Role of Novel Scores in Prediction of Esophageal Varices in Patients with Liver Cirrhosis

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Background and study aim: Early detection of esophageal varices (EVs) is crucial to prevent variceal bleeding. Although endoscopy remains the gold standard for diagnosing EVs, non-invasive scores were suggested as alternative tools to predict their presence. This research aimed to evaluate the diagnostic performance of several novel non-invasive scores in predicting EVs in liver cirrhosis cases.

Patients and Methods: This cross-sectional study included 110 cirrhotic cases from December 2023 till December 2024. Cases were categorized into 2 groups according to Esophagogastroduodenoscopy (EGD) results: Group 1 with EVs (n=61) and Group 2 without EVs (n=49). Patients underwent clinical assessment, laboratory testing, and abdominal ultrasound. Several non-invasive scores were calculated and analyzed for their association with EVs confirmed by endoscopy. Statistical comparisons, correlation analyses, and Receiver operating characteristic (ROC) curve analysis were applied to evaluate the predictive accuracy of each score.

Results: Among the 110 patients, 61 (55.5%) had esophageal varices. Novel non-invasive scores like the S-index, PALPI, PAPAS, King score, Lok score, and AARPRI illustrated significantly greater values in cases with EVs and the most marked differences were observed in the S-index and PAPAS scores. The S-index illustrated the greatest diagnostic accuracy with an AUC of 0.914 at a cutoff value of 1.05, achieving 90.2% sensitivity and 87.8% specificity.

Conclusion: Non-invasive scores, particularly the S-index and PAPAS, are effective tools for predicting EVs in cirrhotic cases and may reduce the need for screening endoscopy in low-risk individuals.

INTRODUCTION

Liver cirrhosis (LC) is a progressive condition resulting from chronic hepatocellular injury, characterized by fibrosis, regenerative nodules, and increased intrahepatic vascular resistance [1]. This resistance leads to portal hypertension (PH), caused by both architectural distortion of hepatic sinusoids and an imbalance between vasodilator and vasoconstrictive mediators [2].

One of the major complications of PH is the development of portosystemic collaterals, particularly EVs, which are present in about fifty percent of cases had cirrhosis and are closely correlated with the degree of liver dysfunction. Esophageal variceal bleeding (EVB) occurs in about 10-30% of cases yearly and is related to a high short-term rate of the death of 17–57% [3–5].

The hepatic venous pressure gradient (HVPG) is deemed the gold standard for diagnosing and assessing the PH degree [6, 7]. Meanwhile, EGD remains the standard tool for detecting EVs. Nevertheless, hepatic venous pressure gradient measurement and endoscopy are invasive, expensive, and not ideal for routine screening especially since less than half of cirrhotic patients may actually have varices. Because the development of EVs is closely correlated with liver fibrosis and raised intrahepatic resistance, several non-invasive fibrosis markers (NFMs) like the fibrosis-4 index (FIB-4), AST/ALT ratio (AAR), AST-to-platelet ratio index (APRI), model for end-stage liver disease (MELD), King score, in addition Fibrosis Index have been proposed as alternatives for predicting EVs [8–14].

This study aimed to evaluate the role of these non-invasive novel scores as S-index, Platelet-Albumin-Bilirubin Index (PALBI), Platelet-Albumin Prothrombin-INR-Serum Bilirubin Score (PAPAS), King Score, Lok Score, and the AST/ALT Ratio to Platelet Ratio Index (AARPRI) in predicting the presence of esophageal varices in cirrhotic patients.

PATIENTS AND METHODS

Study design and Subjects

This cross-sectional study has been conducted on 110 cases diagnosed with liver cirrhosis. The cases have been chosen from the outpatient and/or inpatient departments of Tropical Medicine at Menoufia University Hospital between December 2023 and December 2024. Eligible participants were adults aged eighteen years or older with liver cirrhosis of any etiology, diagnosed depended on clinical presentation, laboratory investigations, in addition to ultrasonographic results. Cases who were younger than 18 years, had a portosystemic shunt operation, a history of hepatic surgery, liver metastases, or hepatocellular carcinoma have been excluded from this study. Moreover, cases had thrombosis of any portion of the portal venous system, previous or current myeloproliferative disorders, earlier splenectomy or a history of transjugular intrahepatic portosystemic shunt (TIPS) were excluded. Cases have been classified into 2 groups regarding the absence or existence of EVs confirmed by EGD. Group 1 involved 61 cirrhotic cases had EVs, while Group 2 consisted of 49 cirrhotic patients without EVs.

Clinical Assessment

Every case has been subjected to complete history taking, involving gender, age, smoking status, as well as body mass index (BMI). Special attention was given to the history of liver-related symptoms like abdominal pain, ascites, jaundice, hepatic encephalopathy, hematemesis, melena, fever, and peripheral edema. Comorbid conditions were also noted. Physical examination included general assessment for signs of liver dysfunction (e.g., pallor, jaundice, spider nevi, palmar erythema, flapping tremors, and lower limb edema) and local abdominal examination for ascites, hepatosplenomegaly, caput medusae, and any other relevant findings.

Laboratory Investigations

Routine laboratory tests have been carried out for all cases, involving complete blood count (CBC), kidney function tests (blood urea and serum creatinine), liver function tests (ALT, AST, alkaline phosphatase, albumin, total and direct bilirubin, GGT), coagulation profile (INR, prothrombin time), and. Serological tests for viral hepatitis (HBsAg and anti-HCV) were also done .

The Child-Pugh score was utilized to classify the degree of hepatic cirrhosis, incorporating clinical and laboratory variables (Figure 1).

Radiological Evaluation

Abdominal ultrasonography was performed in all patients to assess liver size and echotexture, spleen size, portal vein diameter, and the presence of ascites. When a focal hepatic lesion was detected, triphasic abdominal CT was performed to exclude hepatocellular carcinoma or other focal lesions.

Esophagogastroduodenoscopy

EGD has been conducted in all cases to detect esophageal varices. The varices have been graded as small, medium, or large according to the Baveno criteria [15]. The existence of red signs and other endoscopic findings were also recorded.

Non-Invasive Scoring Systems

Several non-invasive indices have been determined for every case to assess their utility in expecting the existence of esophageal varices. These scoring systems involved the Model for End-Stage Liver Disease (MELD), AST to Platelet Ratio Index (APRI), AST/ALT Ratio (AAR), Fibrosis-4 (FIB-4) Score, S-index, Platelet-Albumin-Bilirubin Index (PALBI), Platelet-Albumin Prothrombin-INR-Serum Bilirubin Score (PAPAS), King Score, Lok Score, and the AST/ALT Ratio to Platelet Ratio Index (AARPRI). Each score was computed based on relevant clinical and laboratory parameters, such as patient age, platelet count, levels of liver enzymes (ALT and AST), international normalized ratio (INR), serum albumin, and serum bilirubin .

Statistical Data Analysis :

The gathered information has been tabulated and statistically examined utilizing the Statistical Package for the Social Sciences (SPSS), version 26 (IBM Corp., Armonk, NY, United States of America), on an IBM-compatible computer. Descriptive statistics included presentation of qualitative data as numbers and percentages, while quantitative data were expressed as means and standard deviations (SD) for normally distributed variables, and as medians with interquartile ranges (IQR) and ranges (minimum–maximum) for non-normally distributed parameters. Analytical statistics included the Pearson Chi-squared test (χ^2) for comparing qualitative variables between study groups, and the Fisher's exact test (FE) for 2×2 tables when expected cell counts were below five. For quantitative parameters, the Student's t-test has been utilized to compare normally distributed information, while the Mann–Whitney U test has been applied for non-normally distributed data. The diagnostic performance of non-invasive scores has been evaluated using ROC curve analysis, where sensitivity (true positives) was plotted on the Y-axis and 1–specificity (false positives) on the X-axis across various cutoff values. The area under the curve (AUC) has been applied to assess the diagnostic accuracy of the non-invasive scores. A p-value of below 0.05 has been deemed statistically significant.

Table 1: Non-Invasive Scores Used for Predicting Esophageal Varices

Score Name	Formula
MELD (Model for End-Stage Liver Disease)[16]	9.57 × ln (Creatinine) + 3.78 × ln(Total Bilirubin) + 11.2 × ln(INR) + 6.43
APRI (AST to Platelet Ratio Index) [17]	(AST / upper limit of normal) × 100 / Platelet count (10^9/L)
AAR (AST/ALT Ratio) [17]	aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio
FIB-4 (Fibrosis-4 Index)[18]	(Age × AST) / (Platelet count × √ALT)
S-index [19]	1000 × gamma glutamyl transferase / (Platelet count × Albumin²)
PALBI (Platelet-Albumin-Bilirubin Index)[20]	2.02 × $\log_{10}$(Bilirubin) - 0.37 × ($\log_{10}$ Bilirubin)² - 0.04 × Albumin - 3.48 × $\log_{10}$(Platelets) + 1.01 × ($\log_{10}$ Platelets)²
PAPAS Score [21]	0.0255 + (0.0031 × Age) + (0.1483 × log(ALP)) + (0.004 × log(AST)) + (0.0908 × log(AFP + 1)) - (0.028 × log(Platelet count))
King Score [22]	(Age × AST × INR) / Platelet count
Lok Score [23]	-5.56 – 0.0089 × Platelets + 1.26 × (AST/ALT) + 5.27 × INR
AARPRI (AST to ALT Ratio / Platelet Ratio Index) [24]	AAR / (Platelet count / 150)

ALT: alanine aminotransferase, AST: aspartate transferase, PC: prothrombin concentration, INR: international normalised ratio, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, AFP: alpha-Fetoprotein.

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RESULTS

A total of 110 cases with liver cirrhosis have been involved in this research. They were selected from a larger cohort of 156 cirrhotic cases and 46 cases were excluded based on exclusion criteria .

Table 2 demonstrates esophageal varices in relation to sociodemographic data and co-morbid diseases of the studied patients. Most of the cases were males (73.6%), their mean age was 50.48 ±11.40, the mean BMI was 26.97 ±3.75 and 69.1 % of the patients were smokers. The most frequent comorbidity observed was diabetes mellitus, existing in 43.6 percent of cases and hypertension has been documented in 16.4% of patients. There was a highly statistically significant variance among the examined groups according to age (p value equal 0.001) and BMI (p value <0.001). The mean age was higher among patients with EVs (53.64 ±9.45) and the mean BMI was higher among cirrhotic patients with EVs (28.90 ±3.44). Moreover, there was no statistically significant variance between the examined groups regarding co-morbid diseases (p value above 0.05).

According to the etiology of cirrhosis in the studied cases. The majority of cases had cirrhosis because of Hepatitis C virus (HCV), accounting for 76.3% of the cases (Supp. table 1).

Regarding the relation between esophageal varices and clinical data of the examined cases. There was a greatly statistically significant variance among the examined groups according to systolic blood pressure (SBP), pulse, temperature, lower limb edema and palpable spleen (p value below 0.001) and there was a statistically significant variance among the examined groups regarding pallor (p value: 0.002), jaundice (p value: 0.037) as well as ascites (p value: 0.011) (Supp. table 2).

Table 3 shows esophageal varices in relation to laboratory findings between the examined cases. There was a greatly statistically significant variance among the examined groups according to hemoglobin, TLC, platelets, AST, ALT, direct bilirubin, total bilirubin, INR, serum Albumin, blood Urea, ALP, GGT and AFP (p value below 0.001), However there was a statistically insignificant variance among the examined groups regarding serum creatinine (p value: 0.369).

Endoscopic finding among the studied patients showed that esophageal varices were present in 61 patients, with 26.3% having small and medium-sized varices (grade I-II) and 29.1% having large varices (grade III-IV). Among those with esophageal varices, 48.1% had isolated varices, while 2.7% had GOV 1 and 4.5% had GOV 2 (Supp. Table 3).

In Table 4, all assessed scoring systems showed statistically significant differences among the two groups, with P-values < 0.001, indicating a strong correlation among elevated scores and the existence of EVs. Cases had EVs had significantly greater mean values for all scores, including MELD, APRI, AAR, S-index, FIB-4, PAPAS, Lok score, King score, PALBI as well as AARPRI. The most marked differences were observed in the S-index and PAPAS scores, with Student t test values of 16.038 and 13.349, respectively, reflecting their potential as strong discriminatory markers for the presence of EVs.

Table 5 presents that, there was significant difference among large (grade III-IV) and small/medium (grade I-II) EVs across all examined scores, including MELD, APRI, AAR, FIB-4, S-index, PALBI, PAPAS, King score, Lok score, and AARPRI, as indicated by the P-values (< 0.05). Patients with large EVs (grade III-IV) exhibited significantly higher mean values for MELD, APRI, AAR, S-index, FIB-4, PAPAS, Lok score, King Score, PALBI and AARPRI. The most marked differences were observed in the Lok score and King score, with t-values of 9.428 and 11.481, respectively, indicating their strong discriminative power.

Table 6 provides the diagnostic accuracy of non-invasive scores to expect esophageal varices among the studied cases. The S-index and PAPAS score exhibited the highest sensitivity (96.72% and 98.36%, respectively), indicating strong potential in correctly identifying patients with esophageal varices. In terms of specificity, the S-index again showed the best result (95.92%), followed closely by AAR (89.80) and APRI (89.80). The PAPAS and S-index scores had the highest overall accuracy (96.8% and 96.8%, respectively), supported by their excellent AUC values (both 0.968), suggesting they are reliable predictors. Conversely, traditional scores like MELD and King score showed relatively lower sensitivity and AUC values, indicating less diagnostic power in this

context. Moreover, scores such as Lok and PALBI also demonstrated good performance with high specificity and accuracy (89.9% and 93.3%, respectively) (Figure 2).

Table 7 evaluates the diagnostic accuracy of non-invasive scores between different classes of EVs. The APRI score showed outstanding performance, with a sensitivity of 96.87%, specificity of 96.55%, the highest overall accuracy (99.2%), supported by an excellent AUC of 0.992, making it a highly reliable marker. The Lok score also demonstrated exceptional diagnostic power, achieving 100% sensitivity and 98.6% specificity, with an accuracy of 98.7% and a high AUC of 0.987. Likewise, the King score exhibited high sensitivity and specificity (93.75% and 95.10%, respectively), with an accuracy of 95.8% and an AUC of 0.958 .

Other scores such as PALBI, S-index, and PAPAS also performed well, all with specificity above 90% and high predictive values. In contrast, traditional scores like MELD, AAR, and FIB-4 showed lower AUCs (ranging from 0.760 to 0.777), suggesting limited utility in discriminating between variceal classes (Figure 3).

Table (2): Esophageal varices in relation to sociodemographic data & co-morbid diseases of the studied cases (number equal 110)

Variable	Total (110)	Esophageal varices		Test of significance	P value
		Present (n=61)	**Absent (n=49)**		
		No. (%)	**No. (%)**		
Sex **Male** **Female**	 81 (73.6) 29 (26.4)	 42 (68.9) 19 (31.1)	 39 (79.6) 10 (20.4)	$\chi2$=1.61	0.292
Age (Years) **Mean ±SD** **Range**	 50.48 ±11.40 20-68	 53.64 ±9.45 22-68	 46.55 ±12.45 20-59	t=3.30	0.001*
BMI (Kg/m^2) **Mean ±SD** **Range**	 26.97 ±3.75 18-35	 28.90 ±3.44 20-35	 24.57 ±2.55 18-28	t=7.34	<0.001**
Smoking **Smoker** **Non-smoker**	 76 (69.1) 34 (30.9)	 41 (67.2) 20 (32.8)	 35 (71.4) 14 (28.6)	$\chi2$=0.23	0.789
DM **Present** **Absent**	 48 (43.6) 62 (56.4)	 23 (37.7) 38 (62.3)	 25 (51.0) 24 (49.0)	$\chi2$= 1.45	0.228
Hypertension **Present** **Absent**	 18 (16.4) 92 (83.6)	 7 (11.5) 54 (88.5)	 11 (22.4) 38 (77.6)	$\chi2$= 1.66	0.198
AF **Present** **Absent**	 5 (4.5) 105 (95.5)	 3(4.9) 58(95.1)	 2(1.9) 47(98.1)	$\chi2$= 0.0	1.000
Bronchial Asthma **Present** **Absent**	 3 (2.7) 107 (97.3)	 2(3.3) 59(96.7)	 1(2.04) 48(98)	$\chi2$= 0.0	1.000
COPD				$\chi2$= 0.97	0.325

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Present **Absent**	3 (2.7) 107 (97.3)	3(4.9) 58(95.1)	0(0) 49(100)		
Heart failure **Present** **Absent**	12 (10.9) 98 (89.1)	7(11.5) 54(88.5)	5(10.2) 44(89.8)	$\chi2$= 0.0	1.000
Hypothyroidism **Present** **Absent**	5 (4.5) 105 (95.5)	2(3.3) 59(96.7)	3(6.1) 46(93.9)	$\chi2$= 0.063	0.802
RA **Present** **Absent**	2 (1.8) 108 (98.2)	2(3.3) 59(96.7)	0(0) 49(100)	$\chi2$= 0.315	0.575
SLE **Present** **Absent**	2 (1.8) 108 (98.2)	1(1.6) 60(98.4)	1(2.04) 48(98)	$\chi2$= 0.0	1.000

BMI: Body mass index, DM: Diabetes Mellitus, AF: Atrial fibirillation, RA: Rheumatoid arthritis, COPD: Chronic obstructive pulmonary disease, SLE: Systemic lupus Erythromatosis, *: Statistically significant, **: Highly significant, SD: Standard deviation, $\chi2$: Chi-squared test, t: Student t test.

Table (3): Esophageal varices in relation to laboratory results among the examined cases (n=110)

Variable	Esophageal varices		Test of significance	P value
	Present (n=61)	**Absent (n=49)**		
	Mean ±SD	**Mean ±SD**		
Hemoglobin (gm/dl**)**	9.66 ±1.17	12.17 ±0.64	t=13.42	<0.001*
TLC (10^3)	9.19 ±2.39	4.23 ±0.88	t=15.03	<0.001*
Platelets (10^3)	75.85 ±9.96	175.47 ±42.28	t=17.82	<0.001*
ALT (IU)	80.41 ±20.62	48.59 ±5.08	t=11.63	<0.001*
AST (IU)	95.47 ±9.49	38.84 ±10.61	t=29.16	<0.001*
Total bilirubin (mg/dl)	2.78 ±1.09	1.92 ±1.11	U=1.69	<0.001*
Direct bilirubin (mg/dl)	1.23 ±0.56	0.71 ±0.39	U=5.12	<0.001*
Serum Albumin(mg/dl)	2.37 ±0.67	2.79 ±0.39	t=3.89	<0.001*
PC %	43.82 ±14.36	55.34 ±7.52	t=5.08	<0.001*
INR	1.72 ±0.31	1.43 ±0.18	t=6.18	<0.001*
Urea (mg/dl)	70.18 ±15.31	55.36 ±15.61	t=4.99	<0.001*
Creatinine (mg/dl)	1.34 ±0.18	1.31 ±0.14	t=0.90	0.369

ALP (IU/L)	118.90 ±27.04	95.07 ±6.47	t=6.66	<0.001*
GGT (IU/L)	49.61 ±6.93	43.02 ±7.10	t=4.91	<0.001*
AFP (ng/ml)	4.20 ±1.74	1.26 ±0.41	U=7.60	<0.001*

*: Statistically significant, t: Student t test, U: Mann-Whitney U test, TLC: Total Leukocyte Count, ALT: Alanine aminotransferase, AST: Aspartate transferase, PC: Prothrombin Concentration, INR: International normalised ratio, ALP: Alkaline Phosphatase, GGT: Gamma-glutamyl transferase, AFP: Alpha-Fetoprotein.

Table (4): Esophageal varices in relation to non-invasive scores among the studied patients (n=110)

	Presence of EVs						T-Test	
	Present (n=61)			**Absent (n=49)**				
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**t**	**P-value**
MELD	17.344	±	2.768	14.265	±	2.556	5.998	<0.001*
APRI	2.301	±	0.443	1.776	±	0.252	7.397	<0.001*
AAR	1.207	±	0.220	0.801	±	0.223	9.591	<0.001*
FIB-4	6.053	±	1.811	3.625	±	1.129	8.188	<0.001*
S-index	74.062	±	4.831	51.256	±	9.719	16.038	<0.001*
PALBI	-2.131	±	0.332	-2.754	±	0.284	10.423	<0.001*
PAPAS	1.521	±	0.074	1.225	±	0.153	13.349	<0.001*
King score	46.156	±	13.906	30.040	±	8.516	7.108	<0.001*
Lok score	3.592	±	1.070	1.958	±	0.610	9.519	<0.001*
AARPRI	3.785	±	0.552	2.921	±	0.604	7.830	<0.001*

EVs: Esophageal varices, *: Statistically significant, t: Student t test, SD: Standard deviation.

Table (5): Different classes of Esophageal varices in relation to non-invasive scores among the studied patients (n=61)

	Classes of EVs						T-Test	
	Large (grade III-IV) (n=32)			**Small and medium sized (grade I-II) (n=29)**				
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**t**	**P-value**
MELD	18.344	±	3.288	16.241	±	1.431	3.179	0.002*
APRI	2.654	±	0.257	1.911	±	0.218	12.125	<0.001*
AAR	1.275	±	0.273	1.133	±	0.098	2.651	0.010*
FIB-4	6.871	±	2.049	5.150	±	0.880	4.183	<0.001*
S-index	75.758	±	5.937	72.191	±	2.019	3.076	0.003*
PALBI	-1.899	±	0.257	-2.387	±	0.182	8.478	<0.001*
PAPAS	1.559	±	0.069	1.480	±	0.054	4.997	<0.001*
King score	56.335	±	9.986	34.924	±	7.410	9.428	<0.001*
Lok score	4.432	±	0.603	2.666	±	0.596	11.481	<0.001*
AARPRI	4.006	±	0.454	3.541	±	0.554	3.594	0.001*

EVs: Esophageal varices**,** t: Student t test**,** SD: Standard deviation**.**

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Table (6): Diagnostic accuracy of non-invasive scores to expect esophageal varices among the studied cases (n=110)

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
MELD	>15	78.69	83.67	85.7	75.9	79.6%	0.796
APRI	>1.99	70.49	89.80	89.6	71.0	83.3%	0.833
AAR	>1.02	80.33	89.80	90.7	78.6	89.6%	0.896
FIB-4	>4.8	73.77	85.71	86.5	72.4	87.4%	0.874
S-index	>68	96.72	95.92	96.7	95.9	96.8%	0.968
PALBI	>-2.54	86.89	85.71	88.3	84.0	93.3%	0.933
PAPAS	>1.36	98.36	87.76	90.9	97.7	96.8%	0.968
King score	>34.32	75.41	75.51	79.3	71.2	83.4%	0.834
Lok score	>2.25	88.52	77.55	83.1	84.4	89.9%	0.899
AARPRI	>3.21	77.05	81.63	83.9	74.1	83.4%	0.834

AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value.

Table (7): Diagnostic accuracy of non-invasive scores between different classes of EVs (n=61)

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
MELD	>17	78.12	86.21	86.2	78.1	77.7%	0.777
APRI	>2.23	96.87	96.55	96.9	96.6	99.2%	0.992
AAR	>1.25	71.87	93.10	92.0	75.0	77%	0.770
FIB-4	>6.8	68.75	100.00	100.0	74.4	76%	0.760

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S-index	>74.2	84.37	93.10	93.1	84.4	88%	0.880
PALBI	>-2.1	81.25	100.00	100.0	82.9	93.7%	0.937
PAPAS	>1.53	75.00	93.10	92.3	77.1	86.4%	0.864
King score	>43	93.75	93.10	93.7	93.1	95.8%	0.958
Lok score	>3.4	100.00	89.66	91.4	100.0	98.7%	0.987
AARPRI	>4.1	71.87	93.10	92.0	75.0	84.3%	0.843

AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value.

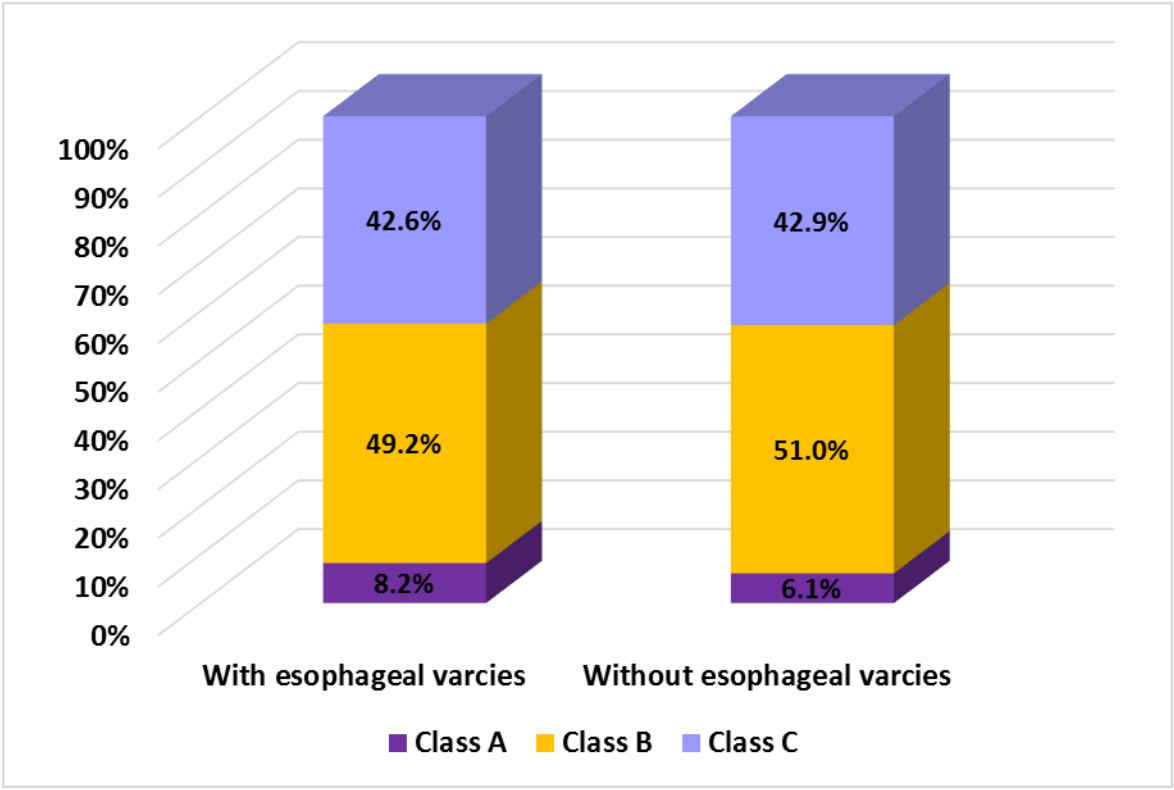

Figure (1): Child classification in relation to esophageal varices.

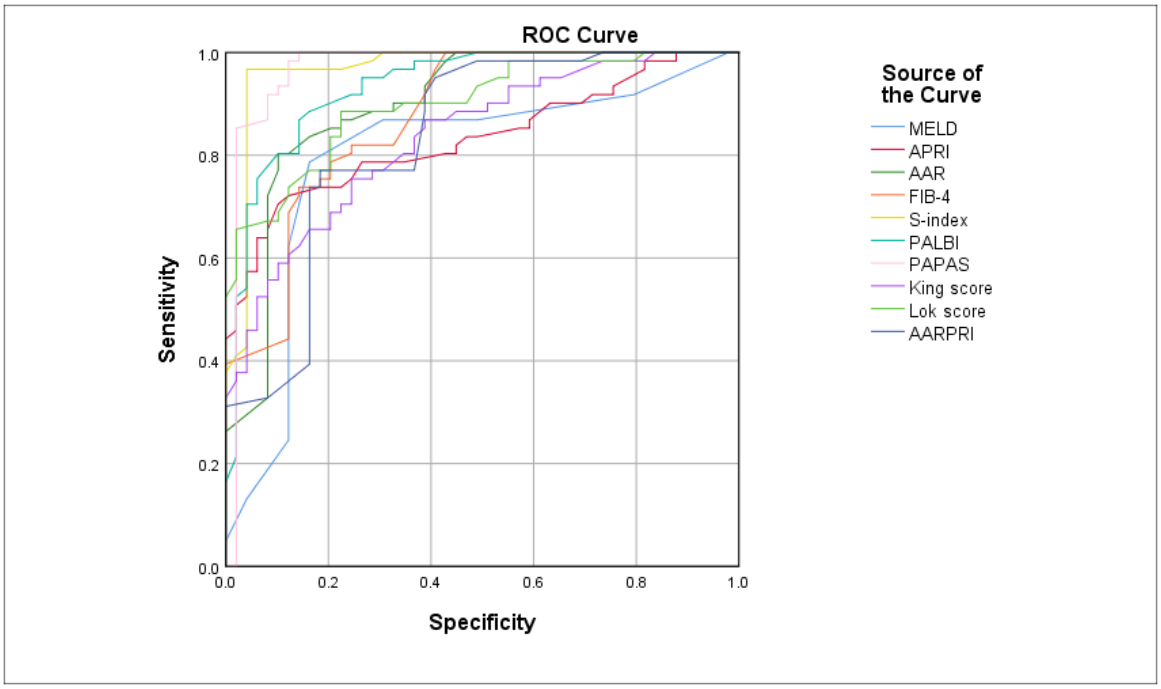

Figure (2): Roc curve of non-invasive scores in predication of esophageal varices.

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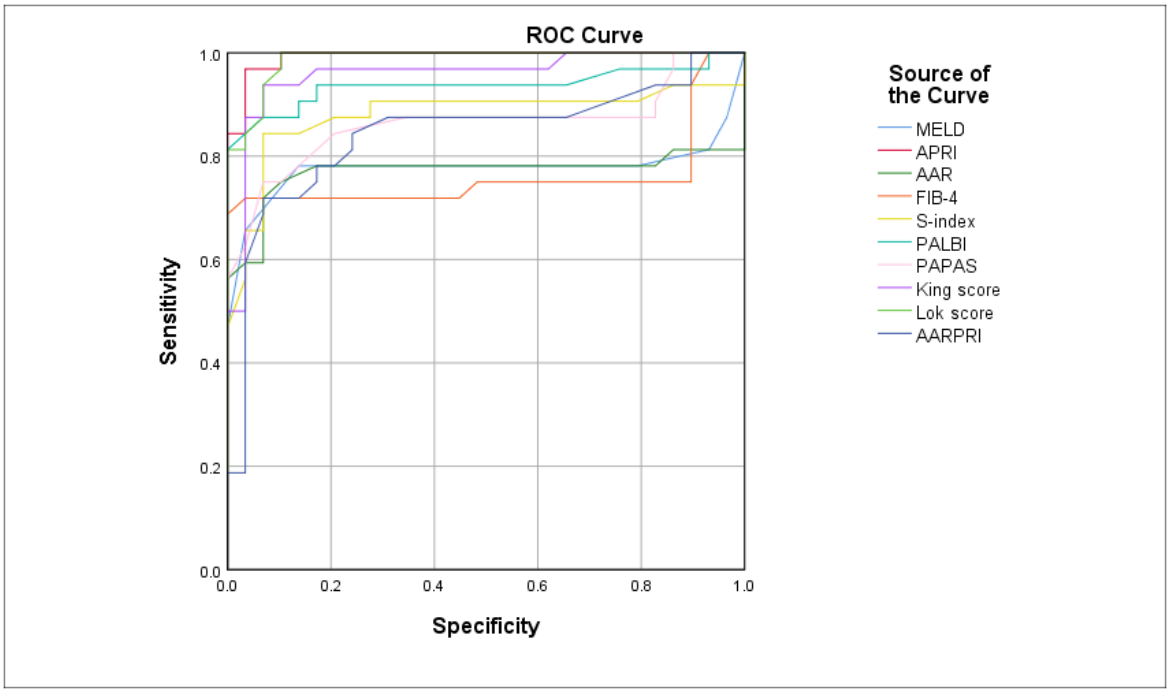

Figure (3): Roc curve of non-invasive scores between different classes of EVs.

DISCUSSION

Esophageal varices are one of the majority serious complications of portal hypertension in cases had liver cirrhosis, carrying a great risk of death and morbidity because of potential hemorrhage. Early detection and risk stratification of varices are crucial to guide prophylactic therapy and prevent life-threatening hemorrhagic events [25]. While endoscopy remains the gold standard for diagnosing esophageal varices, it is invasive, costly, and frequently poorly tolerated by cases. As an outcome, there is growing interest in the utility of non-invasive markers that can accurately predict the degree and existence of varices without the required for endoscopic screening [26 .[

Identifying reliable, non-invasive predictors can improve patient care by minimizing unnecessary procedures, enabling earlier intervention, and allocating healthcare resources more efficiently. Therefore, several scoring systems have been proposed and evaluated across diverse patient populations, aiming to establish practical and accurate non-endoscopic alternatives [27]. This research aimed to validate the role of non-invasive novel scores in prediction of esophageal varices in cases had liver cirrhosis.

Regarding to the esophageal varices in relation to sociodemographic data and comorbid diseases of the studied patients, the present investigation demonstrated a highly statistically significant association among the presence of esophageal varices and both higher age (p equal 0.001) and increased BMI (p below 0.001). These outcomes agreed with Enomoto et al., who observed that cases had gastroesophageal varices had significantly higher BMI values, with a mean BMI of 24.8 ± 3.6 kilograms per square meter in comparison with 22.9 ± 3.1 kilograms per square meter in those without varices (p below 0.01). This supports the idea that increased visceral adiposity may contribute to elevated portal pressure through hepatic steatosis and systemic inflammation, even in compensated cirrhosis [28].

Supporting this association, Mueller, reported that patients with early liver injury had significantly elevated sinusoidal pressure (7.3 ± 1.1 mmHg) compared to healthy controls (4.2 ± 0.8 mmHg), and linked this elevation to increased BMI and hepatic steatosis [29]. In addition to, Ryou et al., who emphasized that increased BMI contributes to hepatic steatosis and elevated portal venous pressure, with portal hypertension occurring in up to 50% of cases had nonalcoholic fatty liver disease (NAFLD), thereby increasing the risk of esophageal varices even in the absence of cirrhosis [30]. Conversely these results disagreed with Eslam et al., who stated that diabetes mellitus was significantly related to the existence of esophageal varices, with a prevalence of 38% among cases had varices in comparison with 21% without varices (p below 0.01). However, BMI alone was not found to be an independent predictor. They emphasized that insulin resistance and diabetes-related microvascular changes may contribute more directly to portal hypertension and variceal formation than body mass alone [31].

According to the esophageal varices in correlation with clinical data of the studied cases, the current research revealed that the existence of esophageal varices was significantly related to lower systolic blood pressure, increased pulse rate, elevated temperature, lower limb edema, palpable spleen, and more advanced ascites ($p < 0.001$). Significant associations were also noted with pallor (p equal 0.002), jaundice (p equal 0.037), and the degree of ascites (p equal 0.011). These outcomes in line with ElNaggar et al., who discovered that palpable spleen and splenic diameter >15 cm were significantly correlated with the existence of esophageal varices (p value below 0.001). Additionally, ascites and lower limb edema were more commonly detected in cases with varices, suggesting advanced portal hypertension. The study emphasized that simple bedside clinical findings such as palpable spleen and existence of ascites could serve as non-invasive indicators for variceal screening in cirrhotic cases [32]. In addition to, Kumar et al., who discovered that the existence of esophageal varices in cirrhotic patients was significantly associated with clinical signs such as splenomegaly (present in 92% of cases had varices), ascites (in 76%), and pallor (in 70%) [33]. However, these results disagreed with Agha et al., found no significant correlation among splenomegaly or ascites and the existence of esophageal varices ($p > 0.05$). Their findings suggested that clinical signs such as splenic enlargement or ascites may not reliably predict varices without incorporating laboratory parameters. This discrepancy might be clarified by variances in diagnostic criteria or measurement techniques for splenomegaly and ascites used in their study compared to the current one [34].

According to the esophageal varices in relation to laboratory findings between the examined patients, the present study revealed a highly statistically significant association among the existence of esophageal varices and lower hemoglobin, serum albumin, platelet count, prothrombin concentration, as well as elevated TLC, liver enzymes (ALT, AST, ALP, GGT), bilirubin levels, INR, urea, and AFP ($p < 0.001$). These Findings agreed with Cyriac et al., who demonstrated that mean platelet count has been significantly lower in cases had varices ($89 \times 10^3/\mu L$ vs. $154 \times 10^3/\mu L$, $p < 0.001$), hemoglobin was reduced (10.4 ± 1.8 vs. 11.8 ± 2.1 g/dL, $p = 0.004$), and albumin levels were lower (2.6 ± 0.4 against 3.1 ± 0.5 g/dL, p below 0.001). Also, AST and total bilirubin were significantly greater, and INR was elevated in patients with varices. This indicates that laboratory markers reflecting cytopenia and hepatic synthetic dysfunction are useful non-invasive predictors of esophageal varices, supporting their potential role in screening and risk stratification in cirrhotic populations [35]. Similarly, El-Daly et al., observed a strong inverse association between platelet count and variceal grade among cases had chronic hepatic illness. Their results illustrated that cases had large varices had a significantly lower mean platelet count ($80 \times 10^3/\mu L$) compared to those with small varices ($120 \times 10^3/\mu L$), with a significant p-value of <0.001. This supports the use of thrombocytopenia as a surrogate marker for variceal severity and portal hypertension progression [36]. In contrast, these results disagreed with Abbas et al., who found that although thrombocytopenia was significantly associated with the existence and grade of esophageal varices (mean platelet count: $78 \times 10^3/\mu L$ in patients with large varices vs. $142 \times 10^3/\mu L$ in those without varices, $p < 0.001$), elevated AFP and GGT alone were not strong independent predictors. Specifically, mean AFP

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was 3.1 ± 1.9 ng/mL in variceal patients vs. 2.7 ± 1.6 ng/mL in non-variceal (p = 0.09) and GGT levels showed no significant difference (p equal 0.12). This recommends that while cytopenia remains a strong marker, dependance on individual biochemical parameters like AFP or GGT may be insufficient, emphasizing the importance of using combined clinical, endoscopic, and laboratory models for accurate prediction and staging of esophageal varices [37].

According to the esophageal varices in relation to non-invasive scores among the studied patients, the present study revealed that all evaluated non-invasive scores involving MELD, FIB 4, AAR, APRI, S index, PALBI, PAPAS, King's score, Lok score, and AARPRI were significantly greater in cases had esophageal varices in comparison with those without (p < 0.001). The most pronounced differences were noted in the S index and PAPAS scores. These outcomes in line with Glisic et al., who illustrated that the Lok score (AUC = 0.81) and FIB-4 score (AUC = 0.79) had strong predictive accuracy for identifying esophageal varices in cirrhotic cases. This indicates that non-invasive markers reflecting liver fibrosis and portal hypertension can effectively substitute for early endoscopic screening in resource-limited settings [38]. Additionally, Agbim et al., reported that non-invasive serum markers and elastography showed diagnostic accuracies ranging from 70% to 85% in assessing liver fibrosis and portal hypertension, supporting their clinical utility in predicting variceal presence [39]. However, these results disagreed with Kwape et al., that although PALBI, APRI, and FIB-4 scores were significantly greater in cases had esophageal varices, their individual predictive performance was suboptimal in compensated cirrhosis, with sensitivities below 65% and AUC values ranging from 0.62 to 0.70. This suggests that non-invasive lab scores may have limited standalone utility in early-stage cirrhosis, and their diagnostic accuracy may vary based on disease severity and scoring thresholds [40].

According to the different classes of esophageal varices in relation to non-invasive scores among the studied patients, the present study revealed that all non-invasive scores—including MELD, FIB-4, AAR, APRI, S-index, PALBI, PAPAS, King score, Lok score, and AARPRI—were significantly higher in cases had large esophageal varices (grade III–IV) in comparison with those with small or medium varices (grade I–II), with the most prominent differences observed in King and Lok scores. These results agreed with Ebada et al., that both Lok score and FIB-4 were significantly elevated in cases with grade III–IV varices, with mean Lok scores of 3.4 ± 0.9 in large varices versus 2.1 ± 0.7 in small varices (p < 0.001), and FIB-4 scores of 5.8 ± 1.6 versus 3.9 ± 1.2 (p < 0.001). These scores can be used to non-invasively predict variceal severity, supporting their role in clinical risk stratification and endoscopic prioritization [41]. However, this finding was not consistent with Sungkar et al., who observed that while the Lok score was significantly greater in cases had esophageal varices (mean Lok score: 2.9 ± 0.7 against 2.1 ± 0.6, p equal 0.003), it did not significantly differ between patients with small and large varices (p = 0.09), indicating limited ability to discriminate variceal grades. This suggests that while the Lok score may help identify the presence of varices, it may not be sufficient as a standalone tool for grading severity [42]. Similarly, Bangaru et al., found that Lok scores averaged 3.5 ± 1.0 in patients with large varices compared to 2.0 ± 0.6 in those with small or medium varices (p < 0.001), and FIB-4 scores were 5.7 ± 1.7 versus 4.0 ± 1.3, respectively (p < 0.001) [43].

Regarding to the diagnostic accuracy of non-invasive scores to expect esophageal varices, the present study found that the S-index and PAPAS scores demonstrated the highest diagnostic accuracy, with both achieving 96.8% accuracy and AUC values of 0.968. These outcomes in accordance with Li et al., who stated that the S-index had an AUC of 0.930 and the PAPAS score had an AUC of 0.912 for predicting esophageal varices in cirrhotic patients, highlighting their superior predictive performance. The high accuracy in both researches can be due to the inclusion of parameters reflecting platelet count, liver inflammation, and synthetic function, which are closely correlated with the pathophysiology of portal hypertension [44]. In contrast this finding disagreed with Wang et al., who reported that the FIB-4 score (AUC = 0.86) and Lok score (AUC = 0.84) showed better diagnostic reliability than the PAPAS score (AUC = 0.76) for predicting esophageal varices in their study cohort. The

lower AUC of PAPAS in their results could reflect its limited utility in settings where platelet count or albumin levels are less strongly associated with portal hypertension progression [45].

One of the main strengths of the current investigation is the comprehensive assessment of numerous non-invasive clinical, ultrasonographic, laboratory, in addition endoscopic parameters in a relatively large cohort of cirrhotic cases (n=110), which enhances the reliability and generalizability of the findings. Additionally, the study utilized a wide range of validated non-invasive scores (e.g., APRI, FIB-4, S-index, Lok score, PAPAS), allowing for comparative assessment of their predictive value for esophageal varices. The prospective design and inclusion of both clinical and biochemical parameters provided an integrated view of variceal risk stratification in cirrhosis, particularly in the Egyptian population where HCV-related cirrhosis is highly prevalent.

However, this research has certain restrictions. 1st, it has been carried out in a single center, that might restrict the external validity of the results across different regions or populations. Second, the research didn't evaluate the longitudinal results or progression of esophageal varices over time, limiting its predictive application in long-term follow-up. Third, the potential influence of treatment history, nutritional status, or portal vein thrombosis on variceal development was not assessed. Lastly, some of the non-invasive scores used lack universally accepted cut-off values, which may affect clinical interpretation and comparison across studies.

CONCLUSION

Several clinical, laboratory, and ultrasonographic parameters, along with non-invasive scoring systems like the S-index, PAPAS, and Lok score, can effectively expect the existence of esophageal varices in cases had hepatic cirrhosis. These findings support the utility of non-invasive tools in recognizing high-risk cases who require endoscopic screening, especially in resource-limited settings. Early identification of at-risk patients through non-invasive means might diminish the burden of unnecessary endoscopies and allow for timely prophylactic interventions to prevent variceal bleeding.

Disclosure

Ethical considerations:

Following a detailed presentation of the study's objectives and research questions, all participants have been informed about the nature of the investigation and were given the opportunity to give written informed consent prior to participation. The study's methodology, including the sample size determination, received approval from the Research Ethics Committee of the Faculty of Medicine, Menoufia University, Egypt (IRB approval number:3/2023 TROP24). The investigation has been carried out in line with the ethical standards outlined in the Declaration of Helsinki.

Author contribution: We declare that all listed authors have made substantial contributions to all of the following three parts of the manuscript**:**

-Research design, or acquisition, analysis or interpretation of data;

-drafting the paper or revising it critically;

-approving the submitted version**.**

We also declare that no-one who qualifies for authorship has been excluded from the list of authors**.**

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Conflict of interest

None

HIGHLIGHTS

- Our Findings support that non-invasive novel scores are reliable, cost-effective tools for EV screening, potentially reducing unnecessary endoscopies in low-risk cirrhotic patients, especially in resource-limited settings.
- S-index and PAPAS scores showed the highest diagnostic accuracy (AUC = 0.968), with sensitivities of 96.7–98.4% and specificities of 87.8–95.9%, outperforming traditional scores like MELD and King score.

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