.15 were associated with gastro-oesophageal varices according to Thomopoulos et al,[12] and Serag et al,[16] respectively. Shankar et al,[9] described a positive correlation between PVD and grades of oesophageal varices and also between spleen size and variceal grading.

The current study had some limitations. Liver biopsy was not performed which is the gold standard for establishing the diagnosis of cirrhosis of liver. Liver biopsy has now become obsolete since the introduction of fibroscan and other markers of fibrosis. But these are expensive and indirect markers and they have their own limitations. So patients were diagnosed as cirrhosis clinically with stigmata of chronic liver disease and clinical evidence of portal hypertension and these findings were further supported with ultrasonological and endoscopic findings. Estimation of spleen size and portal vein diameter by ultrasonography is operator dependent. A larger sample size and proper sampling with case controlled studies and randomized controlled trials would have provided a clearer picture.

CONCLUSIONS

In cirrhotic patients with portal hypertension, low serum albumin, low platelets count and ultrasonographic measurement of portal vein diameter and spleen size are useful in predicting presence of gastro-oesophageal varices. This would be useful in areas where endoscopy facilities are not available. Further, regular follow up endoscopies can be avoided. Non-invasive parameters can hereby, be recommended as indirect predictors for presence of gastro-oesophageal varices in patients with cirrhosis of liver. These would thus be valuable in cirrhotic patients in the long-term monitoring, follow ups and management.

Conflict of Interest: None.

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