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Diagnostic Accuracy of APRI, AAR, FIB-4, FI, and King Scores for Diagnosis of Esophageal Varices in Liver Cirrhosis: A Retrospective Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Aspartate aminotransferase-to-platelet ratio index (APRI), aspartate aminotransferase-to-alanine aminotransferase ratio (AAR), FIB-4, fibrosis index (FI), and King scores might be alternatives to the use of upper gastrointestinal endoscopy for the diagnosis of esophageal varices (EVs) in liver cirrhosis. This study aimed to evaluate their diagnostic accuracy in predicting the presence and severity of EVs in liver cirrhosis.

Material/Methods: All patients who were consecutively admitted to our hospital and underwent upper gastrointestinal endoscopy between January 2012 and June 2014 were eligible for this retrospective study. Areas under curve (AUCs) were calculated. Subgroup analyses were performed according to the history of upper gastrointestinal bleeding (UGIB) and splenectomy.

Results: A total of 650 patients with liver cirrhosis were included, and 81.4% of them had moderate-severe EVs. In the overall analysis, the AUCs of these non-invasive scores for predicting moderate-severe EVs and presence of any EVs were 0.506–0.6 and 0.539–0.612, respectively. In the subgroup analysis of patients without UGIB, their AUCs for predicting moderate-severe varices and presence of any EVs were 0.601–0.664 and 0.596–0.662, respectively. In the subgroup analysis of patients without UGIB or splenectomy, their AUCs for predicting moderate-severe varices and presence of any EVs were 0.627–0.69 and 0.607–0.692, respectively.

Conclusions: APRI, AAR, FIB-4, FI, and King scores had modest diagnostic accuracy of EVs in liver cirrhosis. They might not be able to replace the utility of upper gastrointestinal endoscopy for the diagnosis of EVs in liver cirrhosis.

MeSH Keywords: **Blood Platelets • Endoscopy • Esophageal and Gastric Varices • Hypertension, Portal • Liver Cirrhosis**

Abbreviations: **AST** – aspartate aminotransferase; **PLT** – platelets; **APRI** – aspartate aminotransferase-to-platelet ratio; **ALT** – alanine aminotransferase; **AAR** – aspartate aminotransferase-to-alanine aminotransferase ratio; **FI** – fibrosis index; **RBC** – red blood cell; **Hb** – hemoglobin; **WBC** – white blood cell; **PT** – prothrombin time; **APTT** – activated partial thromboplastin time; **INR** – international normalized ratio; **ALB** – albumin; **TBIL** – total bilirubin; **ALP** – alkaline phosphatase; **GGT** – γ-glutamine transferase; **Cr** – creatinine; **MELD** – model for end-stage liver disease; **ROC** – receiver operating characteristic curve; **AUC** – area under curve; **EV** – esophageal varices; **UGIB** – upper gastrointestinal bleeding

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Background

Liver cirrhosis is one of the most common causes of death in the world [1,2]. Natural history of liver cirrhosis is primarily divided into four stages [3,4]. Stage 1, 2, 3, and 4 are characterized respectively by neither varices nor ascites, varices without ascites or bleeding, ascites with or without varices, and variceal bleeding with or without ascites, respectively. The prognosis is gradually worsened with increased stage of liver cirrhosis. Notably, the mortality is 3.4% per year in patients with varices who have never bled. By comparison, the mortality is up 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 should be actively employed [5,6].

Upper gastrointestinal endoscopy is the golden diagnostic test of varices in liver cirrhosis. However, because of its invasiveness and discomfort, most of patients are reluctant to undergo this procedure. Recently, numerous non-invasive markers of varices have been explored in patients with liver cirrhosis [7–9]. However, they may be rarely used in clinical practices [10]. Herein, we aimed to evaluate the diagnostic accuracy of aspartate aminotransferase (AST) to platelet (PLT) ratio index (i.e., APRI), AST to alanine aminotransferase (ALT) ratio (i.e., AAR), FIB-4, fibrosis index (FI), and King scores in predicting the presence of varices and high-risk varices in liver cirrhosis. These non-invasive scores were selected, because they were readily available from regular laboratory tests and demographic data [11–15].

Material and Methods

Study design

All patients who were consecutively admitted to our hospital between January 2012 and June 2014 were considered in this retrospective study. The inclusion criteria were as follows: 1) patients were diagnosed with liver cirrhosis; 2) patients underwent both laboratory tests and endoscopic examinations. The exclusion criteria were as follows: 1) patients were diagnosed with malignant tumors; 2) patients did not undergo endoscopic examinations to evaluate the presence and degree of esophageal varices (EVs); and 3) the relevant laboratory data were missing. Notably, repeated admissions were not excluded. In other words, if one patient underwent endoscopy two or more times at different admissions during the enrollment period, all results would be included in our study. This was primarily because we just observed the association between non-invasive scores and varices. Some data had been reported in our previous papers [16–19]. This study was approved by the Ethics Committee of our hospital (number k(2015)11). Due to the retrospective nature of this study, patient written informed consents were waived.

Data collection

We collected the following data from electronic medical records: age, sex, etiology of liver diseases, ascites, hepatic encephalopathy (HE), history of upper gastrointestinal bleeding (UGIB), history of splenectomy, endoscopic findings, red blood cell (RBC), hemoglobin (Hb), white blood cell (WBC), PLT, ALT, AST, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), albumin (ALB), total bilirubin (TBIL), alkaline phosphatase (ALP), γ-glutamine transferase (GGT) and creatinine (Cr). Additionally, we calculated the Child-Pugh [20], model for end-stage of liver disease (MELD) [21], APRI [11], AAR [12], FIB-4 [13], FI [14], and King scores [15].

Child-Pugh score = ALB score + TBIL score + INR score + ascites score + HE score
MELD score = 9.57x ln(Cr) + 3.78 × ln(TBIL) + 11.2 × ln (INR) + 6.43
APRI = [(AST/ULN) × 100]/PLT
AAR = AST/ALT
FIB-4 = (age*AST)/PLT*ALT$^{1/2}$
FI = 8–0.01*PLT-ALB
King = age*AST*INR/PLT

Evaluation of EVs

Grade of EVs was classified into no, mild, moderate, and severe according to the 2008 Hangzhou consensus, which was proposed by the Chinese Society of Gastroenterology, Chinese Society of Hepatology, and Chinese Society of Digestive Endoscopy [22]. This classification is widely employed in China and is primarily based on the general rules by Japanese Society for Portal Hypertension, Baveno consensus, AASLD practice guidelines, and clinical practices in China [5,6,23]. We re-evaluated the grade of EVs by reviewing the original medical records and endoscopic results. Gastric varices were not considered in this study. Before the statistical analysis, we were blind to the correlation of EVs with non-invasive scores.

Statistical analysis

Categorical data were expressed as frequencies (percentages) and compared by using the chi-square tests. Continuous data were expressed as mean ± standard deviation and compared by using the independent sample t-tests. Receiver operating characteristic (ROC) curves were performed to evaluate and compare the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores for the prediction of EVs (moderate-severe versus no-mild EVs; with versus without EVs). The diagnostic performances were expressed as area under curve (AUC), sensitivity,

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Table 1. Overall analysis.

Variables	Total Pts (n=650)	Moderate-large varices Pts (n=529)	No-mild varices Pts (n=121)	P value	With varices Pts (n=557)	Without varices Pts (n=93)	P value
Sex (male/female)	425/225	353/176	72/49	0.132	373/184	52/41	**0.038**
Age (years)	53.54±11.75	53.61±11.82	53.27±11.48	0.774	53.38±11.85	54.51±11.14	0.393
Etiology of liver diseases, n (%)				0.396			0.386
Hepatitis B virus	199 (30.6)	169 (31.9)	30 (24.8)		176 (31.6)	23 (24.7)	
Hepatitis C virus	46 (7.1)	38 (7.2)	8 (6.6)		39 (7.0)	7 (7.5)	
Hepatitis B virus + Hepatitis C virus	5 (0.8)	5 (0.9)	0 (0)		5 (0.9)	0 (0)	
Alcohol	154 (23.7)	119 (22.5)	35 (28.9)		128 (23.0)	26 (28.0)	
Hepatitis B virus + Alcohol	47 (7.2)	40 (7.6)	7 (5.8)		41 (7.4)	6 (6.5)	
Unknown	122 (18.8)	91 (17.2)	31 (25.6)		97 (17.4)	25 (26.9)	
Others	77 (11.8)	67 (12.7)	10 (8.3)		71 (12.7)	6 (6.5)	
Ascites, n (%)				**0.029**			**0.007**
No	364 (56.0)	284 (53.7)	80 (66.1)		298 (53.5)	66 (71.0)	
Mild	91 (14.0)	75 (14.2)	16 (13.2)		83 (14.9)	8 (8.6)	
Moderate to severe	195 (30.0)	170 (32.1)	25 (20.7)		176 (31.6)	19 (20.4)	
Hepatic encephalopathy, n (%)				0.676			0.491
No	637 (98.0)	519 (98.1)	118 (97.5)		545 (97.8)	92 (98.9)	
Grade I–II	13 (2.0)	10 (1.9)	3 (2.5)		12 (2.2)	1 (1.1)	
Grade III–IV	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
History of UGIB (yes/no)	532/118	467/62	65/56	**<0.001**	489/68	43/50	**<0.001**
Varices, n (%)				NA			NA
No	93 (14.3)	0 (0)	93 (76.9)		0 (0)	93 (100)	
Mild	28 (4.3)	0 (0)	28 (23.1)		28 (5.0)	0 (0)	
Moderate	78 (12.0)	78 (14.7)	0 (0)		78 (14.0)	0 (0)	
Severe	451 (69.4)	451 (85.3)	0 (0)		451 (81.0)	0 (0)	
Laboratory tests							
RBC	3.04±0.79	2.96±0.75	3.37±0.88	**<0.001**	2.99±0.75	3.32±0.95	**<0.001**
Hb	86.50±27.44	83.38±25.61	100.16±30.91	**<0.001**	84.23±25.58	100.13±33.71	**<0.001**
WBC	4.43±3.08	4.33±3.02	4.90±3.30	0.065	4.34±3.01	4.99±3.41	0.059
PLT	98.20±87.98	94.94±87.34	112.43±89.72	**0.049**	94.88±86.72	118.05±93.27	**0.019**
TBIL	26.25±29.22	25.30±26.60	30.40±38.54	0.084	25.84±26.74	28.72±41.20	0.38
DBIL	12.92±21.12	12.18±18.92	16.15±28.72	0.062	12.51±18.92	15.37±31.23	0.227
IBIL	13.27±10.68	13.08±10.32	14.08±12.14	0.353	13.27±10.35	13.24±12.52	0.979
ALB	33.21±6.36	32.80±6.38	34.98±6.00	**0.001**	32.86±6.33	35.30±6.20	**0.001**

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Table 1 continued. Overall analysis.

Variables	Total Pts (n=650)	Moderate-large varices Pts (n=529)	No-mild varices Pts (n=121)	P value	With varices Pts (n=557)	Without varices Pts (n=93)	P value
ALT	34.30±57.40	31.07±27.93	48.42±118.91	**0.003**	31.20±27.63	52.87±135.00	**0.001**
AST	48.36±78.81	46.09±78.86	58.31±78.14	0.124	46.47±77.33	59.71±86.68	0.134
ALP	100.37±85.17	97.68±83.63	112.17±91.06	0.091	98.79±84.73	109.89±87.62	0.245
GGT	95.05±235.38	77.22±135.85	173.01±459.24	**<0.001**	81.82±145.57	174.29±505.32	**<0.001**
BUN	6.55±4.21	6.66±4.32	6.06±3.63	0.154	6.63±4.25	6.10±3.93	0.262
Cr	62.29±40.95	61.88±37.85	64.10±52.54	0.591	61.60±37.11	66.45±59.04	0.291
PT	16.02±3.45	16.17±3.50	15.36±3.13	**0.019**	16.17±3.46	15.14±3.27	**0.008**
APTT	41.93±8.82	41.95±9.21	41.85±6.90	0.907	42.05±9.12	41.21±6.70	0.396
INR	1.30±0.39	1.31±0.39	1.23±0.34	**0.021**	1.31±0.39	1.20±0.35	**0.01**
Child-Pugh class, n (%)				0.062			**0.012**
A	308 (47.4)	239 (45.2)	69 (57.0)		251 (45.1)	57 (61.3)	
B	279 (42.9)	237 (44.8)	42 (34.7)		248 (44.5)	31 (33.3)	
C	63 (9.7)	53 (10.0)	10 (8.3)		58 (10.4)	5 (5.4)	
Child-Pugh score	6.60±1.76	7.03±1.76	6.64±1.72	**0.027**	7.04±1.78	6.45±1.54	**0.003**
MELD score	5.07±5.72	5.18±5.61	4.59±6.18	0.301	5.22±5.59	4.20±6.44	0.114
APRI score	2.15±3.88	2.15±4.11	2.15±2.60	1	2.16±4.03	2.09±2.80	0.864
AAR score	1.51±0.69	1.51±0.68	1.51±0.74	0.897	1.52±0.68	1.48±0.76	0.564
FIB-4 score	6.61±7.17	6.71±7.44	6.15±5.86	0.444	6.74±7.36	5.81±5.94	0.25
FI score	–26.19±6.53	–25.75±6.54	–28.10±6.18	**<0.001**	–25.81±6.48	–28.48±6.40	**<0.001**
King score	61.17±213.86	63.56±235.06	50.74±64.08	0.552	63.21±229.33	48.99±67.93	0.553

AAR – AST to ALT ratio; ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APRI – AST to platelets ratio index; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; AUC – area under curve; BUN – blood urea nitrogen; Cr – creatinine; DBIL – direct bilirubin; FI – fibrosis index; FIB-4 – fibrosis 4 index; GGT – gamma-glutamyl transpeptidase; Hb – hemoglobin; IBIL – indirect bilirubin; INR – international normalized ratio; MELD – model for end stage liver disease; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; TBIL – total bilirubin; UGIB – upper gastrointestinal bleeding; WBC – white blood cell.

specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value. AUCs were compared by using DeLong test. Optimal cut-off values were chosen while the sum of sensitivity and specificity would be maximal. Subgroup analysis was performed in patients without any previous history of UGIB, in those with Child-Pugh class A or B+C, and in those without any previous history of splenectomy. A two-sided P<0.05 was considered statistically significant. All statistical analyses were performed by using the SPSS software version 18.0 (SPSS Inc. Chicago, IL, USA).

Results

Patients

Overall, 650 patients were eligible in our study. The characteristics of all patients are shown in Table 1. Among them, 81.4% had moderate-severe EVs, 81.8% had previous history of UGIB, and 52.6% had Child-Pugh classes B and C.

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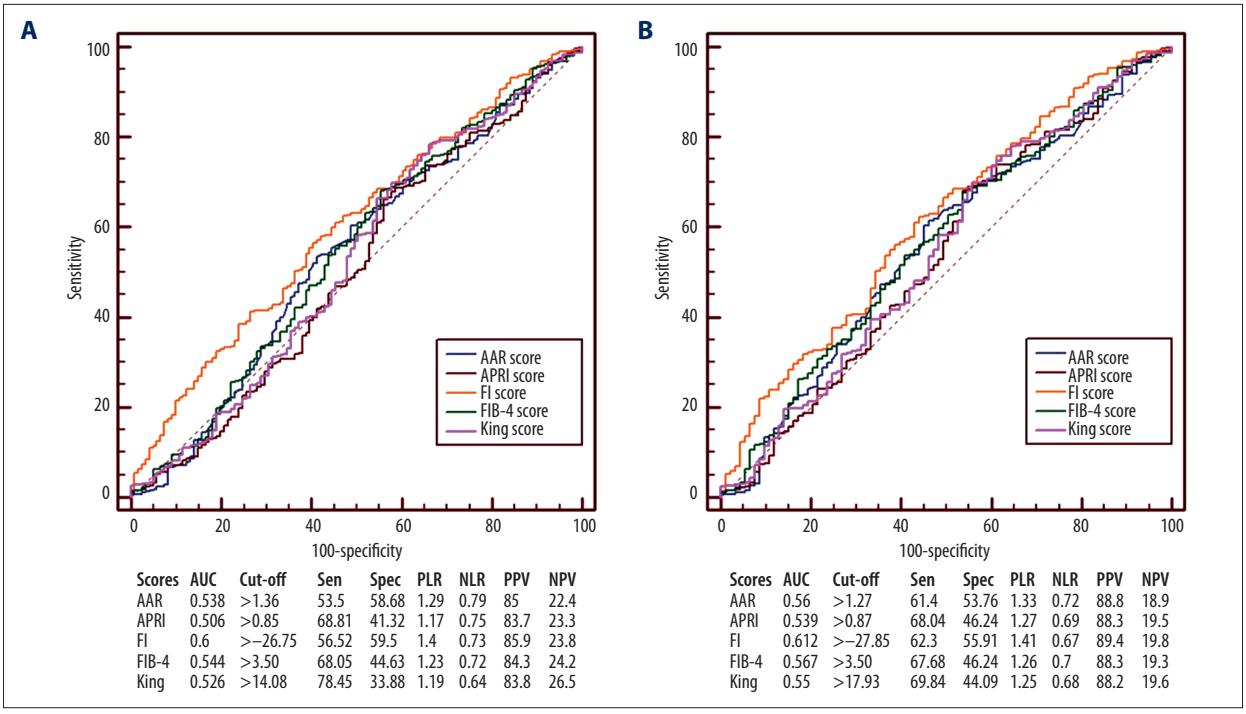
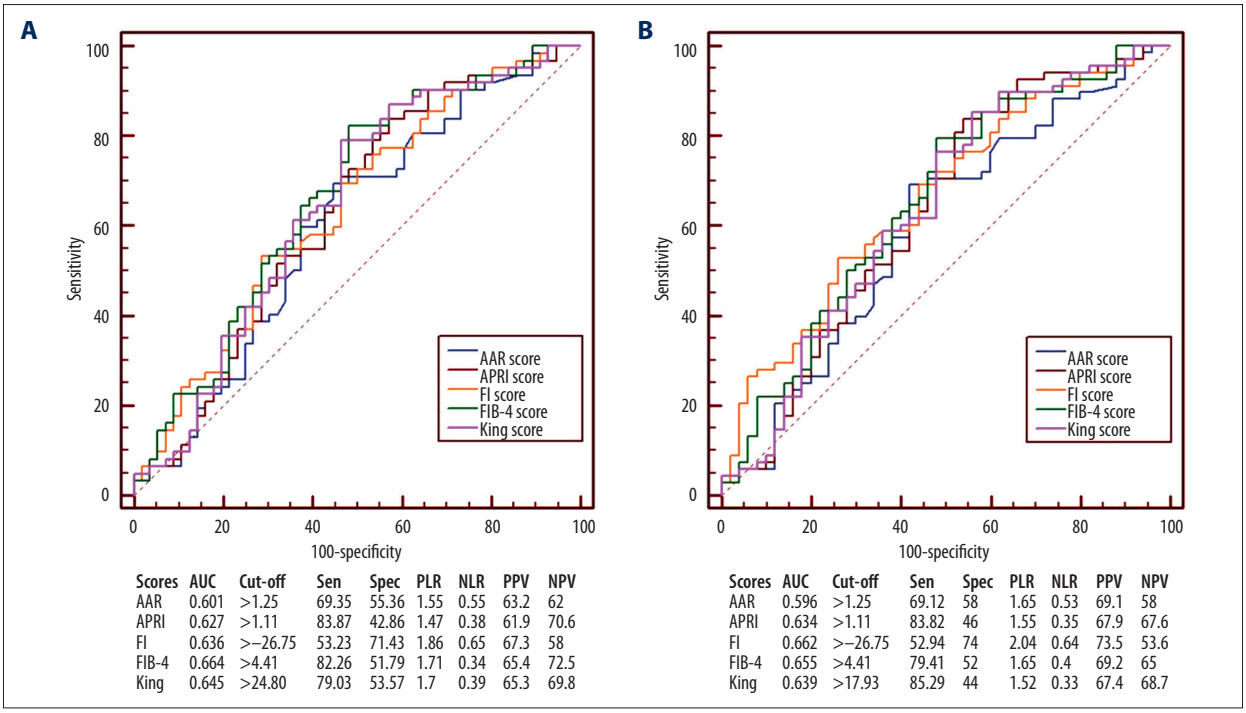


Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.538	>1.36	53.5	58.68	1.29	0.79	85	22.4
APRI	0.506	>0.85	68.81	41.32	1.17	0.75	83.7	23.3
FI	0.6	>–26.75	56.52	59.5	1.4	0.73	85.9	23.8
FIB-4	0.544	>3.50	68.05	44.63	1.23	0.72	84.3	24.2
King	0.526	>14.08	78.45	33.88	1.19	0.64	83.8	26.5

Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.56	>1.27	61.4	53.76	1.33	0.72	88.8	18.9
APRI	0.539	>0.87	68.04	46.24	1.27	0.69	88.3	19.5
FI	0.612	>–27.85	62.3	55.91	1.41	0.67	89.4	19.8
FIB-4	0.567	>3.50	67.68	46.24	1.26	0.7	88.3	19.3
King	0.55	>17.93	69.84	44.09	1.25	0.68	88.2	19.6

Figure 1. Receiver operating characteristic curves showing the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores in predicting the presence of varices in liver cirrhosis. (**A**) Prediction of moderate-severe varices. (**B**) Prediction of varices. AUC – area under curve; PLR – positive likelihood ratio; PPV – positive predictive value; NLR – negative likelihood ratio; NPV – negative predictive value; Sen – sensitivity; Spec – specificity.



Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.601	>1.25	69.35	55.36	1.55	0.55	63.2	62
APRI	0.627	>1.11	83.87	42.86	1.47	0.38	61.9	70.6
FI	0.636	>–26.75	53.23	71.43	1.86	0.65	67.3	58
FIB-4	0.664	>4.41	82.26	51.79	1.71	0.34	65.4	72.5
King	0.645	>24.80	79.03	53.57	1.7	0.39	65.3	69.8

Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.596	>1.25	69.12	58	1.65	0.53	69.1	58
APRI	0.634	>1.11	83.82	46	1.55	0.35	67.9	67.6
FI	0.662	>–26.75	52.94	74	2.04	0.64	73.5	53.6
FIB-4	0.655	>4.41	79.41	52	1.65	0.4	69.2	65
King	0.639	>17.93	85.29	44	1.52	0.33	67.4	68.7

Figure 2. Receiver operating characteristic curves showing the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores in predicting the presence of varices in liver cirrhosis without UGIB. (**A**) Prediction of moderate-severe varices. (**B**) Prediction of varices. AUC – area under curve; PLR – positive likelihood ratio; PPV – positive predictive value; NLR – negative likelihood ratio; NPV – negative predictive value; Sen – sensitivity; Spec – specificity.

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Table 2. Subgroup analysis of patients without UGIB.

Variables	Total Pts (n=118)	Moderate-large varices Pts (n=62)	No-Mild varices Pts (n=56)	P value	With varices Pts (n=68)	Without varices Pts (n=50)	P value
Sex (male/female)	69/49	36/26	33/23	0.924	38/30	31/19	0.505
Age (years)	55.09±11.02	55.89±10.86	54.21±11.24	0.41	54.90±11.59	55.35±10.32	0.828
Etiology of liver diseases, n (%)				**0.041**			0.161
Hepatitis B virus	28 (23.7)	19 (30.6)	9 (16.1)		19 (27.9)	9 (18.0)	
Hepatitis C virus	8 (6.8)	5 (8.1)	3 (5.4)		6 (8.8)	2 (4.0)	
Hepatitis B virus + Hepatitis C virus	1 (0.8)	1 (1.6)	0 (0)		1 (1.5)	0 (0)	
Alcohol	30 (25.4)	13 (21.0)	17 (30.4)		14 (20.6)	16 (32.0)	
Hepatitis B virus + Alcohol	8 (6.8)	5 (8.1)	3 (5.4)		5 (7.4)	3 (6.0)	
Unknown	33 (28.0)	11 (17.7)	22 (39.3)		15 (22.1)	18 (36.0)	
Others	10 (8.4)	8 (12.9)	2 (3.6)		8 (11.8)	2 (4)	
Ascites, n (%)				0.524			0.172
No	69 (58.5)	34 (54.8)	35 (62.5)		35 (51.5)	34 (68.0)	
Mild	18 (15.3)	9 (14.5)	9 (16.1)		13 (19.1)	5 (10.0)	
Moderate to severe	31 (26.3)	19 (30.6)	12 (21.4)		20 (29.4)	11 (22.0)	
Hepatic encephalopathy, n (%)				0.34			0.389
No	117 (99.2)	61 (98.4)	56 (100)		67 (98.5)	50 (100)	
Grade I–II	1 (0.8)	1 (1.6)	0 (0)		1 (1.5)	0 (0)	
Grade III–IV	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Varices, n (%)				NA			NA
No	50 (42.4)	0 (0)	50 (89.3)		0 (0)	50 (100)	
Mild	6 (5.1)	0 (0)	6 (10.7)		6 (8.8)	0 (0)	
Moderate	20 (16.9)	20(32.3)	0 (0)		20 (29.4)	0 (0)	
Severe	42 (35.6)	42 (67.7)	0 (0)		42 (61.8)	0 (0)	
Laboratory tests							
RBC	3.72±0.74	3.68±0.69	3.76±0.79	0.571	3.68±0.68	3.78±0.82	0.459
Hb	116.69±25.85	115.45±25.58	118.07±26.30	0.585	115.12±25.03	118.84±27.03	0.442
WBC	4.26±2.29	3.94±2.39	4.62±2.13	0.106	3.91±2.34	4.74±2.14	0.051
PLT	90.72±59.50	76.92±50.82	106.00±64.91	**0.007**	76.76±50.41	109.70±65.88	**0.003**
TBIL	31.02±36.80	30.39±21.34	31.72±48.73	0.845	30.15±20.97	32.20±51.28	0.767
DBIL	16.79±29.45	15.40±17.11	18.33±38.93	0.592	15.33±16.68	18.77±41.03	0.533
IBIL	14.19±9.92	14.94±8.40	13.37±11.39	0.394	14.75±8.35	13.44±11.78	0.482
ALB	35.30±6.13	34.04±5.84	36.70±6.20	**0.018**	33.97±5.98	37.11±5.92	**0.006**
ALT	55.03±122.69	45.95±46.68	65.07±171.49	0.4	44.84±44.79	68.88±181.27	0.295

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Table 2 continued. Subgroup analysis of patients without UGIB.

Variables	Total Pts (n=118)	Moderate-large varices Pts (n=62)	No-Mild varices Pts (n=56)	P value	With varices Pts (n=68)	Without varices Pts (n=50)	P value
AST	70.42±102.52	74.45±106.22	65.95±99.02	0.655	72.15±101.98	68.06±104.24	0.832
ALP	120.34±87.20	124.76±99.60	115.46±71.59	0.565	126.68±100.69	111.73±64.50	0.36
GGT	143.04±223.66	138.85±240.15	147.68±205.94	0.832	142.13±238.07	144.28±204.81	0.959
BUN	5.61±3.35	5.37±2.18	5.89±4.29	0.402	5.37±2.11	5.94±4.52	0.365
Cr	64.85±55.02	58.35±27.04	72.05±74.35	0.178	57.34±26.15	75.06±78.15	0.084
PT	15.07±2.41	15.42±2.20	14.67±2.58	0.093	15.45±2.38	14.55±2.41	**0.044**
APTT	42.74±6.58	43.31±6.43	42.10±6.74	0.323	43.79±6.90	41.31±5.89	**0.043**
INR	1.19±0.25	1.23±0.24	1.15±0.27	0.094	1.23±0.25	1.14±0.25	**0.042**
Child-Pugh class, n (%)				0.633			0.211
A	62 (52.5)	30 (48.4)	32 (57.1)		31 (45.6)	31 (62.0)	
B	47 (39.8)	27 (43.5)	20 (35.7)		31 (45.6)	16 (32.0)	
C	9 (7.6)	5 (8.1)	4 (7.1)		6 (8.8)	3 (6.0)	
Child-Pugh score	6.69±1.73	6.89±1.81	6.48±1.63	0.206	6.96±1.86	6.34±1.49	0.056
MELD score	4.72±5.83	5.16±4.71	4.24±6.88	0.392	4.97±4.77	4.39±7.07	0.591
APRI score	3.13±5.13	3.69±6.44	2.50±3.01	0.209	3.58±6.18	2.51±3.13	0.261
AAR score	1.58±0.84	1.68±0.89	1.48±0.79	0.206	1.66±0.87	1.48±0.80	0.266
FIB-4 score	8.24±8.27	9.87±9.66	6.45±5.98	**0.024**	9.58±9.38	6.42±6.10	**0.04**
FI score	–28.21±6.23	–26.81±5.83	–29.76±6.25	**0.01**	–26.74±5.98	–30.21±6.07	**0.002**
King score	81.27±176.82	101.92±231.32	58.40±78.43	0.183	97.82±221.78	58.76±80.67	0.237

AAR – AST to ALT ratio; ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APRI – AST to platelets ratio index; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; AUC – area under curve; BUN – blood urea nitrogen; Cr – creatinine; DBIL – direct bilirubin; FI – fibrosis index; FIB-4 – fibrosis 4 index; GGT – gamma-glutamyl transpeptidase; Hb – hemoglobin; IBIL – indirect bilirubin; INR – international normalized ratio; MELD – model for end-stage liver disease; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; TBIL – total bilirubin; UGIB – upper gastrointestinal bleeding; WBC – white blood cell.

Overall analysis

Moderate-severe versus no-mild EVs

Compared with the no-mild EVs group, the moderate-severe EVs group had significantly higher proportions of ascites and history of UGIB, significantly higher PT, INR, Child-Pugh score, and FI score, but significantly lower RBC, Hb, PLT, ALB, ALT, and GGT (Table 1).

FI score had the largest AUC (AUC=0.6), followed by FIB-4 (AUC=0.544), AAR (AUC=0.538), King (AUC=0.526), and APRI scores (AUC=0.506) (Figure 1A). AUC of FI score was not significantly different from that of FIB-4 (P=0.1041) or AAR score (P=0.0892), but was significantly larger than that of King (P=0.0293) and APRI scores (P=0.0093).

With versus without EVs

Compared with the no EVs group, the EVs group had significantly higher proportions of male, ascites, history of UGIB, and Child-Pugh class B+C, significantly higher PT, INR, Child-Pugh score, and FI score, but significantly lower RBC, Hb, PLT, ALB, ALT, and GGT (Table 1).

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Table 3. Subgroup analysis of patients without UGIB at Child-Pugh class A.

Variables	Total Pts (n=62)	Moderate-large varices Pts (n=30)	No-mild varices Pts (n=32)	P value	With warices Pts (n=31)	Without varices Pts (n=31)	P value
Sex (male/female)	33/29	17/13	16/16	0.599	17/14	16/15	0.799
Age (years)	54.61±11.50	55.19±11.42	54.06±11.74	0.702	55.09±11.24	54.12±11.93	0.741
Etiology of liver diseases, n (%)				0.159			0.244
Hepatitis B virus	22 (35.5)	14 (46.7)	8 (25.0)		14 (45.2)	8 (25.8)	
Hepatitis C virus	3 (4.8)	2 (6.7)	1 (3.1)		2 (6.5)	1 (3.2)	
Hepatitis B virus + Hepatitis C virus	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Alcohol	11 (17.7)	4 (13.3)	7 (21.9)		4 (12.9)	7 (22.6)	
Hepatitis B virus + Alcohol	3 (4.8)	2 (6.7)	1 (3.1)		2 (6.5)	1 (3.2)	
Unknown	20 (32.3)	6 (20.0)	14 (43.8)		7 (22.6)	13 (41.9)	
Others	3 (4.8)	2 (6.7)	1 (3.1)		2 (6.5)	1 (3.2)	
Ascites, n (%)				0.947			1
No	58 (93.5)	28 (93.3)	30 (93.8)		29 (93.5)	29 (93.5)	
Mild	4 (6.5)	2 (6.7)	2 (6.3)		2 (6.5)	2 (6.5)	
Moderate to severe	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Hepatic encephalopathy, n (%)				NA			NA
No	62 (100)	30 (100)	32 (100)		31 (100)	31 (100)	
Grade I–II	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Grade III–IV	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Varices, n (%)				NA			NA
No	31 (50.0)	0 (0)	31 (96.9)		0 (0)	31 (100)	
Mild	1 (1.6)	0 (0)	1 (3.1)		3 (3.2)	0 (0)	
Moderate	8 (12.9)	8 (26.7)	0 (0)		8 (25.8)	0 (0)	
Severe	22 (35.5)	22 (73.3)	0 (0)		22 (71.0)	0 (0)	
Laboratory tests							
RBC	3.95±0.71	3.40±0.57	3.90±0.83	0.588	3.99±0.56	3.91±0.84	0.637
Hb	122.03±25.39	123.23±23.38	120.91±27.47	0.722	123.00±23.02	121.06±27.91	0.767
WBC	3.82±1.52	3.37±1.10	4.24±1.75	**0.023**	3.38±1.08	4.26±1.78	**0.022**
PLT	87.34±50.03	76.10±44.14	97.88±53.52	0.087	76.48±43.45	98.19±54.38	0.088
TBIL	19.43±9.53	20.66±7.61	18.27±11.04	0.327	20.57±7.50	18.29±11.22	0.35
DBIL	7.66±3.93	7.93±3.25	7.34±4.52	0.56	7.88±3.20	7.37±4.59	0.614
IBIL	11.72±5.90	12.63±4.78	10.87±6.75	0.242	12.53±4.74	10.92±6.85	0.287
ALB	38.68±4.62	38.09±4.44	39.23±4.79	0.338	38.12±4.37	39.23±4.87	0.347
ALT	45.19±50.60	46.07±48.51	44.38±53.25	0.897	46.00±47.70	44.39±54.13	0.901

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Table 3 continued. Subgroup analysis of patients without UGIB at Child-Pugh class A.

Variables	Total Pts (n=62)	Moderate-large varices Pts (n=30)	No-mild varices Pts (n=32)	P value	With warices Pts (n=31)	Without varices Pts (n=31)	P value
AST	51.81±51.21	56.17±61.74	47.72±39.50	0.521	55.61±60.78	48.00±40.12	0.563
ALP	100.61±70.72	109.89±94.03	91.92±37.51	0.321	113.83±95.02	87.40±27.91	0.142
GGT	104.42±177.76	89.47±144.00	118.44±205.82	0.526	105.42±167.13	103.42±190.57	0.965
BUN	5.10±2.34	5.22±1.30	4.99±3.03	0.704	5.26±1.30	4.94±3.07	0.594
Cr	60.24±49.09	54.74±10.69	65.39±67.66	0.398	54.95±10.57	65.53±68.78	0.4
PT	14.11±1.55	14.51±1.62	13.74±1.42	**0.05**	14.42±1.67	13.81±1.39	0.119
APTT	40.95±5.49	41.21±5.67	40.70±5.39	0.718	41.32±5.61	40.58±5.43	0.6
INR	1.09±0.15	1.14±0.16	1.05±0.14	**0.036**	1.13±0.17	1.06±0.14	0.089
Child-Pugh score	5.35±0.48	5.33±0.48	5.38±0.49	0.737	5.32±0.48	5.39±0.50	0.603
MELD score	2.42±3.99	3.13±3.17	1.76±4.58	0.179	3.06±3.14	1.78±4.66	0.21
APRI score	2.29±2.75	2.44±2.73	2.15±2.80	0.68	2.40±2.69	2.18±2.84	0.75
AAR score	1.29±0.44	1.29±0.36	1.29±0.50	0.979	1.28±0.36	1.30±0.50	0.835
FIB-4 score	6.26±5.03	6.84±4.46	5.71±5.53	0.382	6.73±4.42	5.79±5.61	0.462
FI score	–31.55±4.68	–30.85±4.44	–32.20±4.87	0.258	–30.88±4.37	–32.21±4.95	0.266
King score	51.28±70.67	57.61±75.38	45.34±66.61	0.499	56.39±74.42	44.17±67.55	0.573

AAR – AST to ALT ratio; ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APRI – AST to platelets ratio index; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; AUC – area under curve; BUN – blood urea nitrogen; Cr – creatinine; DBIL – direct bilirubin; FI – fibrosis index; FIB-4 – fibrosis 4 index; GGT – gamma-glutamyl transpeptidase; Hb – hemoglobin; IBIL – indirect bilirubin; INR – international normalized ratio; MELD – model for end-stage liver disease; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; TBIL – total bilirubin; UGIB – upper gastrointestinal bleeding; WBC – white blood cell.

FI score had the largest AUC (AUC=0.612), followed by FIB-4 (AUC=0.567), AAR (AUC=0.56), King (AUC=0.55), and APRI scores (AUC=0.539) (Figure 1B). AUC of FI score was not significantly different from that of FIB-4 (P=0.2510), AAR (P=0.2167), King (P=0.1144), or APRI score (P=0.0873).

Subgroup analysis in patients without UGIB

Moderate-severe versus no-mild EVs

Compared with the no-mild EVs group, the moderate-severe EVs group had significantly higher FIB-4 and FI scores, but significantly lower PLT and ALB (Table 2).

FIB-4 score had the largest AUC (AUC=0.664), followed by King (AUC=0.645), FI (AUC=0.636), APRI (AUC=0.627), and AAR scores (AUC=0.601) (Figure 2A). AUC of FIB-4 score was not significantly different from that of FI (P=0.6317), King (P=0.3537), AAR (P=0.3037), or APRI score (P=0.1571).

With versus without EVs

Compared with the no EVs group, the EVs group had significantly higher PT, APTT, INR, FIB-4 score, and FI score, but significantly lower PLT and ALB (Table 2).

FI score had the largest AUC (AUC=0.662), followed by FIB-4 (AUC=0.655), King (AUC=0.639), APRI (AUC=0.634), and AAR scores (AUC=0.596) (Figure 2B). The AUC of FI score was not significantly different from that of FIB-4 (P=0.9120), King (P=0.6968), APRI (P=0.6530), or AAR score (P=0.3083).

Subgroup analysis in patients without UGIB at Child-Pugh class A

Moderate-severe versus no-mild EVs

Compared with the no-mild EVs group, the moderate-severe EVs group had significantly higher PT and INR, but a significantly lower WBC (Table 3).

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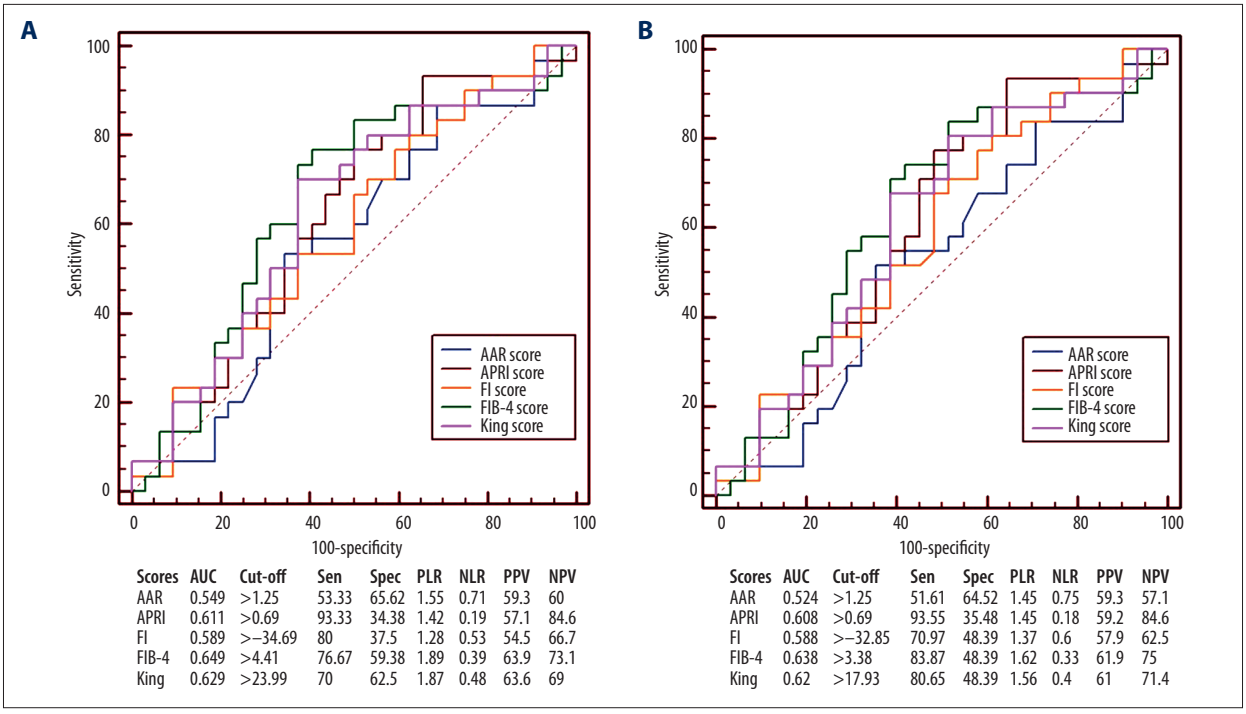
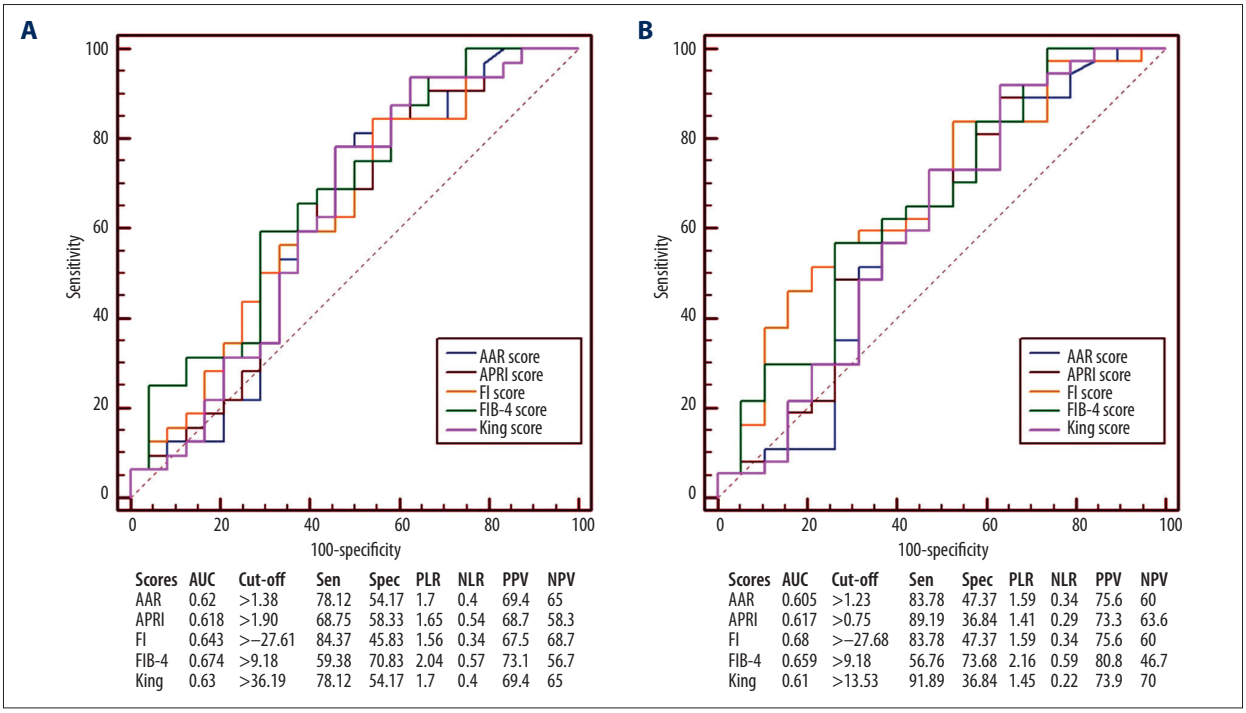


Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.549	>1.25	53.33	65.62	1.55	0.71	59.3	60
APRI	0.611	>0.69	93.33	34.38	1.42	0.19	57.1	84.6
FI	0.589	>–34.69	80	37.5	1.28	0.53	54.5	66.7
FIB-4	0.649	>4.41	76.67	59.38	1.89	0.39	63.9	73.1
King	0.629	>23.99	70	62.5	1.87	0.48	63.6	69

Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.524	>1.25	51.61	64.52	1.45	0.75	59.3	57.1
APRI	0.608	>0.69	93.55	35.48	1.45	0.18	59.2	84.6
FI	0.588	>–32.85	70.97	48.39	1.37	0.6	57.9	62.5
FIB-4	0.638	>3.38	83.87	48.39	1.62	0.33	61.9	75
King	0.62	>17.93	80.65	48.39	1.56	0.4	61	71.4

Figure 3. Receiver operating characteristic curves showing the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores in predicting the presence of varices in liver cirrhosis without UGIB at Child-Pugh class A. (**A**) Prediction of moderate-severe varices. (**B**) Prediction of varices. AUC – area under curve; PLR – positive likelihood ratio; PPV – positive predictive value; NLR – negative likelihood ratio; NPV – negative predictive value; Sen – sensitivity; Spec – specificity.



Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.62	>1.38	78.12	54.17	1.7	0.4	69.4	65
APRI	0.618	>1.90	68.75	58.33	1.65	0.54	68.7	58.3
FI	0.643	>–27.61	84.37	45.83	1.56	0.34	67.5	68.7
FIB-4	0.674	>9.18	59.38	70.83	2.04	0.57	73.1	56.7
King	0.63	>36.19	78.12	54.17	1.7	0.4	69.4	65

Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.605	>1.23	83.78	47.37	1.59	0.34	75.6	60
APRI	0.617	>0.75	89.19	36.84	1.41	0.29	73.3	63.6
FI	0.68	>–27.68	83.78	47.37	1.59	0.34	75.6	60
FIB-4	0.659	>9.18	56.76	73.68	2.16	0.59	80.8	46.7
King	0.61	>13.53	91.89	36.84	1.45	0.22	73.9	70

Figure 4. Receiver operating characteristic curves showing the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores in predicting the presence of varices in liver cirrhosis without UGIB at Child-Pugh classes B and C. (**A**) Prediction of moderate-severe varices. (**B**) Prediction of varices. AUC – area under curve; PLR – positive likelihood ratio; PPV – positive predictive value; NLR – negative likelihood ratio; NPV – negative predictive value; Sen – sensitivity; Spec – specificity.

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Table 4. Subgroup analysis patients without UGIB at Child-Pugh class B and C.

Variables	Total Pts (n=56)	Moderate-large varices Pts (n=32)	No-mild varices Pts (n=24)	P value	With varices Pts (n=37)	Without varices Pts (n=19)	P value
Sex (male/female)	36/20	19/13	17/7	0.376	21/16	15/4	0.101
Age (years)	55.63±10.55	56.55±10.45	54.41±10.78	0.457	54.74±12.02	57.36±6.79	0.383
Etiology of liver diseases, n (%)				0.355			0.617
Hepatitis B virus	6 (10.7)	5 (15.6)	1 (4.2)		5 (13.5)	1 (5.3)	
Hepatitis C virus	5 (8.9)	3 (9.4)	2 (8.3)		4 (10.8)	1 (5.3)	
Hepatitis B virus + Hepatitis C virus	1 (1.8)	1 (3.1)	0 (0)		1 (2.7)	0 (0)	
Alcohol	19 (33.9)	9 (28.1)	10 (41.7)		10 (27.0)	9 (47.4)	
Hepatitis B virus + Alcohol	5 (8.9)	3 (9.4)	2 (8.3)		3 (8.1)	2 (10.5)	
Unknown	13 (23.2)	5 (15.6)	8 (33.3)		8 (21.6)	5 (26.3)	
Others	7 (12.5)	6 (18.8)	1 (4.2)		6 (16.2)	1 (5.3)	
Ascites, n (%)				0.763			0.436
No	11 (19.6)	6 (18.8)	5 (20.8)		6 (16.2)	5 (26.3)	
Mild	14 (25.0)	7 (21.9)	7 (29.2)		11 (29.7)	3 (15.8)	
Moderate to severe	31 (55.4)	19 (59.4)	12 (50.0)		20 (54.1)	11 (57.9)	
Hepatic encephalopathy, n (%)				0.382			0.47
No	55 (98.2)	31 (96.9)	24 (100)		36 (97.3)	19 (100)	
Grade I–II	1 (1.8)	1 (3.1)	0 (0)		1 (2.7)	0 (0)	
Grade III–IV	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Varices, n (%)				NA			NA
No	19 (33.9)	0 (0)	19 (79.2)		0 (0)	19 (100)	
Mild	5 (8.9)	0 (0)	5 (20.8)		5 (13.5)	0 (0)	
Moderate	12 (21.4)	12 (37.5)	0 (0)		12 (32.4)	0 (0)	
Severe	20 (35.7)	20 (62.5)	0 (0)		20 (54.1)	0 (0)	
Laboratory tests							
RBC	3.47±0.70	3.38±0.68	3.57±0.72	0.321	3.41±0.66	3.57±0.76	0.418
Hb	110.79±25.26	108.16±25.74	114.29±24.72	0.373	108.51±25.02	115.21±25.83	0.352
WBC	4.76±2.84	4.48±3.08	5.13±2.50	0.398	4.36±2.97	5.53±2.48	0.147
PLT	94.46±68.76	77.69±57.08	116.83±77.46	**0.034**	77.00±56.17	128.47±79.29	**0.007**
TBIL	43.86±49.60	39.50±25.78	49.66±70.19	0.453	38.18±25.02	54.90±77.92	0.236
DBIL	26.93±40.35	22.41±21.48	32.97±56.61	0.337	21.58±20.53	37.37±62.91	0.168
IBIL	16.93±14.50	17.10±10.37	16.71±15.11	0.911	16.61±10.16	17.56±16.44	0.789
ALB	31.57±5.42	30.24±4.23	33.34±6.35	**0.033**	30.50±4.86	33.65±5.96	**0.038**
ALT	65.91±170.15	45.84±45.67	92.67±255.18	0.313	43.86±42.84	108.84±286.09	0.178

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Table 4 continued. Subgroup analysis patients without UGIB at Child-Pugh class B and C.

Variables	Total Pts (n=56)	Moderate-large varices Pts (n=32)	No-mild varices Pts (n=24)	P value	With varices Pts (n=37)	Without varices Pts (n=19)	P value
AST	91.02±136.48	91.59±134.20	90.25±142.36	0.971	86.00±125.87	100.79±158.35	0.705
ALP	142.19±98.51	138.69±104.10	146.84±92.52	0.762	137.44±105.29	151.43±85.69	0.619
GGT	185.80±260.43	185.16±299.19	186.67±203.82	0.983	172.89±282.97	210.95±214.69	0.609
BUN	6.18±4.14	5.50±2.78	7.08±5.39	0.161	5.46±2.62	7.57±5.96	0.072
Cr	69.96±60.95	61.72±36.15	80.93±83.08	0.247	59.35±34.22	90.62±91.26	0.069
PT	16.12±2.74	16.27±2.36	15.92±3.22	0.638	16.31±2.51	15.75±3.18	0.479
APTT	44.72±7.15	45.28±6.57	43.98±7.94	0.506	45.85±7.26	42.51±6.55	0.097
INR	1.30±0.29	1.32±0.27	1.28±0.33	0.651	1.32±0.28	1.27±0.33	0.489
Child-Pugh score	8.18±1.36	8.34±1.31	7.96±1.43	0.299	8.32±1.42	7.89±1.24	0.268
MELD score	7.27±6.49	7.07±5.15	7.54±8.06	0.79	6.57±5.32	8.63±8.32	0.265
APRI score	4.05±6.77	4.86±8.48	2.97±3.28	0.305	4.57±7.93	3.04±3.57	0.429
AAR score	1.90±1.05	2.03±1.08	1.73±1.01	0.286	1.97±1.04	1.77±1.09	0.502
FIB-4 score	10.44±10.40	12.70±12.16	7.42±6.53	0.06	11.97±11.60	7.46±6.87	0.126
FI score	–24.51±5.65	–23.02±4.23	–26.51±6.71	**0.021**	–23.27±4.84	–26.94±6.43	**0.02**
King score	114.47±242.56	143.47±310.32	75.81±90.42	0.306	132.53±290.18	79.31±96.92	0.442

AAR – AST to ALT ratio; ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APRI – AST to platelets ratio index; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; AUC – area under curve; BUN – blood urea nitrogen; Cr – creatinine; DBIL – direct bilirubin; FI – fibrosis index; FIB-4 – fibrosis 4 index; GGT – gamma-glutamyl transpeptidase; Hb – hemoglobin; IBIL – indirect bilirubin; INR – international normalized ratio; MELD – model for end-stage liver disease; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; TBIL – total bilirubin; UGIB – upper gastrointestinal bleeding; WBC – white blood cell.

FIB-4 score had the largest AUC (AUC=0.649), followed by King (AUC=0.629), APRI (AUC=0.611), FI (AUC=0.589), and AAR scores (AUC=0.549) (Figure 3A). AUC of FIB-4 score was not significantly different from that of King (P=0.5172), FI (P=0.4906), APRI (P=0.3419), or AAR score (P=0.3025).

With versus without EVs

Compared with the no EVs group, the EVs group had a significantly lower WBC (Table 3).

FIB-4 score had the largest AUC (AUC=0.638), followed by King (AUC=0.62), APRI (AUC=0.608), FI (AUC=0.588), and AAR scores (AUC=0.524) (Figure 3B). The AUC of FIB-4 score was not significantly different from that of FI (P=0.5732), King (P=0.5542), APRI (P=0.4411), or AAR score (P=0.2463).

Subgroup analysis in patients without UGIB at Child-Pugh class B and C

Moderate-severe versus no-mild EVs

Compared with the no-mild EVs group, the moderate-severe EVs group had a significantly higher FI score, but significantly lower PLT and ALB (Table 4).

FIB-4 score had the largest AUC (AUC=0.674), followed by FI (AUC=0.643), King (AUC=0.63), AAR (AUC=0.62), and APRI scores (AUC=0.618) (Figure 4A). The AUC of FIB-4 score was not significantly different from that of FI (P=0.7411), AAR (P=0.5294), King (P=0.2340), or APRI score (P=0.1717).

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Table 5. Subgroup analysis of patients without UGIB or splenectomy.

Variables	Total Pts (n=112)	Moderate-large varices Pts (n=57)	No-mild varices Pts (n=55)	P value	With varices Pts (n=62)	Without varices Pts (n=50)	P value
Sex (male/female)	66/46	33/24	33/22	0.821	35/27	31/19	0.553
Age (years)	55.19±10.50	55.49±10.91	54.88±10.15	0.757	55.06±10.73	55.35±10.32	0.885
Etiology of liver diseases, n (%)				**0.047**			0.149
Hepatitis B virus	28 (25.0)	19 (33.3)	9 (16.4)		19 (30.6)	9 (18.0)	
Hepatitis C virus	6 (5.4)	3 (5.3)	3 (5.5)		4 (6.5)	2 (4.0)	
Hepatitis B virus + Hepatitis C virus	1 (0.9)	1 (1.8)	0 (0)		1 (1.6)	0 (0)	
Alcohol	28 (25.0)	11 (19.3)	17 (30.9)		12 (19.4)	16 (32.0)	
Hepatitis B virus + Alcohol	7 (6.3)	4 (7.0)	3 (5.5)		4 (6.5)	3 (6.0)	
Unknown	32 (28.6)	11 (19.3)	21 (38.2)		14 (22.6)	18 (36.0)	
Others	10 (9.0)	8 (14.0)	2 (3.6)		8 (12.9)	2 (4.0)	
Ascites, n (%)				0.495			0.202
No	66 (58.9)	31 (54.4)	35 (63.6)		32 (51.6)	34 (68.0)	
Mild	16 (14.3)	8 (14.0)	8 (14.5)		11 (17.7)	5 (10.0)	
Moderate to severe	30 (26.8)	18 (31.6)	12 (21.8)		19 (30.6)	11 (22.0)	
Hepatic encephalopathy, n (%)				0.324			0.367
No	111 (99.1)	56 (98.2)	55 (100)		61 (98.4)	50 (100)	
Grade I–II	1 (0.9)	1 (1.8)	0 (0)		1 (1.6)	0 (0)	
Grade III–IV	0	0 (0)	0 (0)		0 (0)	0 (0)	
Varices, n (%)				NA			NA
No	50 (44.6)	0 (0)	50 (90.9)		0 (0)	50 (100)	
Mild	5 (4.5)	0 (0)	5 (9.1)		5 (8.1)	0 (0)	
Moderate	17 (15.2)	17 (29.8)	0 (0)		17 (27.4)	0 (0)	
Severe	40 (35.7)	40 (70.2)	0 (0)		40 (64.5)	0 (0)	
Laboratory tests							
RBC	3,72±0.75	3.67±0.70	3.77±0.80	0.511	3.67±0.69	3.78±0.82	0.452
Hb	116.52±25.46	114.95±24.51	118.15±26.54	0.509	114.65±24.19	118.84±27.03	0.388
WBC	4.22±2.32	3.88±2.47	4.58±2.12	0.111	3.80±2.39	4.74±2.14	**0.032**
PLT	86.51±56.75	68.74±40.66	104.93±65.01	**0.001**	67.81±39.71	109.70±65.88	**<0.01**
TBIL	31.39±37.63	30.93±21.79	31.87±49.17	0.895	30.74±21.52	32.20±51.28	0.839
DBIL	17.21±30.15	15.98±17.66	18.49±39.27	0.662	15.95±17.29	18.77±41.03	0.625
IBIL	14.14±10.01	14.89±8.38	13.36±11.49	0.42	14.70±8.39	13.44±11.78	0.509
ALB	35.33±6.03	33.82±5.63	36.89±6.09	**0.007**	33.89±5.78	37.11±5.92	**0.005**
ALT	54.96±125.56	44.88±46.45	65.42±173.05	0.389	43.74±44.76	68.88±181.27	0.294

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Table 5 continued. Subgroup analysis of patients without UGIB or splenectomy.

Variables	Total Pts (n=112)	Moderate-large varices Pts (n=57)	No-mild varices Pts (n=55)	P value	With varices Pts (n=62)	Without varices Pts (n=50)	P value
AST	70.61±104.86	75.81±110.16	62.22±99.78	0.595	72.66±106.15	68.06±104.24	0.819
ALP	120.29±85.90	129.11±102.22	111.15±64.53	0.271	127.19±99.89	111.73±64.50	0.346
GGT	145.40±228.06	146.47±249.14	144.29±206.25	0.96	146.31±246.88	144.28±204.81	0.963
BUN	5.62±3.42	5.40±2.24	5.86±4.33	0.476	5.37±2.16	5.94±4.52	0.379
Cr	65.27±56.43	58.48±28.12	72.31±75.01	0.196	57.37±27.32	75.06±78.15	0.099
PT	15.03±2.43	15.37±2.23	14.68±2.60	0.136	15.42±2.39	14.55±2.41	0.057
APTT	42.46±6.48	42.97±6.26	41.97±6.72	0.416	43.41±6.82	41.31±5.89	0.088
INR	1.19±0.25	1.22±0.23	1.15±0.27	0.153	1.23±0.25	1.14±0.25	0.06
Child-Pugh class, n (%)				0.478			0.206
A	59 (52.7)	27 (47.4)	32 (58.2)		28 (45.2)	31 (62.0)	
B	45 (40.2)	26 (45.6)	19 (34.5)		29 (46.8)	16 (32.0)	
C	8 (7.1)	4 (7.0)	4 (7.3)		5 (8.1)	3 (6.0)	
Child-Pugh score	6.69±1.72	6.91±1.79	6.45±1.63	0.16	6.97±1.85	6.34±1.49	0.054
MELD score	4.69±5.98	5.13±4.90	4.24±6.94	0.432	4.94±4.97	4.39±7.07	0.627
APRI score	3.22±5.24	3.90±6.68	2.51±3.04	0.163	3.79±6.43	2.51±3.13	0.198
AAR score	1.59±0.85	1.72±0.91	1.46±0.78	0.119	1.68±0.89	1.48±0.80	0.219
FIB-4 score	8.51±8.38	10.42±9.85	6.53±6.00	**0.014**	10.19±9.57	6.42±6.10	**0.017**
FI score	–28.20±6.15	–26.51±5.59	–29.94±6.26	**0.003**	–26.57±5.76	–30.21±6.07	**0.002**
King score	83.77±180.99	107.44±240.35	59.24±78.90	0.16	103.95±231.20	58.76±80.67	0.19

AAR – AST to ALT ratio; ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APRI – AST to platelets ratio index; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; AUC – area under curve; BUN – blood urea nitrogen; Cr – creatinine; DBIL – direct bilirubin; FI – fibrosis index; FIB-4 – fibrosis 4 index; GGT – gamma-glutamyl transpeptidase; Hb – hemoglobin; IBIL – indirect bilirubin; INR – international normalized ratio; MELD – model for end-stage liver disease; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; TBIL – total bilirubin; UGIB – upper gastrointestinal bleeding; WBC – white blood cell.

With versus without EVs

Compared with the no EVs group, the EVs group had a significantly higher FI score, but significantly lower PLT and ALB (Table 4).

FI score had the largest AUC (AUC=0.68), followed by FIB-4 (AUC=0.659), APRI (AUC=0.617), King (AUC=0.61), and AAR scores (AUC=0.605) (Figure 4B). The AUC of FI score was not significantly different from that of FIB-4 (P=0.8261), APRI (P=0.5687), King (P=0.5217), or AAR score (P=0.5058).

Subgroup analysis in patients without UGIB or splenectomy

Moderate-severe versus no-mild EVs

Compared with the no-mild EVs group, moderate-severe EVs group had significantly higher FIB-4 and FI scores, but significantly lower PLT and ALB (Table 5).

FIB-4 score had the largest AUC (AUC=0.69), followed by FI and King (AUC=0.66 for both of them), APRI (AUC=0.651), and AAR scores (AUC=0.627) (Figure 5A). The AUC of FIB-4 score was not significantly different from that of FI (P=0.6041), AAR (P=0.2949), APRI (P=0.1353), or King score (P=0.1330).

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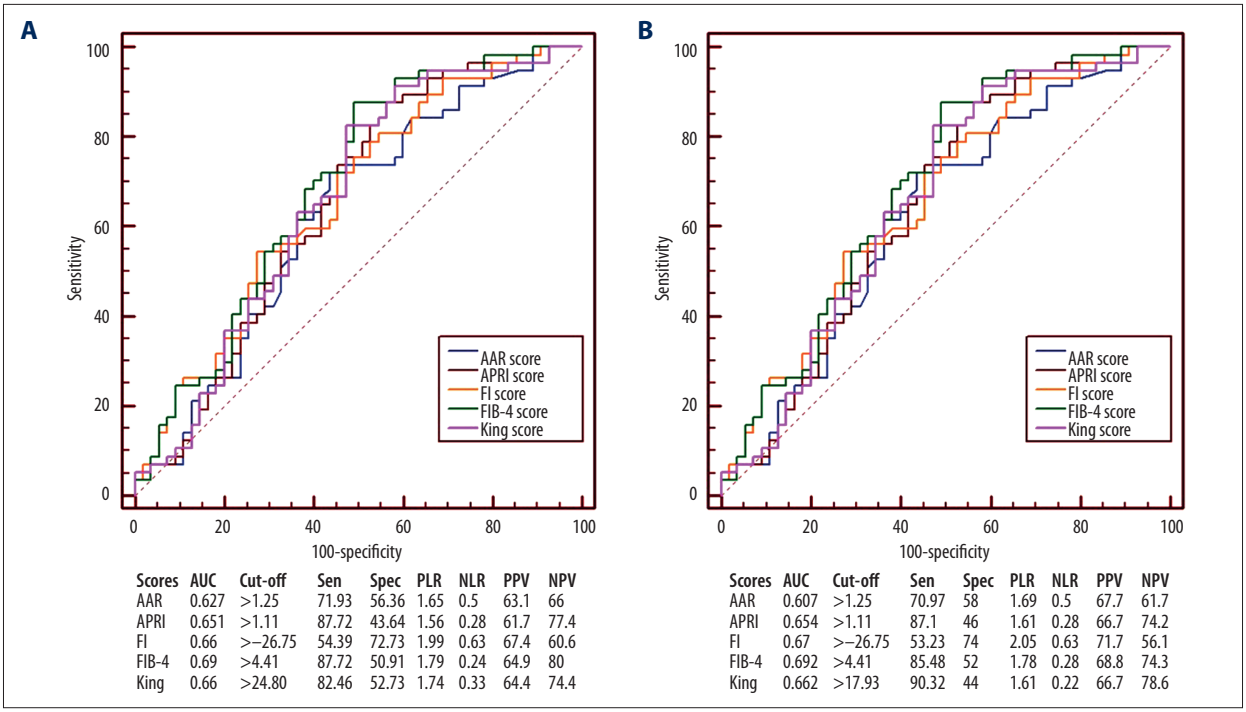

Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.627	>1.25	71.93	56.36	1.65	0.5	63.1	66
APRI	0.651	>1.11	87.72	43.64	1.56	0.28	61.7	77.4
FI	0.66	>–26.75	54.39	72.73	1.99	0.63	67.4	60.6
FIB-4	0.69	>4.41	87.72	50.91	1.79	0.24	64.9	80
King	0.66	>24.80	82.46	52.73	1.74	0.33	64.4	74.4

Scores	AUC	Cut-off	Sen	Spec	PLR	NLR	PPV	NPV
AAR	0.607	>1.25	70.97	58	1.69	0.5	67.7	61.7
APRI	0.654	>1.11	87.1	46	1.61	0.28	66.7	74.2
FI	0.67	>–26.75	53.23	74	2.05	0.63	71.7	56.1
FIB-4	0.692	>4.41	85.48	52	1.78	0.28	68.8	74.3
King	0.662	>17.93	90.32	44	1.61	0.22	66.7	78.6

Figure 5. Receiver operating characteristic curves showing the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores in predicting the presence of varices in liver cirrhosis without UGIB or splenectomy. (**A**) Prediction of moderate-severe varices. (**B**) Prediction of varices. AUC – area under curve; PLR – positive likelihood ratio; PPV – positive predictive value; NLR – negative likelihood ratio; NPV – negative predictive value; Sen – sensitivity; Spec – specificity.

With versus without EVs

Compared with the no EVs group, the EVs group had significantly higher FIB-4 and FI scores, but significantly lower WBC, PLT, and ALB (Table 5).

FIB-4 score had the largest AUC (AUC=0.692), followed by FI (AUC=0.67), King (AUC=0.662), APRI (AUC=0.654), and AAR scores (AUC=0.607) (Figure 5B). The AUC of FIB-4 score was not significantly different from that of FI (P=0.7167), AAR (P=0.1783), APRI (P=0.1578), or King score (P=0.1423).

Discussion

Non-invasive markers of varices are primarily derived from non-invasive assessment of liver fibrosis. For example, APRI was first developed by Wai and colleagues to identify the presence of significant fibrosis and liver cirrhosis in patients with chronic hepatitis C [11]. Similarly, AAR, FIB-4, FI, and King scores were originally used for the assessment of liver fibrosis and its severity in patients with hepatitis C [12–15]. More importantly, they were calculated based on some regular laboratory data (i.e., AST, ALT, ALB, INR, and PLT). By comparison, several other non-invasive markers might not be easily accessible, such as Forns' index (composed of age, GGT, cholesterol, and PLT [24]), Fibrometer (composed of PLT, prothrombin index, AST, alpha-2 macroglobulin, hyaluronate, urea, and age [25]), and Hepascore (composed of bilirubin, GGT, hyaluronic acid, alpha-2 macroglobulin, age, and sex) [26]. Indeed, cholesterol, hyaluronic acid or hyaluronate, and alpha-2 macroglobulin are not detected in our everyday clinical practices, although our recent study has explored the predictive role of four major serum liver fibrosis markers, including hyaluronic acid, laminin, amino-terminal propeptide of type III procollagen, and collagen IV, for predicting the presence of gastroesophageal varices in 118 patients with liver cirrhosis [16]. Thus, only APRI, AAR, FIB-4, FI, and King scores, rather than Forns' index, Fibrometer, or Hepascore, were evaluated in the present study.

The characteristics of our study population should be noted, as follows.

First, considering that a valid score can be generalized for any clinical conditions, all cirrhotic patients undergoing endoscopic examinations should be eligible for our study.

Second, the history of UGIB was not restricted in the overall analysis. Because not all episodes of acute UGIB were attributed to the varices in patients with liver cirrhosis [27], we should also identify whether the source of acute UGIB was

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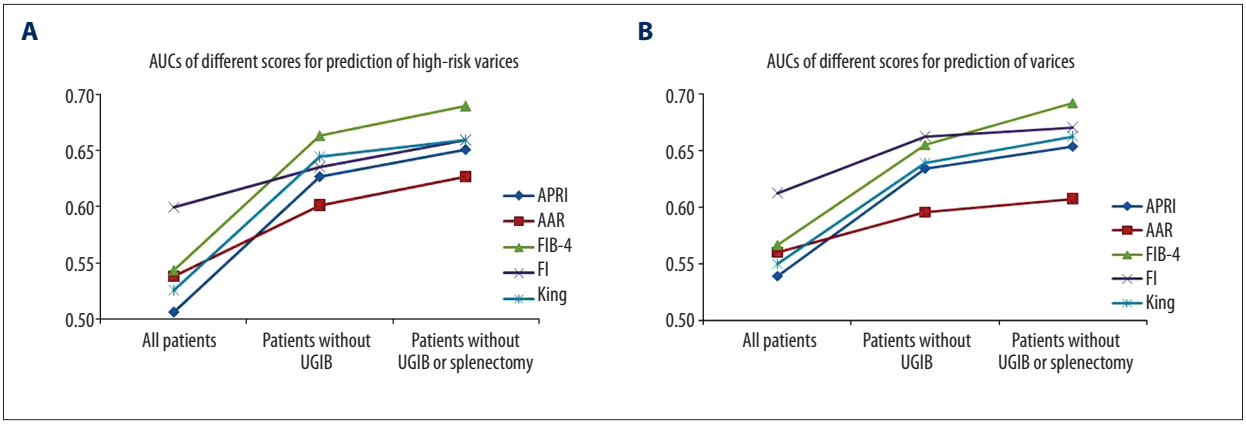

Figure 6. Areas under curves showing the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores in different study populations. (**A**) Prediction of moderate-severe varices. (**B**) Prediction of varices.

from varices, peptic ulcer, or others. Indeed, this was important and helpful in choosing the appropriate drugs.

Third, moderate and severe EVs were ascribed to one group, because the treatment strategy was similar in both of them [5].

Fourth, in our study, only a very low proportion of patients presented with grade I-II hepatic encephalopathy at their admissions, and none of them presented with grade III-IV hepatic encephalopathy. This could be because patients must be clearly conscious during upper gastrointestinal endoscopic examinations.

Our study demonstrated that the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores was modest. These findings were largely consistent with the results of our recent meta-analysis (PROSPERO registration number: CRD42015017519) [28]. Additionally, it appeared that FIB-4 and FI scores had better diagnostic accuracy than other non-invasive scores. However, their diagnostic accuracy was not significantly different among most comparative analyses.

Our study also showed that the diagnostic accuracy of APRI, AAR, FIB-4, FI, and King scores might be gradually improved as the study population was further refined (Figure 6). These findings suggested that candidates undergoing non-invasive assessment of varices should be appropriately selected. Indeed, if there was a history of splenectomy in a patient with liver cirrhosis, the PLT would remarkably increase and then return back to a normal level [29]. In this setting, the association of PLT with portal hypertension would be also masked, thereby weakening the diagnostic accuracy of non-invasive scores which include PLT.

Except for the retrospective nature, it should be acknowledged that a majority of patients undergoing endoscopic examinations had positive EVs in our study. This phenomenon might be primarily because most of our patients were at a more advanced stage or had decompensated cirrhosis and our physicians preferred to prescribe the endoscopy to patients with more severe liver cirrhosis. Given the potential bias of patient selection, the eligibility criteria should be refined in further prospective studies.

Conclusions

APRI, AAR, FIB-4, FI, and King scores had modest diagnostic accuracy for varices in liver cirrhosis. It would be difficult to replace the use of upper gastrointestinal endoscopy for the diagnosis of varices by these non-invasive scores. In future, an optimal non-invasive score should be established and validated in prospective multicenter studies.

Conflict of interest

None.

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