

ORIGINAL ARTICLE

Prediction of Esophageal Varices by Non-Invasive Markers in Patients of Hepatic Cirrhosis due To Chronic Hepatitis C

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Correspondence to: Hafiza Faiza Rauf, Email: drfaiza51@gmail.com, Cell: 0333-4909181**ABSTRACT****Background:** Esophageal varices develop as a consequence of portal hypertension in patients with chronic liver disease. Predicting the 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.**Objective:** To evaluate the accuracy of combined non-invasive parameters in predicting the presence of esophageal varices in patients with hepatic cirrhosis due to chronic hepatitis C, using the positive predictive value (PPV) as a measure of performance.**Methods:** In this cross-sectional study conducted in the Department of Medicine, Unit-I, Sir Ganga Ram Hospital, Lahore, 125 patients fulfilling the inclusion criteria were included. Platelet count, Prothrombin Time/International Normalized Ratio (PT/INR) and portal vein diameter was assessed. Upper gastrointestinal endoscopy was done in all patients to check the presence or absence of esophageal varices.**Results:** Mean age of the patients was 52.52 ± 8.39 years with 64% males. Mean PT was 10.09 ± 3.13 , mean INR was 1.75 ± 0.22 , mean platelet count was 83.56 ± 13.47 while mean portal vein diameter was 13.79 ± 0.84 . In 61 patients (48.8%) esophageal varices were present on endoscopy and in 85 patients (68%) esophageal varices were predicted by combined non-invasive parameters. Positive predictive value of combined non-invasive parameters was 71.7%.**Practical implications:** Noninvasive predictors can be used as a screening tool to decide need for preventive drug therapy in esophageal varices and thus help reduce the workload and financial burden of routine endoscopies in all cirrhosis patients.**Conclusion:** The results suggest that combined non-invasive parameters may be a useful tool in the prediction of esophageal varices in patients with hepatic cirrhosis**Keywords:** Esophageal varices, Non-invasive predictors, Portal hypertension**INTRODUCTION**

Global estimates reveal that about 58 million people have chronic hepatitis C virus infection, with nearly 1.5 million new cases per year.¹ The overall prevalence of HCV in Pakistan is 8.6% with even higher rates in the rural and periurban regions.^{2,3} Furthermore, this prevalence is progressively increasing.³

Liver cirrhosis is irreversible scarring of liver caused by continuous and long term liver damage. Chronic hepatitis C is the leading cause of cirrhosis as about 15-30% of HCV infected patients advance to cirrhosis within 20 years.¹

Common causes of death in liver cirrhosis are hemorrhage from esophageal varices, spontaneous bacterial peritonitis, septicemia, hepatic encephalopathy, renal failure and hepatocellular carcinoma.^{4,5} Esophageal varices are dilated submucosal veins at the lower end of the esophagus, which develop as a consequence of portal hypertension and are present in about 50% of patients with liver cirrhosis.⁶ The grade of esophageal varices often correlates with the severity of liver disease. The death rate owing to first episode of esophageal variceal bleed is between 15-20% which increases with advancing liver disease.⁷

The routine method to investigate esophageal varices is upper gastrointestinal endoscopy, which is an invasive procedure. Non-endoscopic parameters are now known to be independent predictors for diagnosis of esophageal varices. These parameters include presence of ascites, platelet count, prothrombin time, splenic diameter, portal vein diameter, platelet count to spleen diameter ratio, serum albumin and serum bilirubin.⁸ Several studies have observed that these non-invasive parameters are strong predictors of esophageal varices.^{8,9,10}

Several studies have also been done in Pakistan that have used these non-invasive parameters but most of them have analysed each parameter separately and only a few have used various combined scores to predict esophageal varices.^{11,12,13}

In a developing country like Pakistan endoscopy facilities are limited, expensive, and the endoscopic workload is high. Furthermore, patients are fearful of endoscopy due to its invasive nature. In our setting, noninvasive predictors can be helpful as a screening tool to help physicians initiate drug therapy to prevent

variceal bleeding while waiting for diagnostic and/or therapeutic endoscopy.

METHODS**Setting:** Department of Medicine, Unit-I, Sir Ganga Ram Hospital, Lahore.**Study Design:** Cross-sectional study.**Sample Size:** Sample size of 125 cases was calculated with 95% confidence interval, 5% margin of error and taking expected percentage of positive predictive value of non-invasive parameters as 70%.**Sampling Technique:** Non-probability consecutive sampling**Sample Selection:** Inclusion Criteria: Male and female patients aged between 20 -65 years with liver cirrhosis due to hepatitis C diagnosed by ultrasonography.**Exclusion Criteria:** Patients with history of variceal bleeding or band ligation, hepatic encephalopathy, previous or current treatment with beta blockers and diuretics, ascites or portal vein thrombosis detected by ultrasonography.**Data Collection:** After obtaining informed consent 125 patients admitted in Medical Unit-I of Sir Ganga Ram Hospital, fulfilling the inclusion criteria were enrolled in our study. Platelet count and Prothrombin Time/International Normalized Ratio (PT/INR) was determined by blood tests and portal vein diameter was assessed by abdominal ultrasound. Upper gastrointestinal endoscopy was done in all patients to check the presence or absence of esophageal varices. A predesigned proforma was used to record all the findings.**Data Analysis:** SPSS version 20.0 was used for data analysis. Quantitative data like age, platelet count, PT/INR and portal vein diameter were expressed as mean and standard deviation. Cutoff values used for data analysis were platelet count equal to or less than 100,000 per mm^3 , $\text{INR} > 1.5$ and portal vein diameter equal to or more than 13 mm. Qualitative data like gender and presence or absence of esophageal varices on endoscopy were expressed as frequencies and percentages. Sensitivity, specificity, positives predictive value and negative predictive values were calculated.

RESULTS

A total of 125 patients were enrolled during the study period. The mean age of the patients was 52.52±8.39 years (Table 1). There were about two-thirds males and one third females. Mean duration of diagnosis of cirrhosis was 3.03±1.46 years. Mean values of PT, INR, platelet count and portal vein diameter are shown in Table 2. Table 3 shows the comparison of findings of combined non-invasive parameters with endoscopic results and Table 4 demonstrates the calculated statistical values.

There were no false negative results as none of the patients with EV on endoscopy were missed by the combined non-invasive parameters.

Table 1: Demographic Features of the Study Population

Feature		N (%)
Age	20-40 years	15 (12)
	41-65 years	110 (88)
Gender	Male	80 (64)
	Female	45 (36)
Disease Duration	Less than or equal to 5 years	118 (94)
	More than 5 years	7 (6)

Table 2: PT, INR, Platelet Count and Portal Vein Diameter Values

Variable	Mean	SD*
PT	10.09 sec	3.13
INR	1.75	0.22
Platelet Count	83.56 x 1000/mm ³	13.47
Portal Vein Diameter	13.79 mm	0.84

*SD = Standard Deviation

Table 3: Comparison of Combined Non-Invasive Parameters vs Endoscopy for Diagnosis of Esophageal Varices (n = 125)

Parameter	Esophageal Varices	
	Present	Absent
Combined Non-Invasive Parameters	85	40
Endoscopy	61	64

Table 4: Sensitivity, Specificity, Positive and Negative Predictive Values of Combined Non-invasive Parameters

Statistical Parameter	Value
Sensitivity	100%
Specificity	62.5%
Positive Predictive Value	71.7%
Negative Predictive Value	100%

DISCUSSION

A major complication of portal hypertension in patients with cirrhosis is the development of esophageal varices (EV), with an ensuing risk of variceal bleeding. Hence, the first five editions of Baveno consensus on portal hypertension had recommended surveillance with periodic upper gastrointestinal endoscopies in these patients for timely identification of the development of EV and initiation of prophylactic strategy in those at a high risk of bleeding. The Sixth Baveno Consensus on Portal Hypertension (Baveno VI), however, recommended using non-invasive tools to rule out the presence of high risk varices.¹⁴ According to Baveno VI, surveillance endoscopy is not necessary for patients with compensated advanced chronic liver disease who have normal platelets (>150,000/mm³) and a liver stiffness measure (LSM) <20 kPa.¹⁴

Many researchers have identified various non-invasive parameters to predict presence of EV, either alone or in different combination. Some studies have found a high presence of esophageal varices in patients with enlarged portal vein diameter.^{15,16} Ali et al documented EV in 80% of their patients with PVD more than 13 mm.¹⁵ Similarly Rani and colleagues observed 90% sensitivity of enlarged PVD in detecting large EV.¹⁷ Kumar and coworkers from India found a significant association between

PVD and presence of EV.¹¹ However, Jamil et al were not able to elicit PVD alone as a good predictor of EV.⁹

Others have observed that a low platelet count either alone or in combination with other non-invasive markers can be used to predict presence of EV. Bhattarai and coworkers from Nepal, observed that platelet count less than 144,000/mm³ was 87.9% sensitive in detecting EV.¹⁸ Jamil and colleagues found that the ratio of platelet count to splenic diameter (PC/SD) had a sensitivity of 89% and a specificity of 81.4% when detecting EV.⁹ Similarly a large Cochrane review of 17 studies showed a 93% sensitivity and 84% specificity for the PC/SD ratio with 73% PPV and 74% NPV.¹⁹ Chen and his Taiwanese colleagues observed NPV of 97-98% when they used a combined score including albumin, bilirubin and platelet counts to predict EV.²⁰

A study in Pakistan by Alam and Saeed utilized several non-invasive markers for EV including platelet count and INR. They found a PPV of more than 85% for all their indices but the NPV was lower at less than 65%.²¹ Similarly, Manohar and co-researchers found statistically significant correlation between raised INR and presence of EV.²²

We predicted EV on the basis of combined non-invasive parameters in 85 of our patients, all of who had thrombocytopenia, elevated INR and enlarged portal vein diameter (PVD). On endoscopy, EV were present in 61 of these 85 patients and no varices were seen in the remaining 40 patients who were predicted to be free of EV by the combined parameters. The combined non-invasive parameters we used showed a sensitivity of 100% and were able to pick all cases with EV. However, the specificity was lower (62.5%) as 24 subjects without EV were predicted to have them. The positive predictive value (PPV) was calculated to be 71.7% while the negative predictive value (NPV) was 100%. The combined non-invasive parameters in our study did not show any false negative results. This means that this combination of noninvasive parameters is highly sensitive and can be used as a screening test with low chances of missing patients with clinically significant esophageal varices. Endoscopy can then be planned on elective basis for subsequent confirmation and, if needed, therapeutic intervention.

The various studies on non-invasive markers for EV have elicited different sensitivity, specificity, PPV and NPV, among themselves and from our study due to the different parameters used. In addition, the blood indices values observed vary among different laboratories due to the different analysis equipment. Furthermore, ultrasonographic findings are operator dependent and, therefore, can lead to slightly different results in various studies. There is also a wide variation among the number of subjects enrolled which can affect the statistical outcomes.

Our study has some limitations. We only used a limited number of non-invasive parameters for predicting EV in our subjects. For further validation in our population, more extensive research utilizing additional non-invasive markers on a more extensive cohort of patients needs to be performed, to establish the sensitivity and specificity of these markers and their use as a possible replacement for endoscopy in low risk patients.

CONCLUSION

The results suggest that the combined non-invasive parameters may be a useful tool in the screening of esophageal varices in hepatic cirrhosis patients

Conflict of Interest: None

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