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

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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; FL – 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-glutamyl 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 spleenectomy, 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-glutamyl 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 = 9.57 × 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*ALT1/2
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,
| 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 (31.2)                       | 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±6.60                  | 0.001   | 32.86±6.33            | 35.30±6.62                | 0.001   |
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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### Table 1 continued. Overall analysis.

| Variables                      | Total Pts (n=650) | Moderate-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±233.86     | 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.
**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 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.

| 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   | >20.75  | 56.52| 59.5  | 1.4   | 0.73  | 65.9 | 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 |

**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.

| Scores | AUC   | Cut-off | Sen  | Spec  | PLR   | NLR   | PPV  | NPV  |
|--------|-------|---------|------|-------|-------|-------|------|------|
| AAR    | 0.56  | >1.27   | 61.4 | 51.76 | 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   | 67.6 | 46.24 | 1.26  | 0.7   | 88.3 | 19.3 |
| King   | 0.55  | >17.93  | 69.8 | 44.09 | 1.25  | 0.68  | 88.2 | 19.6 |
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             |                                   |                           |         |                         |                           | 0.924   |
| 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±44.77           | 68.88±181.27              | 0.295   |
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).

### 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±5.78          | –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.
### 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 varices 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 (%)      |                  |                                  |                            |         |                        |                           |         |
| Hepatitis B virus                      | 22 (35.5)        | 14 (46.7)                        | 8 (25.0)                   | 0.159   | 14 (45.2)              | 8 (25.8)                   | 0.244   |
| 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 (%)          |                  |                                  |                            |         |                        |                           |         |
| 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 (%)                         |                  |                                  |                            |         |                        |                           |         |
| 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   |
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).

FIB-4 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).

### 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 varices 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±167.13103.42±190.57 | 0.965               |
| BUN                        | 5.10±2.34       | 5.22±1.30                       | 4.99±1.30                 | 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).

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 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).
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. AUC – area under curve; PLR – positive likelihood ratio; PPV – positive predictive value; NLR – negative likelihood ratio; NPV – negative predictive value; Sen – sensitivity; Spec – specificity.

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.

| Scores | AUC | Cut-off | Sen | Spec | PLR | NLR | PPV | NPV |
|--------|-----|---------|-----|------|-----|-----|-----|-----|
| 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 |
|--------|-----|---------|-----|------|-----|-----|-----|-----|
| APRI   | 0.617 | >0.75 | 89.19 | 36.84 | 1.41 | 0.29 | 73.5 | 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  |
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                              | 71.03±68.76      | 77.69±57.08                      | 116.83±77.46              | 0.834   | 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   |
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±260.43185 16±299.19186.67±203.82 | 0.983 | 172.89±282.97210.95±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 | 7.18±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±3.32                 | 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±242.56143.47±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).
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 (%) |                 |                                  |                           |         |                        |                           |         |
| Hepatitis B virus             | 28 (25.0)        | 19 (33.3)                        | 9 (16.4)                  | 0.047   | 19 (30.6)              | 9 (18.0)                  | 0.149   |
| 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 (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                            | 3.77±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   |
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±228.0616  | 146.47±249.14                    | 144.29±206.25             | 0.96    | 146.31±246.88         | 144.28±204.81             | 0.963   |
| BUN       | 5.62±3.4          | 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±1.62                 | 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 FI 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).
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...
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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