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ORIGINAL ARTICLE

Optimized cutoffs of gamma-glutamyl transpeptidase-to-platelet ratio, aspartate aminotransferase-to-platelet ratio index, and fibrosis-4 scoring systems for exclusion of cirrhosis in patients with chronic hepatitis B

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Abstract

Accurate prediction of the extent of fibrosis is of great clinical importance in patients infected with chronic hepatitis B (CHB). This study aimed to compare the performance of gamma-glutamyl transpeptidase-to-platelet ratio (GPR), aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) in evaluating liver fibrosis stages and to identify optimized cutoffs to exclude cirrhosis. Consecutive patients with CHB with liver biopsies were enrolled and randomly divided into derivation and validation cohorts. Areas under the receiver operating characteristic curve were used to evaluate the diagnostic performance of APRI, FIB-4, and GPR to distinguish fibrosis stages. New cutoffs with a sensitivity of at least 90% and a negative predictive value (NPV) of more than 95% were identified. A total of 880 individuals were enrolled in this study. The derivation data set consisted of 617 patients, with 82 patients with cirrhosis. In the validation cohort (n = 263), 29 patients had cirrhosis. APRI, FIB-4, and GPR had comparable diagnostic performance for diagnosing significant fibrosis. GPR outperformed APRI ($p < 0.05$) in the prediction of cirrhosis. A newly identified GPR score of 0.35 had a sensitivity and NPV of 93.9% and 98.0%, respectively, and misclassified 5 of 82 (6.1%) patients with cirrhosis in the derivation group. All new cutoffs identified in this study also reached our goal in the validation cohort. The new GPR score could rule out a larger proportion of individuals without cirrhosis, and the subgroup analysis showed more stable performance. However, the lower cutoff dose increases the need for further testing compared to the conventional cutoff. *Conclusion:* A newly identified cutoff for GPR (<0.35) could rule out more patients without cirrhosis compared to APRI and FIB-4 and have low misclassification rates.

Xiaoqing Liu and Hu Li contributed equally to this work.

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INTRODUCTION

Hepatitis B virus (HBV) is an enveloped DNA virus that chronically infects approximately 257 million people worldwide, according to the World Health Organization (WHO).[1] HBV infection is one of the major causes of cirrhosis and hepatocellular carcinoma (HCC), and an estimated 650,000 people will die annually from chronic hepatitis B (CHB).[1,2]

Accurate assessment of the degree of liver fibrosis is of great clinical importance in determining the optimal antiviral treatment time, monitoring dynamic changes in chronic viral hepatitis, and identifying candidates for surveillance for HCC. Liver biopsy is the gold standard for assessing fibrosis but is not widely used due to its potential risk of complications, cost, sampling error, and interobserver variation. Although transient elastography (FibroScan) is increasingly recognized as an excellent tool for the assessment of hepatic fibrosis, it is expensive and not widely available. Therefore, a simple and noninvasive test based on normal examination of serum is urgently needed to identify the degree of fibrosis. The aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and fibrosis score based on four factors (FIB-4) have been extensively studied and recommended by current treatment guidelines from WHO[2] for resource-limited regions to evaluate the degree of fibrosis. Gamma-glutamyl transpeptidase-to-platelet ratio (GPR) was constructed in 2016 based on patients with CHB infection in West Africa,[3] which was more accurate than APRI and FIB-4 in assessing stages of liver fibrosis.[4–8] However, the diagnostic performance is controversial.[9–13]

The application of conventional cutoffs of APRI and FIB-4 to rule in and rule out cirrhosis results in high rates of misclassification.[14] Sonneveld et al.[14] identified a new cutoff for FIB-4 (≤0.70) that can be used to exclude cirrhosis with high accuracy. However, its derivation cohort came from clinical trials that enrolled patients with high HBV DNA levels and abnormal alanine aminotransferase (ALT); whether this cutoff will apply to patients with low HBV DNA and normal ALT needs to be determined. In addition, the possibility that GPR also has a score that can accurately rule out cirrhosis needs further investigation.

This retrospective study aimed to investigate and compare the diagnostic performance of APRI, FIB-4, and GPR in diagnosing significant fibrosis and cirrhosis and to apply the grid-search method to identify more suitable cutoffs to discriminate fibrosis stages.

MATERIALS AND METHODS

Study population

Consecutive patients with CHB (hepatitis B surface antigen positive >6 months) who underwent liver biopsy at the Second Affiliated Hospital of Chongqing Medical University from November 7, 1997, to October 31, 2021, were enrolled in this study. Individuals with the following conditions were excluded: concomitant fatty liver or other known causes of chronic liver diseases, including alcoholic hepatitis and significant alcohol consumption (>20 g/day), decompensated cirrhosis, or HCC; coinfection with hepatitis C virus/hepatitis D virus/human immunodeficiency virus; concomitant other malignant tumor; insufficient available data; or transaminase levels more than 10 times the upper limit of normal (ULN).

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University, and written consent was obtained from all patients before liver biopsy.

Liver biopsy

Ultrasound-guided liver biopsy was performed using 16-gauge Menghini biopsy needles; all liver specimens were placed in formalin and embedded in paraffin for histological processing. A minimum of 20 mm of liver tissue or at least 11 portal tracts was requested. Liver histology was assessed by two experienced pathologists who were blinded to all the related clinical data. The histological staging of fibrosis was identified based on the Scheuer scoring system and divided into five stages. Pathological stages ≥S2 and S4 were defined as significant fibrosis and cirrhosis, respectively. In the case of inconsistent staging, the specimen was reexamined until an agreement was reached.

Noninvasive tests for the detection of liver fibrosis

APRI, FIB-4, and GPR were calculated as [AST (U/L)/ULN]/[PLT (10^9/L)] × 100,[15] [age (years) × AST (U/L)]/[PLT (10^9/L) × $\sqrt{}$ALT],[16] and [GGT (U/L)/ULN]/[PLT (10^9/L)] × 100,[3] respectively. The ULN of AST, ALT, and GGT was defined as 40 U/L, 40 U/L, and 60 U/L, respectively. These liver biochemical markers were measured within 1 week before liver biopsy.

Statistical analysis

All statistical analyses were performed using R 4.0.2. All enrolled patients were randomly assigned to the derivation and validation cohorts in a 7:3 ratio, respectively. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were summarized as counts and percentages. The Mann-Whitney U test was used to compare continuous variables between

the validation and derivation cohorts. Categorical variables were compared using the chi-squared test or Fisher's exact test. Spearman rank coefficient analysis was used to determine the relationship between the APRI/FIB-4/GPR value and stage of liver fibrosis. Areas under the receiver operating characteristic curve (AUROC) were calculated to evaluate the diagnostic accuracy of the noninvasive tests and were compared using the DeLong test. Cutoffs with the maximum Youden index were also calculated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and negative likelihood ratio (NLR) of each noninvasive test for significant fibrosis (≥S2) and cirrhosis (S4) were obtained by comparing patients of S2-S4 with S0-S1 and S4 with S0-S3, respectively. A two-sided $p < 0.05$ was considered statistically significant.

A grid search of cut-off points aimed for a sensitivity of >90% (e.g., <10% of individuals with cirrhosis were misclassified as noncirrhosis); an NPV of at least 95% was used to identify optimized cutoffs to rule out, and a specificity of at least 95% and PPV of >90% were used to rule in.

RESULTS

Clinical characteristics of the study population

The flow diagram for eligibility for patient screening is shown in Figure S1. Data were collected from a total of 1233 patients with CHB, of whom 880 patients met the inclusion criteria. The main clinical characteristics of the enrolled study patients are summarized in Table 1; no significant differences were observed between the derivation and validation cohorts. Results showed 67.1% (414/617) of patients in the derivation cohort and 65.8% (173/263) of patients in the validation data set had significant fibrosis, and 13.3% (82/617) of patients in the derivation data set and 11.0% (29/263) of patients in the validation data set had cirrhosis.

Correlation of APRI, FIB-4, and GPR scores with the fibrosis stage

Increasing APRI, FIB-4, and GPR scores were correlated with Scheuer fibrosis stages ($p < 0.0001$ for

TABLE 1 Clinical characteristics of patients with CHB

	Derivation data set	Validation data set	*p* value
Number, n	617	263	
Age, years (range)	37 (31–44)	37 (31–44)	0.791
Sex, male (%)	476 (77.1)	193 (73.4)	0.267
HBeAg, positive (%)[a]	282 (45.7)	130 (49.4)	0.325
HBV DNA, log10 IU/mL[b]	5.0 (2.7–6.8)	5.6 (3.3–7.0)	0.071
ALT	54 (31–106)	50 (32–94)	0.325
AST	41 (28–70)	42 (28–70)	0.585
GGT	35 (20–81)	30 (18–65)	0.064
PLT (10^9/L)	135 (95–180)	133 (92–174)	0.368
Inflammation stage, n (%)			
G0	1 (0.1)	1 (0.3)	0.517
G1	124 (20.1)	47 (17.9)	
G2	290 (47.0)	138 (52.5)	
G3	177 (28.7)	69 (26.2)	
G4	25 (4.1)	8 (3.0)	
Fibrosis stage, n (%)			
S0	59 (9.6)	22 (8.4)	0.249
S1	144 (23.3)	68 (25.9)	
S2	173 (28.0)	89 (33.8)	
S3	159 (25.8)	55 (20.9)	
S4	82 (13.3)	29 (11.0)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatits B; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus: HBeAg, hepatitis B e antigen; PLT, platelet.

Continuous variables (HBV DNA, ALT, AST, GGT, PLT) were expressed as median and interquartile range (IQR), and categorical variables were summarized as counts and percentages.

[a]Data missing for 10 patients in the derivation data sets, 5 patients in the validation data sets.

[b]Data missing for 4 patients in the derivation data sets, 5 patients in the validation data sets.

each score). GPR (r = 0.45) had the highest correlation coefficient, followed by those of FIB-4 (r = 0.39) and APRI (r = 0.37). However, substantial overlap was observed in the distribution of the calculated scores. Higher scores of APRI, FIB-4, and GPR were associated with higher rates of cirrhosis (Figure 1). For APRI, cirrhosis was detected in 1 (0.8%) patient in the lowest quintile and 33 (26.8%) in the highest quintile. For FIB-4, cirrhosis was detected in 4 (3.3%) patients in the lowest quintile and 39 (31.7%) patients in the highest quintile. For GPR, cirrhosis was not detected in any patient in the lowest quintile and 38 (30.9%) patients in the highest quintile.

Diagnostic performance of APRI, FIB-4, and GPR to detect significant fibrosis and cirrhosis

The diagnostic performance of APRI, FIB-4, and GPR was evaluated using receiver operating characteristic (ROC) curves (Figure 2) and AUROCs (Table 2). For diagnosing significant fibrosis, the accuracy of APRI, FIB-4, and GPR was poor, and the AUROCs of these three indices were comparable (p > 0.05). Subgroup analyses are presented in Table S1; ALT, hepatitis B e antigen status, sex and age, HBV DNA, and antiviral status had no statistically significant impact on the performance of the diagnosis of significant fibrosis. For cirrhosis, performance of FIB-4 and GPR was similar (0.755 versus 0.773; p = 0.451), and GPR had a better diagnostic value than APRI (0.773 versus 0.733; p = 0.021). In the subgroup analyses (Table S1), the AUROCs of APRI, FIB-4, and GPR in the abnormal ALT (≥ULN) group were significantly lower than those of the normal ALT group. We observed that the AUROC of GPR in female patients was higher than in male patients (0.870 versus 0.742; p = 0.011). We also noticed that patients who received antiviral treatment within 6 months had a lower diagnostic performance than those who did not (AUROC, 0.758 versus 0.573; p = 0.017).

When applying conventional cutoffs to diagnose significant fibrosis, 42.0% (259/617) of patients had an APRI score of 0.5−1.5 and therefore could not be classified. Furthermore, 22.5% (93/414) of patients with significant fibrosis had an APRI score <0.5 and were incorrectly classified as having no significant fibrosis. A majority of the patients (59.1%, 120/203) without significant fibrosis had APRI scores >0.5 in the derivation cohort, and 42.9% (87/203) of those patients had GPR scores >0.32 (Table 2).

For cirrhosis, when conventional cutoffs were applied, 20.1% (124/617) of patients had an APRI score of 1.0−2.0 and thus could not be classified. Moreover, 31.7% (26/82) of patients with cirrhosis were misclassified as having no cirrhosis, with an APRI score <1.0 and a PPV of 28.2% for APRI >2.0. Because there are no widely accepted cutoffs for the diagnosis of

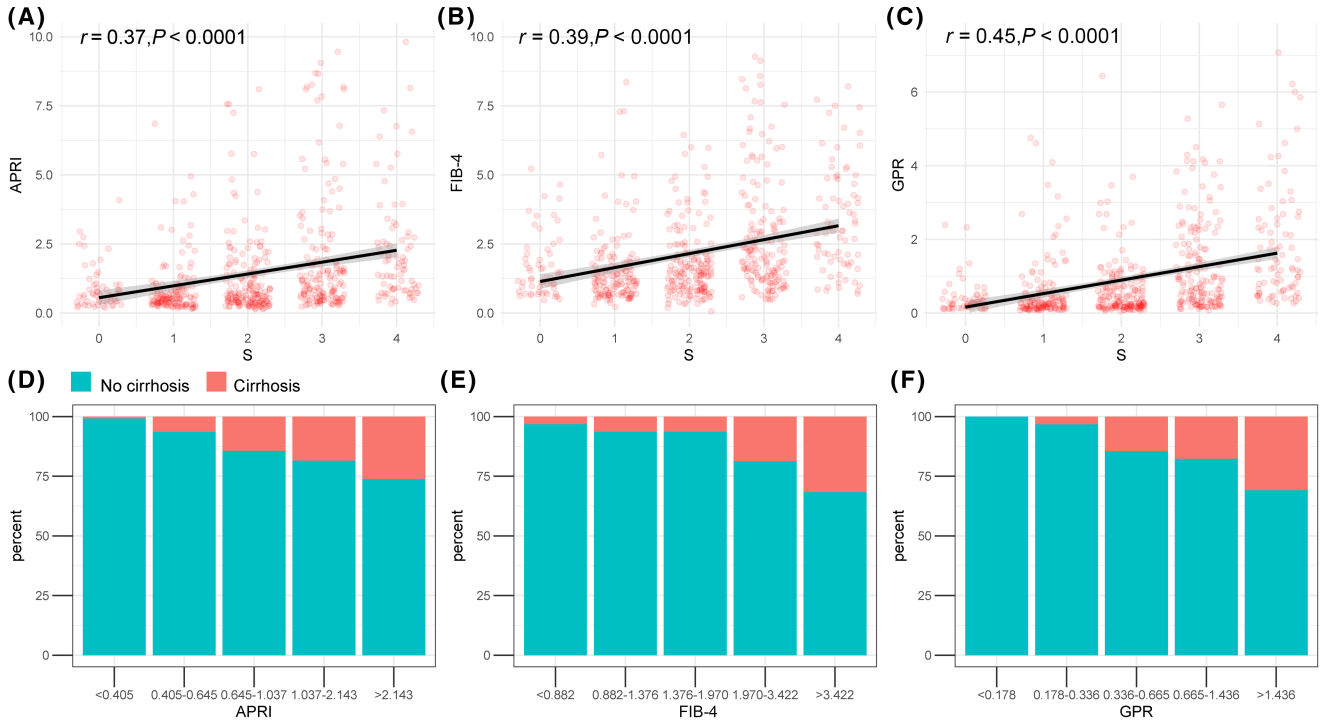

FIGURE 1 Correlation with liver fibrosis stages in the derivation cohort. Association between Scheuer fibrosis stages and (A) APRI, (B) FIB-4, and (C) GPR. The relationship between (D) APRI, (E) FIB-4, and (F) GPR with the presence of cirrhosis. Data were divided into quintiles. Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; GPR, gamma-glutamyl transpeptidase-to-platelet ratio

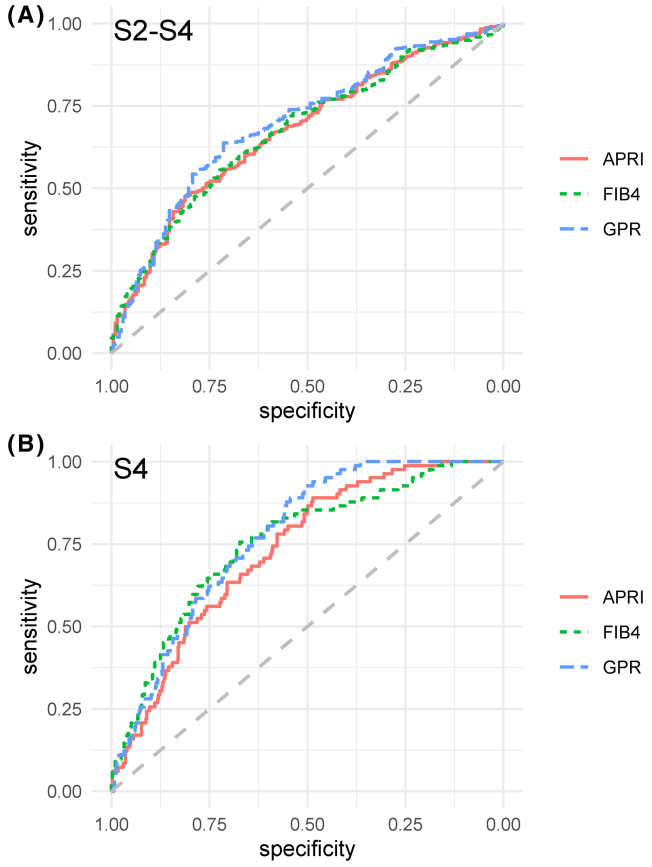

FIGURE 2 ROC curves of APRI, FIB-4, and GPR. ROC curves of APRI, FIB-4, and GPR in (A) prediction of significant fibrosis and (B) cirrhosis in the derivation cohort. Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; ROC, receiver operator characteristic

cirrhosis for FIB-4, we calculated the cutoff with the maximum Youden index. A FIB-4 of 2.04 had a PPV of 0.262 and an NPV of 0.947. Using 0.56 as the cut-off point of the GPR score as recommended by Lemoine et al.,[3] PPV and NPV were 23.4% and 94.8%, respectively (Table 2). In addition, 22.0% (18/82) of patients with cirrhosis had GPR scores below the cut-off value of 0.56.

High rates of misclassification were observed when using conventional cutoffs or when cutoffs calculated by the maximum Youden index were used to discriminate the degree of fibrosis; therefore, these cutoffs were not considered applicable to guide clinical decision making. It is worth noting that all cutoffs for these three indexes had high NPVs (>0.90) to exclude cirrhosis from noncirrhosis. Applying the cutoffs proposed by Sonneveld et al.[14] (APRI ≤0.45, FIB-4 ≤0.7), we could rule out cirrhosis with an NPV >0.95 and sensitivity of >0.90. However, using this cutoff of APRI and FIB-4, only 24.6% and 12.0%, respectively, of patients in our study population could be identified (Table 2). Meanwhile, no cutoffs for GPR have been proposed to exclude cirrhosis with an NPV >0.95 and sensitivity >0.90. Therefore, newly identified cutoffs for these three tests must be established.

Determining optimized cutoffs for APRI, FIB-4, and GPR to exclude cirrhosis in patients with CHB

To identify optimized cutoffs for the diagnosis of cirrhosis, we performed a grid search of cut-off points. The observed sensitivities and NPVs, specificities, and PPVs of the study population are shown in Figure 3. A cut-off point to rule in cirrhosis was not identified for the low PPV values of these three noninvasive tests. The grid search identified an APRI of 0.6, a FIB-4 of 1.1, and a GPR of 0.35 as the optimal cutoff to rule out cirrhosis based on our criteria. The performance of these cutoffs is shown in Table 3. A GPR score <0.35 can rule out cirrhosis in 42.8% of patients (377/880), and only 6.3% (7/111) of patients with cirrhosis were wrongly classified as no cirrhosis in the overall enrolled patients (Table 3). Subgroup analysis showed that GPR had a relatively stable performance in predicting cirrhosis (Table S2). A FIB-4 of 1.1 had a sensitivity of 91.5%, an NLR of 27.2%, and an NPV of 96.0% and misclassified 8.5% (7/82) of patients with cirrhosis. An APRI score of 0.6 had a sensitivity of 90.2%, an NLR of 23.5%, and an NPV of 96.5% and misclassified 9.8% (8/82) of patients with cirrhosis (Table 3). All new cutoffs identified in this study also showed great performance in the validation cohort. In the subgroup analysis, the sensitivity of APRI was influenced by several factors (Table S2). FIB-4 ≤1.1 had a high misclassification rate in patients aged <30 years and in female patients, and 20.0% of patients with cirrhosis were misclassified (Table S2).

For significant fibrosis, we could not identify applicable cutoffs to rule out based on our criteria (Figure S2). However, the identification of APRI ≥4.1 and FIB-4 ≥4.25 could be used to rule in, although this only applied to a very small number of patients (Table S2).

DISCUSSION

The degree of liver fibrosis can be used to determine treatment time and monitor disease progression in CHB. However, simple, accessible, noninvasive tests with high sensitivity and specificity are still lacking in health care resource-limited areas. Although the guidelines recommend APRI and FIB-4, which are derived from patients infected with chronic hepatitis C, as an index to assess the stage of fibrosis in patients with CHB,[2,17,18] the performance of these indices is still controversial. GPR, a newly identified model derived from patients with CHB, exhibited noninferior performance

TABLE 2 Diagnostic performances of APRI, FIB-4, and GPR to detect significant liver fibrosis and cirrhosis in the derivation cohort

Fibrotic levels	Scores	AUROC (95% CI)	Cutoffs	Number identified (%)	Sen	Spe	PPV	NPV	NLR	Acc
Significant liver fibrosis (S2-S4)	APRI	0.673 (0.629–0.717)	<0.5[a]	358 (58.0)	0.775	0.409	0.728	0.472	0.550	0.655
			>1.5[a]		0.370	0.857	0.841	0.400	0.735	0.530
			1.07	–	0.476	0.813	0.838	0.432	0.625	0.587
	FIB-4	0.674 (0.630–0.718)	1.76	–	0.556	0.724	0.804	0.444	0.613	0.611
	GPR	0.697 (0.654–0.741)	0.32[d]	–	0.710	0.571	0.772	0.492	0.508	0.665
			0.43	–	0.638	0.714	0.820	0.492	0.507	0.663
Cirrhosis (S4)	APRI	0.7329 (0.682–0.784)	<1[a]	493 (80.0)	0.683	0.628	0.220	0.928	0.505	0.635
			>2[a]		0.451	0.824	0.282	0.907	0.874	0.775
			≤0.45[c]	152 (24.6)	0.976	0.280	0.172	0.987	0.086	0.373
			0.69	–	0.890	0.486	0.210	0.967	0.226	0.540
	FIB-4	0.755 (0.699–0.810)	<1.45[b]	259 (42.0)	0.853	0.462	0.196	0.954	0.318	0.514
			≤0.7[c]	74 (12.0)	0.988	0.136	0.149	0.986	0.089	0.250
			2.04	–	0.756	0.673	0.262	0.947	0.363	0.684
	GPR	0.773 (0.733–0.757)	0.56[d]	–	0.780	0.607	0.234	0.948	0.362	0.630
			0.44	–	0.890	0.544	0.230	0.970	0.202	0.590

Abbreviations: Acc, accuracy rate; APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, area under the receiver operating characteristic; CI, confidence interval; FIB-4, fibrosis-4; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; NLR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity.

[a]Cut-off values for APRI recommended by the World Health Organization.

[b]Cutoffs recommended by Sonneveld et al.[14] used to rule out cirrhosis.

[c]Conventional cutoff of FIB-4 used to rule out advanced fibrosis.

[d]Cutoffs recommended by Lemoine et al.[3]

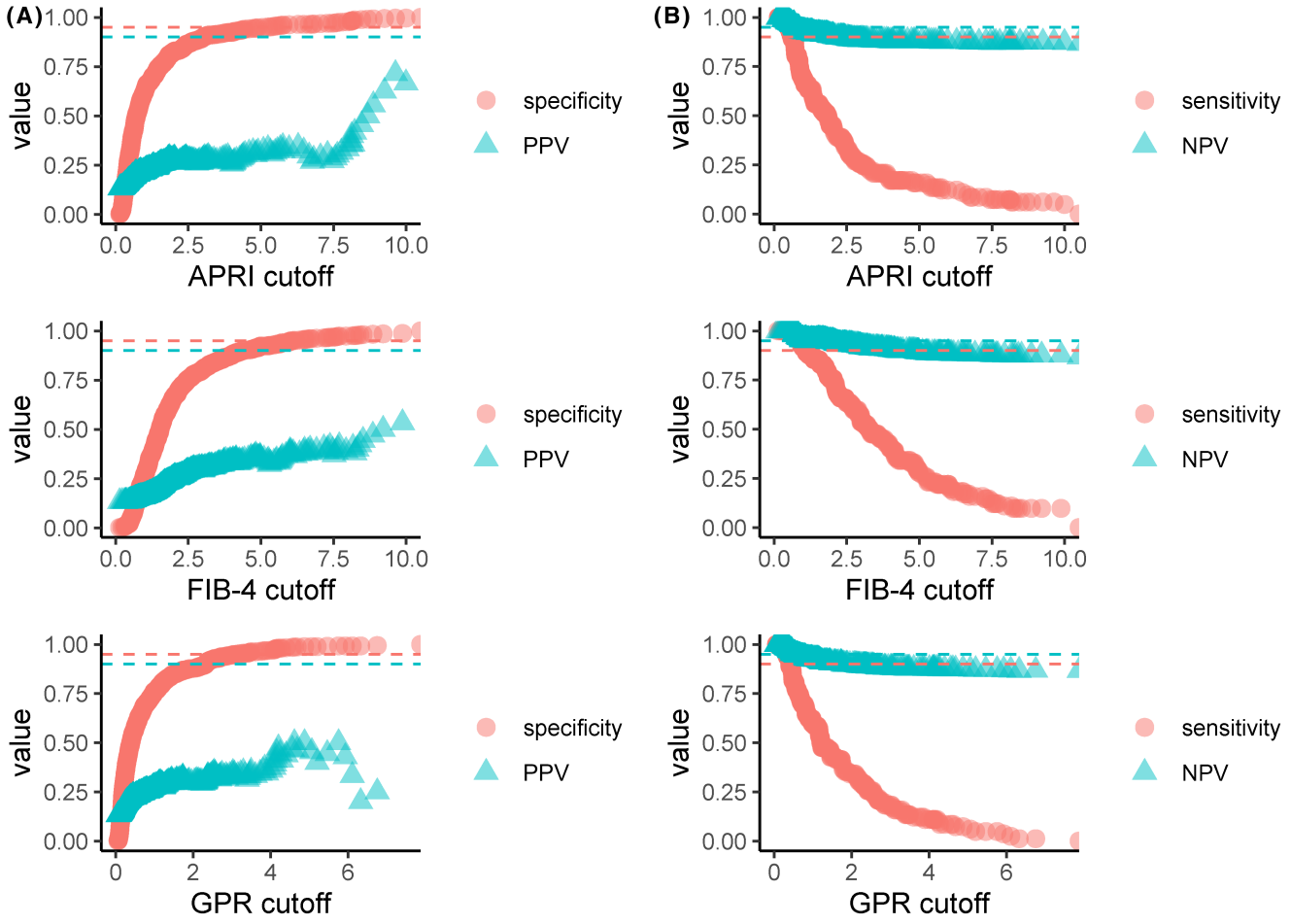

FIGURE 3 Diagnostic performance for the prediction of cirrhosis. (A) Specificity and PPV for various cutoffs of APRI, FIB-4, and GPR; (B) sensitivity and NPV for various cutoffs of APRI, FIB-4, and GPR. Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; NPV, negative predictive value; PPV, positive predictive value

compared to APRI and FIB-4 in several studies,[4–8] but opinions on this differ.[9–13]

In this study, we observed that both APRI and FIB-4 had moderate diagnostic values in identifying significant fibrosis and cirrhosis, but APRI had a lower performance in diagnosing cirrhosis compared to GPR. For all three indices, the AUROC for diagnosing cirrhosis was higher than that for significant fibrosis. Chen et al.[19] reported that the performance of FIB-4 and APRI in identifying cirrhosis seemed to improve at higher ALT levels while GPR was conversely impaired. However, in our study, the AUROCs of the three tests in detecting cirrhosis were decreased with higher ALT levels.

As described above, applying conventional cutoffs or cutoffs with the maximum Youden index of APRI, FIB-4, and GPR, a large number of patients could not be classified or were misclassified. Therefore, these cutoffs are discouraged for guiding clinical decisions. Using the optimal cutoffs recommended by Sonneveld et al.[14] to exclude liver cirrhosis, the sensitivity of APRI (<0.45) was 97.6% and the NPV was 98.7% and the sensitivity of FIB-4 (<0.7) was 98.8% and the NPV was 98.6%. These two cutoffs also showed acceptable performance in patients with normal ALT and patients with low HBV DNA levels (data not shown). However, only 24.6% and 12.0% of patients could be ruled out using these APRI and FIB-4 cutoffs, respectively. Optimized cutoffs for GPR to exclude cirrhosis are still lacking. Therefore, we also performed a grid search of cut-off points to identify optimal cutoffs for ruling out cirrhosis in patients with CHB.

For GPR, we identified a cutoff of 0.35 as the optimal cutoff with high sensitivity (>90%) and NPV (>95%) in both the derivation and validation cohorts. Lowering the cut-off dose increases the need for further testing (in 53.6% with the new GPR cutoff), but the new cutoff has a significantly lower misclassification rate (6.9% with the new GPR cutoff versus 22.0% with the conventional GPR cutoff). The newly identified cutoffs for APRI (≤0.6) and FIB-4 (≤1.1) also showed excellent overall performance in both groups (Table 3). However, the proportion of patients that APRI (31.2%) and FIB-4

TABLE 3 Performance of newly identified cutoffs in the study population

		Cutoff	Number identified	Cirrhosis	Sen	NPV	NLR	Misclassified[a]
APRI	Derivation	≤0.6	231(37.4%)	8	0.902	0.965	0.235	8/82 (9.8%)
	Validation	≤0.6	82 (31.2%)	2	0.931	0.980	0.165	2/29 (6.9%)
FIB-4	Derivation	≤1.1	174 (28.2%)	7	0.915	0.960	0.272	7/82 (8.5%)
	Validation	≤1.1	81 (30.8%)	0	1	1	0.000	0/29 (0.0%)
GPR	Derivation	≤0.35	255 (41.3%)	5	0.939	0.980	0.131	5/82 (6.1%)
	Validation	≤0.35	122 (46.4%)	2	0.931	0.984	0.134	2/29 (6.9%)

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; NLR, negative likelihood ratio; NPV, negative predictive value; Sen, sensitivity.

[a]Proportion of patients with cirrhosis wrongly classified as no cirrhosis.

(30.8%) could rule out was obviously lower than that of GPR (46.4%), and GPR had a more stable performance in all subgroups.

To our knowledge, this is the first study to identify a GPR cutoff with a sensitivity >90% and NPV >95% to rule out cirrhosis. However, several limitations and results of this study need to be highlighted. First, this was a single-center retrospective study with a limited number of patients, without an external validation cohort, and with individual cohorts drawn from only Asian ethnic cohorts. We plan to collect more samples from multiple sites in the future; this will be necessary to verify our established cutoffs. Second, the difference between the thresholds may be related to the difference in the prevalence of cirrhosis in the study population, known as spectrum bias. Third, the optimized cutoffs of GPR, APRI, and FIB-4 in this study can only be used to rule out cirrhosis; a more precise and wide coverage model for the prediction of fibrosis stage is required. Finally, all the clinical data were collected directly from electronic medical records.

In conclusion, the overall performance of APRI, FIB-4, and GPR in predicting significant fibrosis was comparable; however, APRI had lower performance in diagnosing cirrhosis. The application of conventional cutoffs of APRI, FIB-4, and GPR has high rates of misclassification, and its use in the diagnosis of the fibrosis stage is discouraged. The optimized cutoffs identified in this study could be used to rule out cirrhosis with a sensitivity >90% and an NPV of at least 95%. A new cutoff for GPR (<0.35) could rule out more patients without cirrhosis compared to APRI and FIB-4 and would have low misclassification rates and a more stable performance in subgroup analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Peng Hu, Hu Li, and Xiaoqing Liu contributed to the study conception and design. Data collection was performed by Xiaoqing Liu, Li Wei, and Qiao Tang. Analysis was performed by Xiaoqing Liu. The first draft of the manuscript was written by Xiaoqing Liu, and Peng Hu and Hu Li critically revised it. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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