Original Article

Non-invasive predictors to grade esophageal varices in liver cirrhosis patients

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Abstract

Background: Portal hypertension commonly occurs due to liver cirrhosis, and esophageal varices (EV) is one of the major complications associated with it. The most common cause of death in liver cirrhosis is EV bleeding. Hence, GE screening for EV is required, which is an invasive procedure. Regular use of endoscopy results in low compliance due to cost and discomfort for patients. Hence, identifying non-invasive markers that could grade EV provides a useful screening tool for family physicians and primary health centers (PHCs) by referring the patient to higher centers for definitive treatment, which could reduce mortality due to variceal bleeding in cirrhotic patients. **Aims:** To assess non-invasive predictors of grade EV in patients diagnosed with liver cirrhosis. **Settings and Design:** Cross-sectional study. **Methods and Material:** A total of 109 patients with liver cirrhosis underwent clinical and biochemical evaluation, USG abdomen with spleen bipolar diameter, ascitic fluid analysis, and upper GE with a grade of EV are recorded. **Statistical Analysis Used:** SPSS software with Student *t*-test, Chi-square *t*-test, analysis of variance, receiver operator characteristic (ROC) curves, and Spearman correlation with 95% CI is used. $P<0.05$ is considered significant. **Results:** Aminotransferase to Platelet count Ratio Index (APRI) score >1.815, PC/SD ≤909, and SAAG >1.1g/dl showed EV in liver cirrhosis ($P < 0.05$). The order of prediction with ROC curves shows APRI score > PC/SD > SAAG. In grading EV, APRI scores of 1.9–2.5 and >2.5 showed small and large EV, respectively ($P < 0.05$). **Conclusions:** APRI score may be used in PHC as an early intervention to grade EV and refer the patient to higher centers for definitive treatment. This would prevent the progression of varices to rupture and reduce mortality due to variceal bleeds in liver cirrhosis patients.

Keywords: APRI, Aspartate aminotransferase to platelet count ratio index; EV, esophageal varices; GE, gastro-endoscopy; PC/SD, platelet count to spleen diameter ratio; PHC, primary health center; ROC, receiver operator characteristic; SAAG, serum ascites to albumin gradient

Introduction

Portal hypertension (PH) commonly occurs due to liver cirrhosis, and one of the major complications of PH is esophageal varices (EV).[1] The prevalence of EV is 60–80% in liver cirrhosis, and 20–35% is the mortality due to variceal bleeding.[2] The incidence of EV increases by 5% per year, and the rate of progression from small to large varices is approximately 5–10%.[3] Patients who develop EV due to PH are more prone to variceal bleeding, which remains the most common cause of death. About 1/3rd of patients with gastrointestinal bleeding were due to cirrhosis.[3] Within 2 years after diagnosis, there is a 25–35% increased risk of variceal rupture, resulting in a mortality rate of 17–57%.[3] Therefore, for long-term management of patients with liver cirrhosis, prevention of portal hypertensive bleeding remains at the forefront. Gastroendoscopic screening occurs in two situations in liver cirrhosis: at the initial diagnosis and during the follow-up of patients. Large esophageal varices (LEV) are

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associated with an increased risk of variceal bleeding. The reported incidence is 9–49% for LEV.[4] Hence, cirrhotic patients undergo repeated screening endoscopy for the presence of EV. This social and medical burden would rise in the future due to the improved survival of a greater number of patients with chronic liver disease. Therefore, identifying non-invasive methods that could accurately predict EV and identify patients who are more susceptible to bleeding would be a very useful screening tool. This could thus make it possible to find the population with a high probability of LEV that requires confirmation by endoscopy, as the frequent use of endoscopy is limited due to cost and discomfort, making the patient less compliant.

Several studies reported that biochemical, clinical, and ultrasonographic parameters, which are non-invasive, have shown greater predictive power for EV.[5-8] These parameters are directly or indirectly related to PH, which includes splenomegaly and thrombocytopenia. Platelet count/splenic bipolar diameter ratio (PC/SD) can be used as a non-invasive parameter in liver cirrhosis to predict EV, according to a study conducted by Giannini *et al.* (2003).[6] The serum ascites to albumin gradient (SAAG) classifies exudate-transudate in ascites, which is a PH marker. An increased SAA gradient ≥1.1 g/dl correlates with PH, and a low gradient indicates no PH. Hence, the SAAG correlates with the presence of PH.[9,10] In a study conducted by Huan Liu *et al.*[11] 2021, 80–90% of cases were shown to have varices when the Aminotransferase to Platelet count Ratio Index (APRI) score was >1.8. It was shown that the APRI score has a validity rate of 90% or more in detecting EV.[12]

Therefore, the overall outcome after a medical intervention and the clinic-laboratory correlation in the prediction of varices are more feasible. Moreover, very few studies were conducted on platelet scoring systems and clinic-laboratory parameters like APRI, PC/SD, and SAAG in liver cirrhosis patients. Hence, we planned to study the relevance of these parameters to predict EV in liver cirrhosis patients, which can be a useful screening tool for family physicians and primary health centers (PHCs) by referring the patient to higher centers for definitive treatment.

Aim

To study non-invasive parameters to predict EV in patients with liver cirrhosis.

Objectives

1. To study PC/SD, APRI score, and SAAG as non-invasive parameters to predict EV in liver cirrhosis
2. To compare the results of the above parameters with the upper gastroendoscopy report of liver cirrhosis patients

Study Hypothesis

SAAG, PC/SD, and APRI score are good predictors of EV in liver cirrhosis patients.

Subjects and Methods

Study design

Hospital-based cross-sectional study.

Period of study

The study was carried out over a period of 18 months, from 2021 to 2022.

Sample size calculation

By taking a sample representative of the 95% confidence interval and applying the W. Daniel formula, sample size requirement came out to be 109.

After obtaining ethical approval from the institutional Ethics committee (Reg No.:ECR/262/Inst/UP/2013/RR-19) and patient consent, 109 patients with cirrhosis liver attending the medical gastroenterology outpatient department and wards of KGMU Lucknow between the months of March 2021 and September 2022 were selected based upon inclusion and exclusion criteria. All the patients who were selected for the study underwent a complete clinical evaluation. Findings of clinical and physical examination were recorded with special focus on the present or previous history of alcoholism, hematemesis, malena, bleeding per rectum, bleeding tendencies, blood transfusion, oedema, ascites, jaundice, hepatotoxic drug intake, anemia, history of sexually transmitted diseases, intravenous drug abuse, any stigmata of chronic liver disease, dilated abdominal veins, and encephalopathy.

All patients underwent complete blood counts, liver function tests, and ultrasonography of the abdomen to confirm the presence of cirrhosis. Findings of ultrasonography were recorded for spleen bipolar diameter, size of portal vein, ascites, and collaterals. In patients with ascites, ascitic fluid analysis is recorded. An upper gastro-intestinal (GI) endoscopy procedure was done in all the patients to find the presence of varices and grade them.

Inclusion criteria

All the patients who were newly diagnosed with cirrhosis of the liver underwent a physical examination, biochemical evaluation, and ultrasound abdomen. An upper GI endoscopy procedure was done for all the patients selected.

Exclusion criteria

1. Previous or present history of portal hypertensive bleeding disorders
2. Portal vein thrombosis
3. Hepatocellular carcinoma
4. Budd Chiari Syndrome
5. Present or previous treatment history for β blockers, diuretics or vasoactive drugs.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows (15.0 version). The continuous

variables are evaluated by mean (standard deviation) or range value when required. The dichotomous variables are presented in number/frequency and analyzed using the Chi-square or Fisher Extract tests.

Receiver operator characteristic (ROC) curves for multivariate logistic regression analysis to know the predictive power of various parameters are used. For comparison of the means between the two groups, analysis by Student *t*-test, Mann–Whitney U test, and Spearman correlation with a 95% confidence interval was used. A *P* value of < 0.05 is regarded as significant.

Results

The present study was carried out to study non-invasive predictors to grade EV in liver cirrhosis patients. For this purpose, a hospital-based cross-sectional study was carried out. The following were the observations and results of the study.

A total of 109 patients were included in the study; 82% (n = 89) were male and 18% were female (n = 20). The mean age of the patients was 47.69 ± 10.91 years. Grade I EV were found in 31% (n = 34), whereas grade II, grade III, and grade IV were found in 63% (n = 58), 4% (n = 4), and 2% (n = 2) of patients, respectively. Grade II varices were predominated among them.

The APRI was >1.5 in 94.5% (n = 103) of patients, and it was between 0.5 and 1.5 in the remaining 5.5% of patients, with the mean being 2.32 ± 0.41. None of the patients had the APRI score as <0.5. The analysis of variance test applied a *P* value of 0.01, which is statistically significant [Table 1]. When the APRI score is >1.7, sensitivity is 83.3% and specificity is 91.2%. When the APRI score is 1.9–2.5, it shows small EV, and when the APRI score is >2.5, it shows LEV [Table 2]. The correlation between APRI and the grading of varices showed a strong positive correlation (0.76) that was statistically significant [Table 3]. AUROC for the APRI score came out to be 0.931, making it a powerful predictor [Figure 1].

There is a statistically significant difference (*P* value of 0.006) based on the presence and absence of varices. Around 80% of the study population had varices when the SAAG value was more than 1.1g/dl, and all the study population was free from ascites when the SAAG value was less than 1.1g/dl [Table 4]. However, there is no statistically significant association between SAAG and the grading of varices. On point biserial correlation, when SAAG was compared with the grading of varices, there was no correlation (0.04) obtained between them. The auroc for the SAAG score came out to be 0.59, making it a weak predictor in grading EV.

Categorization of patients into two groups based on a cutoff value of 909 for the PC/SD ratio. The PC/SD ratio relation to the grade of varices was found to have a significant association statistically, with a *P* value of 0.029 when the PC/SD was ≤909 [Table 5]. The correlation between PC/SD and the grading of varices showed a weak positive correlation (0.23), which was statistically significant [Table 6]. The AUROC for PC/SD came out to be 0.921, making it a good predictor [Figure 2].

Among all the predictors with respect to ROC curves, the APRI score showed a high area under the curve 0.9. Hence,

Table 1: Distribution according to the Aspartate Aminotransferase to Platelet Count Ratio index

APRI	Frequency	%
0.5-1.5	6	5.5%
>1.5	103	94.5%
Total	109	100%
Mean APRI: 2.32±0.41		

Table 2: APRI with grading of varices

Grading of varices		*n*	Mean	Std. Deviation	*P*
APRI	Absent	6	1.5933	0.15280	0.001
	Grade 1	33	1.9164	0.35230	
	Grade 2	63	2.5437	0.14471	
	Grade 3	4	2.7350	0.02380	
	Grade 4	5	2.7550	0.06364	
	Total	109	2.3102	0.41180	

Table 3: Correlation between APRI and grading of varices

Correlations			
		Grading of varices	APRI
Grading of varices	Pearson correlation	1	0.761**
	Sig. (2-tailed)		0.000
	N	109	109
APRI	Pearson correlation	0.761**	1
	Sig. (2-tailed)	0.000	
	N	109	109

**$p<0.01$, Correlation is significant at the 0.01 level (2-tailed). APRI: Aminotransferase to platelet count ratio index

Table 4: Relationship between SAAG and the presence of varices

SAAGg/dl	Varices	
	Present *n*	Absent *n*
<1.1	12	6
>1.1	48	0
Total	60	6

Table 5: Relationship between PC/SD ratio and grade of varices

Varices		PC/SDRATIO		Total
		>909	≤909	
Grading of varices	I	30	4	34
	II	62	2	64
	III	4	0	4
	IV	0	2	2
	0	4	1	5
Total		100	9	109

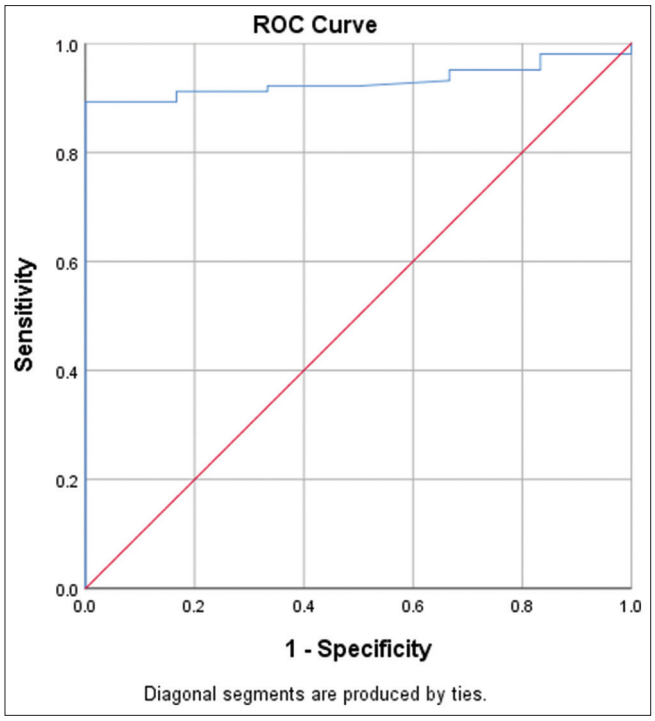

Figure 1: ROC curve of the Aspartate Aminotransferase to platelet count Ratio Index score

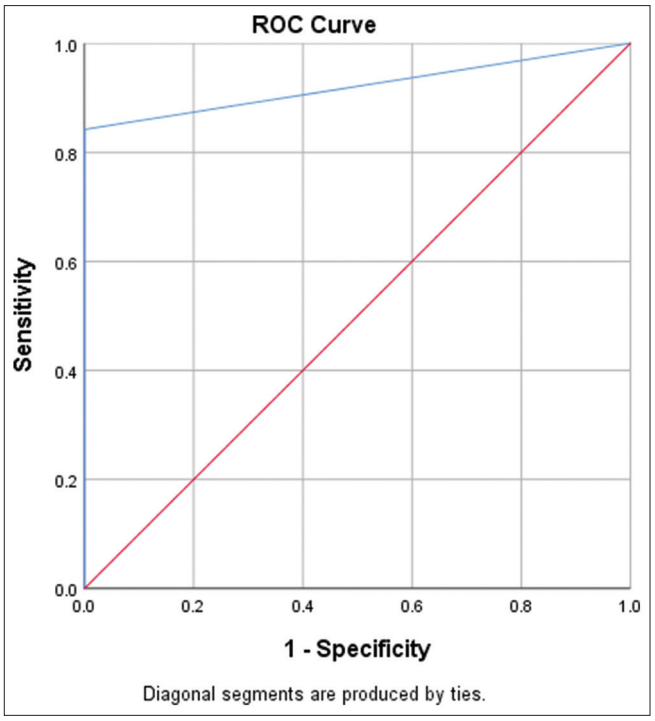

Figure 2: ROC curve of the platelet count to spleen diameter ratio

Area Under the Curve				
Test Result Variable(s):APRI				
Area	Std. Error[a]	*P*	Asymptotic 95% Confidence Interval	
			Lower bound	Upper bound
0.931	0.025	0.001	0.881	0.980

Test result variable(s):PC/SD				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence interval	
			Lower bound	Upper bound
0.921	0.063	0.155	0.798	1.000

Table 6: Correlation between PC/SD and grading of varices

Correlations			
		PC/SD	Grading of varices
PC/SD	Pearson correlation	1	0.238*
	Sig. (2-tailed)		0.013
	N	109	109
Grading of varices	Pearson correlation	0.238*	1
	Sig. (2-tailed)	0.013	
	N	109	109

*p<0.05, Correlation is significant at the 0.05 level (2-tailed). PC/SD: Platelet count/splenic bipolar diameter ratio

APRI is a reliable, non-invasive method to predict and grade EV.

Discussion

The present study is aimed at assess grading Evs by non-invasive parameters in patients with liver cirrhosis using the APRI score, PC/SD, and SAAG. The following are the results of the study.

The mean age of the study participants in the current study was observed to be 47.69 years, with a standard deviation of 10.91 years and a median age of 46. In a study done by Bledark (2017),[13] the mean age was 51.5 with a SD of 13.1. In the current study, among the 109 study subjects, 62% (n = 33) were in the age group of 31–50, and the highest number of patients (38%, 35) were in the age group of 41–50 years. This may be due to lifestyle habits of alcohol intake in the 31–50 age groups.

In the present study based on gender, there were 82% male and 18% female patients. In a study by Cherian *et al.* (2011)[14] on non-invasive predictors of EV, 61% (16 out of 26) of study participants were males, which constitutes to grade II among the grading of varices. Heavy alcohol consumption can be the main cause of liver cirrhosis in males, which ultimately leads to varices.

In the current study, the grading of varices was done according to Conn's Grading system for EV. Based on the above grading system, 89% of the study population had small varices (i.e. grades I and II), 6% had large varices (grades III and IV) and only 5% were without varices. This might be due to the manifestation of other complications of cirrhosis earlier, before the appearance of LEV would make the patient seek the hospital, where the patient might be diagnosed with a small EV by gastroendoscopy. In a study done on predictors of EV and variceal bleeding in liver cirrhosis patients by Bledark raja (2017),[13] it was reported that 31.7% had small varices, 21.6% had large varices, and 18.7% had no varices.

In the current study, among the non-invasive parameters, spleen bipolar diameter among the study subjects with EV had a mean value of 180.61 mm with a standard deviation of 36.66, and among the study subjects with no varices, it had a mean value of 136.45 mm with a standard deviation of 24.07. A statistically significant association was observed with the presence/absence of varices, with a *P* value of 0.045. Spleen bipolar diameter is increased due to splenomegaly caused PH. A similar significant association was observed by Jijo V. Cherian *et al.* (2011)[14] in a study on non-invasive predictors of EV with a *P* value of 0.004. Kumar *et al.* (2006),[8] Thomopolos *et al.* (2003),[5] Madhotra *et al.* (2002),[15] Zaman *et al.* (1999),[16] Pilette *et al.* (1999),[17] F Schepis *et al.* (1999),[18] Chalasani *et al.* (1999)[19] and Torres *et al.* (1996)[20] reported that splenomegaly is an independent predictor of the presence of varices.

Based on the cutoff value of 909 for PC/SD, the study subjects in the present study were divided into two groups. The PC/SD relation to the grade of varices was studied. A significant difference between the presence or absence of EV with a PC/SD of 909 was observed ($P = 0.029$). The above results hold true for studies by Giannini *et al.* (2003)[6] and Kraja *et al.* (2017).[13] Platelet counts may decrease in chronic liver disease due to several other factors. Hence, PC/SD is introduced to take into consideration that the decrease in platelet count most likely depends on hypersplenism caused by PH. Performing unnecessary endoscopy in all patients can be avoided if we take PC/SD > 909 without running the risk of missing cases with EV.

Among the study participants with ascites, 98.4% of them had varices, and 90.7% of the study participants had varices without ascites. There is no significant association between the presence of ascites and the grade of varices (*P* value 0.605).

Although Thomopolos *et al.* (2003)[5] have put ascites as an independent predictor of the presence of large varices, our study does not demonstrate a statistically significant correlation between the presence and grade of varices and ascites. Like the present study, a non-significant association was reported in a study done by Fagundes *et al.*[21]

In our study, patients were grouped based on the range of SAAG values. Among the study sample, SAAG was less than 1.1 in 27.3% of the patients and more than 1.1 in 72.7% of the patients. The reason is that high SAAG ascites is caused due to PH, where there is infiltration of transudate into the peritoneal cavity, and not due to albumin leak, which leads to SAAG >1.1 g/dl. Around 80% of the study population had varices when the SAAG value was more than 1.1. All the study subjects with absence of varices had SAAG values less than 1.1. Similar results were reported by studies done by Gurubacharya *et al.* (2005)[22] and Bibhuti B. Das (2001).[23] High SAAG (>1.1) with varices was found in 72% and 91% of the study population, respectively. The above-mentioned two groups showed statistically significant differences (with a P = value of 0.006) based on the presence and absence of varices. This is consistent with studies by Torres *et al.* (1996)[20] and Gurubacharya *et al.* (2005).[22] However, results in our study showed that there is no statistically significant association between SAAG and the grading of varices.

Huan Liu *et al.* (2021) used the APRI score, and they found a *P* value of <0.05 significant in predicting EV with AUROC values of 0.8 and 0.64, respectively.[11,12] In the present study, it was observed that the APRI score has higher predictive power in the grading of EV showing an AUROC of 0.9, which is consistent with other studies. In grading EV, APRI scores of 1.9–2.5 and >2.5 showed small and large EV, respectively ($P < 0.05$). Hence, the APRI score may be used in PHC as an early intervention to grade EV and refer the patient to higher centers for definitive treatment. This would prevent the progression of varices to rupture and reduce mortality due to variceal bleeding in liver cirrhosis patients attending PHCs.

The APRI score was found to be more relevant in predicting varices. the reason is that aspartate transaminase (AST) levels are raised in liver cirrhosis due to decreased hepatic flow and decreased sinusoidal uptake of AST. On the other hand, platelet counts were lowered due to splenomegaly caused by PH, and when these were combined as a ratio, they correlated well with liver cirrhosis and EV.

The findings in the present study showed that the APRI score, PC/SD, and SAAG may be used as non-invasive parameters to predict EV. Among these parameters, the APRI score has shown higher predictive power to grade EV. In grading EV, APRI scores of 1.9–2.5 and >2.5 showed small and large EV, respectively ($P < 0.05$). Although many studies have been done previously on non-invasive parameters, these studies have focused only on the causative factors of liver cirrhosis or individual parameters. Hence, in the present study, we explored clinico-laboratory and platelet scoring parameters in predicting EV in liver cirrhosis patients, which may lead to significant results through early prediction and therapeutic approaches in PHCs. Thus, it may reduce mortality in chronic liver disease.

However, further studies must be carried out with a larger sample size by incorporating many platelet parameters and platelet scoring systems like MPV (Mean Platelet volume), FIBRO Q index, FIB4 index, etc., in predicting EV non-invasively.

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Conflicts of interest

There are no conflicts of interest.

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