Original Article

Diagnostic Accuracy of Non-invasive Laboratory-Based Fibrosis Scores in Predicting the Presence of Esophageal Varices in Liver Cirrhosis

Rajesh Pandey*, Rahul Pathak, Arun Gnawali, Prem Krishna Khadga, Sashi Sharma, Anurag Jha, Rabin Hamal, Dinesh Koirala, Pawan Parajuli

Department of Gastroenterology and Hepatology, Maharajgunj Medical Campus, TUTH, Institute of Medicine, Kathmandu, Nepal

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Abstract

Introduction: Non-invasive assessment of esophageal varices (EVs) may reduce endoscopic burden and cost. This study aimed to evaluate the diagnostic accuracy of non-invasive fibrosis scores (AAR, APRI, FIB-4, King and Lok scores) for the prediction of varices in liver cirrhosis.

Methods: This prospective study included 100 liver cirrhosis patients who underwent screening endoscopy for EVs. AAR, APRI, FIB-4, King and Lok scores were assessed. The receiver operating characteristic curves (ROC) were plotted to measure and compare the performance of each score for predicting EVs and to obtain the corresponding optimal prediction value.

Results: Of the 100 patients, 70 were males and 30 were females with a mean age of 54.05±11.58 years. Esophageal varices were found in 77 patients out of which 58.44% were high-risk varices. Platelet count and non-invasive fibrosis scores APRI, FIB-4, Lok and King were able to discriminate patients with and without varices. Using area under receiver operating characteristic curve (AUROC), these scores were found to have low to moderate diagnostic accuracy for the presence of EVs and high-risk EVs, where the APRI score had the highest AUROC (0.77 and 0.70) respectively. At a cutoff value > 1.4, APRI score had 90.9% sensitivity, 60.9% specificity and 84 % diagnostic accuracy in predicting the presence of varices, while it had 84.4% sensitivity, 45.5% specificity and 63% diagnostic accuracy in predicting the presence of high-risk varices, at a cutoff value > 2.02.

Conclusion: APRI, AAR, FIB-4, King, and Lok scores had low to moderate diagnostic accuracy in predicting the presence of varices in liver cirrhosis. The APRI score can help select a patient for the endoscopy but cannot replace endoscopy for esophageal varices screening.

Introduction

Cirrhosis is the end-stage for chronic liver disease and is the leading cause of liver-related death globally.[1] Cirrhosis is frequently compensated. The development of complications of portal hypertension and/or liver dysfunction is decompensated cirrhosis. It is defined by the presence of variceal hemorrhage, ascites, encephalopathy, hepatorenal syndrome, jaundice or hepatocellular carcinoma. The transition from a compensated to a decompensated stage occurs at a rate of 5 to 7% per year.[2] Esophageal variceal bleeding is a life-threatening portal hypertension-related complication in liver cirrhosis.[3] Esophageal varices are present at diagnosis in approximately 50% of cirrhotic patients and the rate of development of new varices and increase in grades of varices is 8% per year.[4] The mortality is 3.4% per year in patients with non-bleeding varices. By comparison, the mortality rises to 57% per year in patients with variceal bleeding. Thus, early diagnosis of varices and primary prophylaxis of variceal bleeding in high-risk patients with liver cirrhosis is important in improving survival.[5]

Esophagogastroduodenoscopy (EGD) is the gold standard for diagnosing varices in liver cirrhosis. However, because of its invasiveness and discomfort, most patients are reluctant to undergo this procedure. The progression of fibrosis parallels the increase in portal pressure,[6] as liver fibrosis contributes to the

*Corresponding Author:
Dr. Rajesh Pandey, MBBS, MD
Department of Gastroenterology and Hepatology, Maharajgunj Medical Campus, TUTH, Institute of Medicine, Kathmandu, Nepal
Email: rajeshpandeya@gmail.com, Phone: +977-9849042943

increased hepatic resistance. Several non-invasive markers of varices are primarily derived from the non-invasive assessment of liver fibrosis. They are more convenient and cheap in clinical practices. Aspartate Aminotransferase-platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores have good accuracy in predicting fibrosis.[7, 8] Several studies including meta-analysis have demonstrated that the diagnostic accuracy of APRI, Aspartate aminotransferase-Alanine aminotransferase ratio (AAR), FIB-4, Lok and King score was modest.[7, 9]

In a country like Nepal, where availability and affordability of endoscopy service is still an issue, these non-invasive scores may reduce endoscopic burden, cost, and drawbacks. This study aims to evaluate the diagnostic accuracy of APRI, AAR, FIB-4, Lok scores and King scores in predicting the presence of varices and high-risk varices in liver cirrhosis.

Methods:

This prospective study was carried out at the Department of Gastroenterology, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal from August 2019 to February 2020. This study included 100 adult patients with liver cirrhosis presenting in the outpatient department of Gastroenterology, Tribhuvan University Teaching Hospital, who were selected using the non-probability consecutive sampling method. Cirrhotic patients had diagnostic criteria of liver cirrhosis by clinical (stigmatas of chronic liver disease), biochemical (impaired liver function test consistent with cirrhosis) and ultrasonographic findings (shrunken or enlarged nodular liver with increased echotexture, irregular margins and distorted architecture, with or without a dilated portal vein, thickened gallbladder wall, splenomegaly or ascites).[10] Patients who were less than 18 years of age, were unable to provide informed consent, had active or previous variceal bleeding, had received prior variceal treatment (any type) or variceal bleeding prophylaxis (including nonselective β-blocker use), had pre-existing other comorbidities (hypertension grade 2 or 3, COPD patients requiring oxygen via face mask, chronic kidney disease and heart failure NYHA class III or IV) or were pregnant were excluded from the study.

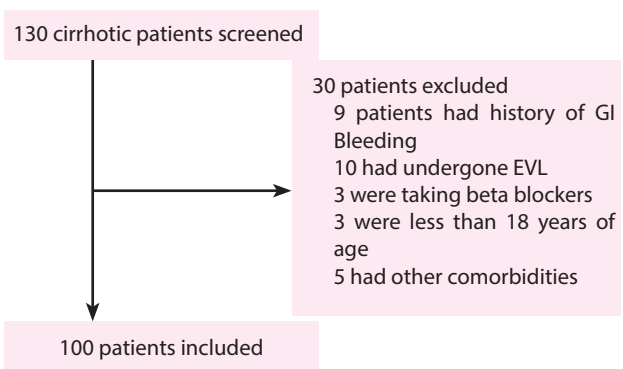

Fig 1: Study design

All patients included in the study were evaluated for clinical, hematological, biochemical and ultrasonographic parameters. Non-invasive fibrosis scores were calculated as follows:

AAR = AST (IU/L)/ALT (IU/L).[11]

APRI = (AST (IU/L)/ AST (Upper Limit of Normal) (IU/L))/Platelets (10^9/L) × 100.[12]

FIB-4 = [Age (years) × AST (IU/L)]/[Platelets (10^9/L) × ALT (IU/L)$^{1/2}$].[13]

King score = Age (years) × AST (IU/L) × INR/Platelets (10^9/L).[14]

Lok Score = - 5.56 - 0.0089 × Platelets (10^9/L)+ 1.26 × AST/ALT + 5.27 ×INR.[9]

All patients underwent EGD to evaluate for the presence and degree of esophageal varices using a Pentax Endoscope EG-2990I. UGI endoscopies were carried out mostly by the single gastroenterologist during the study period. Esophageal varices were classified into small and large varices based on Baveno consensus.[15] The presence or absence of red color signs was also noted. High-risk varices included large varices and small varices with red color signs.

The study was approved by the Institutional Review Committee of the Institute of Medicine, TUTH. Written informed consent was obtained from all patients before enrollment.

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) for Windows version 23 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean and standard deviation (SD), median and interquartile range, and proportions and 95% Confidence Interval (CI) as appropriate. A p-value of < 0.05 was considered statistically significant in all analyses. Continuous variables (such as laboratory data, fibrosis score) were compared using the Student t-test and the Mann-Whitney U test, as appropriate.

To determine test performance for prediction of EVs, a receiver operator characteristic curve was constructed and the area under the ROC curve (AUROC) was calculated. The cutoff value of the variables was determined at the point of the highest sensitivity and specificity. Sensitivity, specificity, predictive values, and likelihood ratios were calculated for these cutoff values.

Results:

Out of 130 patients initially screened, 30 patients were excluded and a hundred patients with liver cirrhosis were included. Mean age was 54.05±11.58 years. Among them, 70 were males and 30 were females. The most common age group involved was 41-65 years (72%), followed by > 65 years (15%) and 16-40 years (13%). As shown in Fig. 2, Alcoholic liver disease was the most common cause of cirrhosis, followed by chronic hepatitis B and chronic hepatitis C.

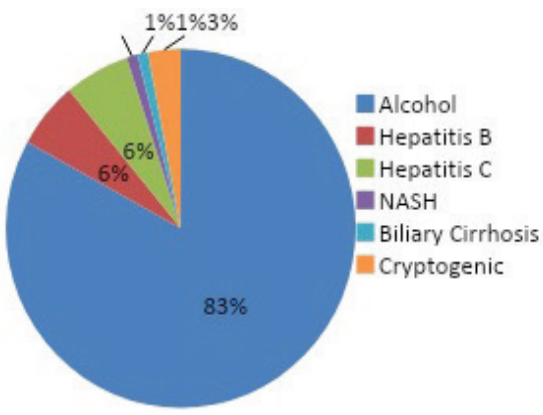

Fig. 2: Etiology of Cirrhosis of Liver

Majority of the patients belonged to Child-Turcotte Pugh Class C (62%), followed by CTP Class B (28%) and CTP Class A (10%). Seventy-seven patients (77%) had esophageal varices. Among

them 32 (41.55%) had small varices without red color signs, 15 (19.48%) had small varices with red color signs and 30 (38.96%) had large varices. Baseline demographic and clinical characteristics of the studied patients with and without varices are summarized in Table 1. Platelet count and non-invasive fibrosis scores APRI, FIB-4, Lok and King were able to discriminate patients with and without varices.

Table 1: Characteristics of patients with and without varices

Variables	Varices (n=77)	No varices (n=23)	p-value
Age (years, Mean ± SD)	52.8 ± 11.1	58.1 ± 12.4	0.330
Laboratory parameters (Mean ± SD)			
Platelets(x10^3/µL)	91.75 ± 64.73	184 ± 96.22	0.001
ALT(IU/L)	51.31 ± 31.51	46.91 ± 40.26	0.195
Total Bilirubin (µmol/L)	145.37 ± 143.82	81.26 ± 121.45	0.078
INR	2.21 ± 1.44	1.70 ± 0.70	0.155
Creatinine (µmol/L)	148.33 ± 110.20	133.62 ± 91.62	0.998
Serum Albumin (gm/L)	27.43 ± 6.07	29.44 ± 10.55	0.251
Child-Pugh score	10.29 ± 2.32	9.17 ± 2.91	0.181
MELD Sodium	25.58 ± 9.13	20.56 ± 8.65	0.495
MELD	24.20 ± 9.31	19.34 ± 8.79	0.556
Fibrosis scores (median and interquartile range)			
APRI	2.96 (1.75-4.96)	1.13 (0.99-2.08)	0.000
AAR	1.92 (1.40-3.17)	1.88 (0.88-3.15)	0.575
Lok Score	1 (0.98-1)	0.99(0.81-1)	0.049
FIB4	9.22 (6.06-16.20)	4.68 (2.38-13.42)	0.007
King	119.00 (54.96 – 244.87)	36.45(27.84-87.23)	0.003

MELD: Model for End Stage Liver Disease; Statistical analysis by student t test and the Mann-Whitney U test

By measuring AUROC score, the diagnostic accuracies of AAR, APRI, FIB-4, King and Lok scores as non-invasive predictors of EVs were studied to determine the score that would have the most clinical utility for prediction (Fig. 2). For predicting EVs, the APRI score had the greatest AUROC of 0.77(95% CI 0.64-0.91), followed by King [0.70 (95% CI 0.56-0.85)], FIB-4 [0.69 (95% CI 0.54-0.83)], Lok scores [0.62 (95% CI 0.48-0.77)] and AAR [0.54 (95% CI 0.39-0.69)].

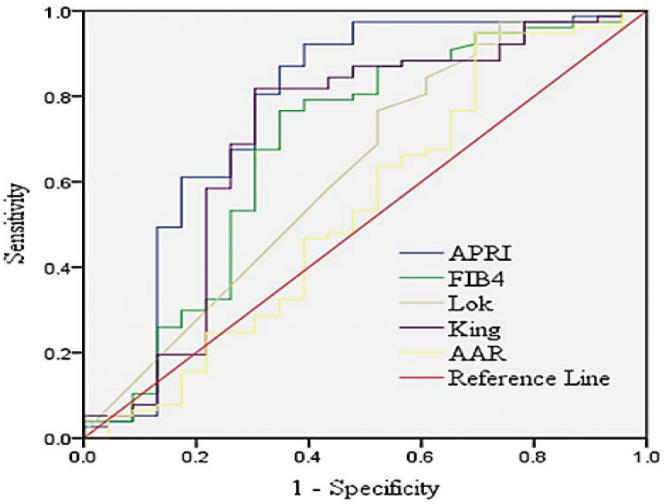

Fig. 2: Receiver operating characteristic curve of fibrosis scores to predict EVs

For predicting high-risk varices (Fig. 3), the APRI score had the greatest AUROC [0.70 (95% CI 0.60-0.81)], followed by King score [0.67 (95% CI 0.57-0.78)], FIB-4 score [0.64 (95% CI 0.53-0.75)], Lok Score [0.60 (95% CI 0.48-0.70)] and AAR [0.47(95% CI 0.36-0.80)].

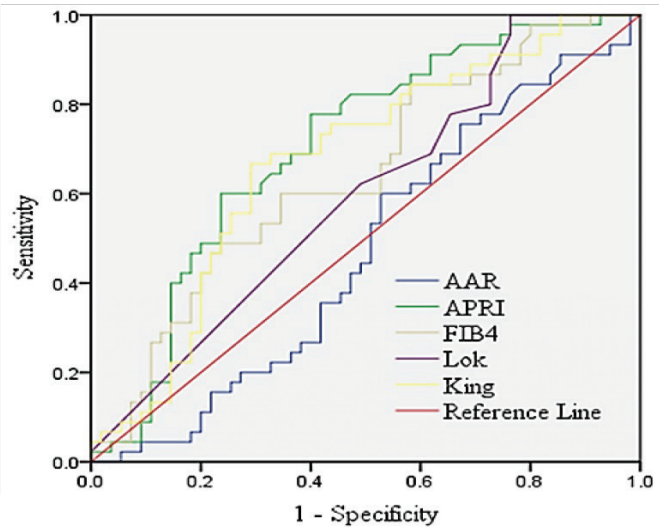

Fig 3: Receiver operating characteristic curve of fibrosis scores to predict high-risk EVs

The optimal cutoff values of the above-mentioned scores to predict the presence of esophageal varices is shown in Table 2. The APRI score had the highest diagnostic indices. At a cutoff value > 1.4, APRI had 90.9 % sensitivity,60.9 % specificity, 88.6% PPV, 66.7 % NPV and 84% accuracy for the prediction of EVs.

Table 2: Diagnostic performance of fibrosis scores for prediction of EVs

	Cutoff value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
APRI	1.4	90.9	60.9	88.6	66.7	84
AAR	1.7	61	47.8	79.7	47.8	58
Lok Score	0.97	76.6	47.8	83.1	37.9	70
FIB-4	6.4	74	65.2	87.7	42.9	72
King Score	46.5	81.8	69.6	90	53.3	79

Table 3 shows the optimal cutoff values of the above-mentioned scores to predict the presence of high-risk esophageal varices. The APRI score had the highest diagnostic indices. At a cutoff value > 2.02, APRI had 84.4% sensitivity, 45.5% specificity, 55.9% PPV, 78.1% NPV and 63% accuracy for the prediction of high-risk varices.

Table 3: Diagnostic performance of fibrosis scores for prediction of high-risk EVs

	Cutoff value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
APRI	2.02	84.4	45.5	55.9	78.1	63
AAR	1.89	51.1	49.1	45.1	55.1	50
Lok Score	0.99	62.2	50.9	50.9	62.2	56
FIB-4	8.92	60	65.5	58.7	66.7	63
King Score	93.28	68.9	67.3	63.3	72.5	68

Discussion:

Screening EGD for varices is important in the management of cirrhosis. However, EGD is an invasive procedure and is not readily accepted by patients. Therefore, there is an increasing interest in developing non-invasive methods for the prediction of EVs. As the development of portal hypertension is due to the progression of hepatic fibrosis, non-invasive fibrosis scores have been used to predict the presence of oesophageal varices in patients with cirrhosis.[2] In this study, the diagnostic accuracy of non-invasive fibrosis scores in predicting the presence of EVs and high-risk EVs was evaluated.

In this study, platelet count, APRI, FIB-4, Lok and King score were significantly able to discriminate patients with and without varices ($p< 0.5$). Adami et al.[16] also showed similar finding with platelet and APRI score.

APRI had the best performance in the prediction of EVs (AUROC=0.77) and high-risk EVs (AUROC=0.70). This finding is similar to those reported by Hassan et al.,[17] Morishita et al.[18] and Zhang et al.[19]. In this study, a cutoff value of > 1.4 was established for the presence of varices, at which sensitivity was 90.9%, specificity was 60.9% and the overall diagnostic accuracy was 84%. Likewise, a cutoff of > 2.02 was established for the presence of high-risk varices, at which sensitivity was 84.4%, specificity was 45.5% and the overall diagnostic accuracy was 63%. In a study done by Pathak et al.[20] using APRI cutoff of > 1.3, sensitivity and specificity were 75 and 64.35% for the diagnosis of EVs. However, Deng, et al.,[7] proposed that at a cutoff value of >0.87, the AUROC was 0.54 for the diagnosis of any grade EVs with 68% sensitivity, 46.2% specificity, while at a cutoff value of >0.85, the AUROC for predicting Large EVs was 0.51, 68.8% sensitivity, and 41.3% specificity.

King Score had an AUROC of 0.70 and 0.67 for the prediction of EVs and high-risk EVs respectively. The cutoff values > 46.5 and > 93.28 were identified for diagnosis of EVs and high-risk EVs with 81.8, 68.9% sensitivity and 69.6, 67.3 % specificity respectively. Hassan et al.[17] showed a cutoff value of 24.7, had an AUROC of 0.80, 80% sensitivity and 76.5% specificity, for the diagnosis of EVs. While for a cut-off value of 39.01, the AUROC was 0.78, sensitivity was 69.6% and specificity was 87.1%, for the prediction of varices needing treatment. However in the retrospective study by Deng et al.,[7] the best cutoff value for the diagnosis of EVs was 17.93, with an AUROC of 0.64, 85.3% sensitivity and 44% specificity and the best cut-off value was 24.80 for diagnosis of high-risk EVs, with an AUROC of 0.65, 97% sensitivity, and 53.6% specificity.

The AUROC for prediction of the presence of varices and high risk varices for FIB-4 were 0.69 and 0.64 respectively and the cutoff values > 6.4 and > 8.92 were identified for diagnosis of EVs and high-risk EVs with 74, 60% sensitivity and 65.2, 65.5% specificity respectively. This finding was similar to the study done by Sebastiani et al.[21] which showed similar AUROC of 0.64 and 0.63 but with different cutoff values of 3.5 and 4.3 for the prediction of EVs and large EVs respectively. However, FIB-4 showed better performance in the study done by Hassan et al. [17] where the cutoff values > 2.8 and 3.4 were used for which AUROCs were 0.80 and 0.81 for diagnosis of EVs and large EVs with 73.3, 78.3% sensitivity and 82.4, 74.2% specificity respectively.

The Lok score was proposed during the Halt-C trial.[22] The AUROC for prediction of the presence of varices and high risk varices for Lok score were 0.62 and 0.60 respectively and the cutoff values > 0.97 and > 0.99 were identified for diagnosis of EVs and high-risk EVs with 76.6, 62.2% sensitivity and 47.8, 50.9% specificity respectively. Castéra et al.[23] had demonstrated the AUROCs of 0.81 and 0.87 for the presence of EVs and large EVs respectively. Stefanescu et al. [24] showed an acceptable AUROC of 0.69 and 0.73 for the presence of EVs and large EVs for the Lok score. In a large cohort, [21] for a cutoff value of 0.9, the Lok Score had an AUROC of 0.77 for the diagnosis of EV, while for a cutoff value of 1.5 the AUROC was 0.69 for the prediction of large EVs.

In this study, AAR had the lowest performance in the prediction of EVs (AUROC =0.54) and high-risk EVs (AUROC = 0.47). The poor diagnostic accuracy of AAR in this study is similar to the findings of the study by Deng et al.,[7] which showed poor AUROCs of AAR for EVs (0.59) and large EVs (0.60). However, Castéra et al.[23] showed AUROCs of AAR for EVs (0.83) and large EVs (0.79). Hassan et al.[17] showed AUROCs of AAR for EVs (0.73) and large EVs (0.68) which is similar to the findings by Calvaruso et al.[25]

Cutoff values of non-invasive fibrosis scores for prediction of EVs and high-risk EVs score and AUROC comparing them with other investigators is summarised in Table 4.

Table 4: Cutoff values of non-invasive fibrosis scores for prediction of EVs and high-risk EVs score and AUROC comparing them with other investigators

	Investigators	Cutoff value for prediction of EVs	AUROC	Cutoff value for prediction of high risk EVs	AUROC
APRI	Our study	>1.4	0.77	>2.02	0.70
	Deng et al.[7]	>0.87	0.54	>0.85	0.51
	Hassan et al.[17]	>0.85	0.79	>1.22	0.79
	Morishita et al.[18]	>1.50	0.68	>1.62	0.67
	Zhang et al.[19]	>1.29	0.68	>1.4	0.73
AAR	Our study	>1.7	0.54	>1.89	0.47
	Calvaruso et al.[25]	>0.80	0.73	>1	0.75
	Castéra et al.[23]	≥1	0.83	≥1	0.79
	Deng et al.[7]	>1.25	0.59	>1.25	0.60
	Hassan et al.[17]	>0.67	0.73	>0.74	0.68
Lok Score	Our study	>0.97	0.62	>0.99	0.60
	Castéra et al.[23]	≥0.6	0.81	≥0.6	0.87
	Sebastiani et al.[21]	>0.9	0.77	>1.5	0.69
	Stefanescu et al.[24]	>0.62	0.69	>0.79	0.73
FIB-4	Our study	>6.4	0.69	>8.92	0.64
	Hassan et al.[17]	>2.8	0.80	>3.4	0.81
	Sebastiani et al.[21]	>3.5	0.64	>4.3	0.63
King Score	Our study	>46.5	0.70	>93.28	0.67
	Deng et al.[7]	>17.93	0.64	>24.80	0.65
	Hassan et al.[17]	>24.7	0.80	>39.01	0.78

Conclusion:

In conclusion, the APRI score showed moderate diagnostic accuracy in predicting the presence of varices and high-risk varices. Whereas, other studied scores had low diagnostic accuracy. The APRI score can help select a patient for endoscopy. However, the studied non-invasive fibrosis scores might not be adequate to replace the use of EGD.

Conflict of interest:

None declared

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