

The Gamma-Glutamyl-Transpeptidase to Platelet Ratio Does not Show Advantages than APRI and Fib-4 in Diagnosing Significant Fibrosis and Cirrhosis in Patients With Chronic Hepatitis B

A Retrospective Cohort Study in China

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Abstract: The gamma-glutamyl-transpeptidase to platelet ratio (GPR) is a new liver fibrosis model, which is reported to be more accurate than aspartate transaminase (AST) to platelet ratio index (APRI) and fibrosis index based on the four factors (Fib-4) for diagnosing significant fibrosis and cirrhosis in patients with chronic hepatitis B (CHB) in West Africa.

The aim of this study is to assess the diagnostic accuracy of GPR for significant fibrosis and cirrhosis in Chinese CHB patients, and explore whether GPR deserves to be popularized in China.

A total of 372 CHB patients who underwent liver biopsies and routine laboratory tests were retrospectively studied. The Scheuer scoring system was adopted as the pathological standard of liver fibrosis. Using liver histology as a gold standard, the diagnostic accuracies of GPR, APRI, and Fib-4 for significant fibrosis and cirrhosis are evaluated and compared by the receiver operating characteristic (ROC) curves and the area under the ROC curves (AUROCs).

Of these 372 patients, 176 (47.3%), 129 (34.7%), and 72 (19.4%) were classified as having significant fibrosis (\geq S2), severe fibrosis (\geq S3), and cirrhosis (S4), respectively. The AUROCs of GPR for significant fibrosis (0.72 vs. 0.78; $P=0.01$), severe fibrosis (0.75 vs. 0.80; $P=0.04$), and cirrhosis (0.78 vs. 0.83; $P=0.02$) were lower than those of APRI. The AUROCs of GPR and Fib-4 for diagnosing significant fibrosis (0.72 vs. 0.70; $P=0.29$), severe fibrosis (0.75 vs. 0.73; $P=0.33$), and cirrhosis (0.78 vs. 0.75; $P=0.38$) were comparable.

GPR is a new serum diagnostic model for liver fibrosis and cirrhosis, but does not show advantages than APRI and Fib-4 in identifying significant fibrosis, severe fibrosis, and cirrhosis in CHB patients in China.

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Abbreviations: ALT = alanine transaminase, APRI = aspartate transaminase to platelet ratio index, AST = aspartate transaminase, AUROC = area under receiver operating characteristic curve, CHB = chronic hepatitis B, CI = confidence interval, Fib-4 = fibrosis index based on the 4 factors, GGT = gamma-glutamyl-transpeptidase, GPR = gamma-glutamyl-transpeptidase to platelet ratio, HBeAg = hepatitis B virus e antigen, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, NPV = negative predictive value, PPV = positive predictive value, ROCcurve = receiver operating characteristic curve.

INTRODUCTION

In China, hepatitis B virus (HBV) infection is moderately endemic, and chronic hepatitis B (CHB) is the main cause of hepatocellular carcinoma (HCC), which is one of the most frequent cancers in China.^{1,2} The CHB patients with significant fibrosis and cirrhosis have a higher chance of developing liver decompensation, HCC, and death.³ To reduce the disease burden of HBV infection, it may be critical to identify patients with significant fibrosis and cirrhosis, and treat them immediately.³ However, liver biopsy, the gold standard for diagnosing liver fibrosis and cirrhosis, is not performed in all hospitals (especially in primary care) because of its invasiveness, expensive procedure, and complications. Transient elastography (Fibroscan), which measures liver stiffness, is increasingly being recognized as an excellent tool for diagnosing liver fibrosis and cirrhosis because of its noninvasive nature, reproducibility, and high diagnostic performance.⁴⁻⁶ However, the Fibroscan device is expensive (€34,000 for the portable machine) and requires annual maintenance (€5000). In China, the machine is often only accessible in the main hospitals in the main cities. Thus, simple, inexpensive, and noninvasive fibrosis models are still urgently needed in China.

In recent years, the development of new serum models for diagnosing liver fibrosis and cirrhosis has been a hot research topic. Simple models such as the aspartate transaminase (AST) to platelet ratio index (APRI) and the fibrosis index based on the four factors (Fib-4) have the advantage of comprising only inexpensive laboratory tests, which are available in primary

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care.⁷ The first WHO guidelines on the prevention, care, and treatment of patients with CHB recommended APRI and Fib-4 as noninvasive tools to detect cirrhosis in resource-limited settings.³ However, the APRI and Fib-4 have faced some problems, such as the low level of sensitivity and positive predictive value (PPV) for diagnosing cirrhosis, and the lack of enough accuracy for diagnosing mild to moderate liver fibrosis. Accordingly, the new fibrosis models are needed urgently.

In June 2015, Lemoine et al identified a new serum fibrosis model, the gamma-glutamyl-transpeptidase (GGT) to platelet ratio (GPR), in a cohort of 135 CHB patients in Gambia, West Africa, and then assessed its diagnostic accuracy in two external validation cohorts (80 patients from Senegal, West Africa, and 63 patients from France, Europe, respectively).⁸ The results show that GPR is more accurate than APRI and Fib-4 in West Africa, but not superior to APRI and Fib-4 in France.⁸ As the authors conclude, because of the small sample, there is no consensus in the three cohorts, GPR needs further evaluation in other cohorts. At present, there is a lack of data about the diagnostic value of GPR for liver fibrosis and cirrhosis in CHB patients in China, and clinical research is needed to verify whether GPR deserves to be popularized in China. Using liver histology as a gold standard, we compared the performances of GPR, APRI, and Fib-4 for diagnosing significant fibrosis and cirrhosis in 372 CHB patients, and explored whether GPR deserves to be popularized in China.

MATERIALS AND METHODS

Study Population

A total of 456 consecutive CHB patients who underwent liver biopsies at department of hepatitis, Shanghai Public Health Clinical Center, between March 2013 and April 2015, were retrospectively screened. CHB was defined as the persistent presence of serum HBV surface antigen (HBsAg) for >6 months.⁹ Patients with the following conditions were excluded from this study: antiviral treatment (30 patients), co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus (11 patients), accompanied by significant alcohol consumption (>20 g/day) (22 patients), nonalcoholic fatty liver disease (17 patients), and autoimmune liver disease (4 patients). Finally, 372 patients were included in this study.

The study protocol was permitted by the ethics committee of Shanghai Public Health Clinical Center, and the procedures were in accordance with the Helsinki declaration of 1975, as revised in 1983.

Liver Histological Examination

An ultrasonography-guided percutaneous liver biopsy was performed using a 16-G disposable needle (Hepafix, B. Braun, Melsungen, Germany) under local anesthesia. Liver samples of minimum length 15 mm were immediately formalin-fixed and paraffin-embedded for histological analysis. Liver biopsy samples of <15 mm length or <6 portal tracts were considered to be inadequate for histopathologic scoring by the histopathologists in our hospital, a tertiary referral teaching hospital in China. The Scheuer scoring system was adopted as the pathological standard of liver fibrosis.¹⁰ Liver fibrosis was classified into five stages: S0, no fibrosis; S1, fibrosis confined to portal tracts, periportal spaces, and perisinusoidal spaces, or fibrous scar in the hepatic lobule; hepatic lobular structure integrity; S2, bridging fibrosis; most of the hepatic lobular structure integrity;

S3, a lot of fibrous septa are separated and/ or involve the hepatic lobule with distortion of the lobular structure, but without cirrhosis; and S4: early period of cirrhosis (liver parenchyma is damaged extensively, with diffuse fiber hyperplasia, liver cells are in various degrees of regeneration, and false lobule is formed). All biopsy samples were interpreted independently by two liver pathologists who were blinded to any clinical information including the results of noninvasive tests. If they failed to reach an agreement, a third highly experienced hepatopathologist reviewed the material under the microscope and the results were given by joint discussion of three pathologists.

Routine Laboratory Tests

Fasting blood samples were obtained and routine laboratory tests were performed at the time of liver biopsy. The HBV serological markers were detected with commercially available enzyme-linked immunosorbent assay (ELISA) kits (ARCHITECT i2000 SR, Abbott, Wiesbaden, Germany). Routine blood was detected with an automated hematology analyzer (XT-2000i, Sysmex, Kobe, Japan). The serum biochemical parameters including ALT, AST, and GGT were measured by full automation biochemist analyzer (7600 Series, Hitachi, Tokyo, Japan). HBV DNA levels were quantified by the real-time PCR system (ABI 7500; Applied Biosystems, Foster City, CA), with the lowest detection limit at 500 copies/mL.

Models Calculation

The formulas for GPR, APRI, and Fib-4 are as follows: (1) $GPR = (GGT \text{ (IU/L)} / ULN \text{ of GGT}) / \text{platelet count } (10^9 / L) \times 100$; (2) $APRI = (AST \text{ (IU/L)} / ULN \text{ of AST}) / \text{platelet count } (10^9 / L) \times 100$; (3) $Fib-4 = (\text{age (years)} \times AST \text{ (IU/L)}) / (\text{platelet count } (10^9 / L) \times (ALT \text{ (IU/L)})^{1/2})$.

Statistical Analysis

The baseline characteristics of patients are presented as follows: normal distribution data as mean \pm standard deviation, non-normal distribution continuous data as median (interquartile range (IQR)), and categorical variables as number (percentage). Chi-square test (for categorical variables), Mann-Whitney test (for non-normal distribution continuous variables), and *t* test (for normal distribution variables) were performed to identify the statistical differences between two groups.¹¹ The correlations of serum models with liver fibrosis stages were analyzed using the Spearman test. The diagnostic performance of serum model for liver fibrosis and cirrhosis was estimated by the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUROC).¹² All significance tests were two-tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using the SPSS statistical software version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics of Patients

The baseline characteristics of patients are presented in Table 1. The majority of patients were men (69.1%), HBeAg positive (57.5%), and middle aged (39 ± 11 years). Median HBV DNA, ALT, AST, GGT, BMI, and size of liver biopsy were 5.4 log₁₀ copies/mL (IQR = 3.8–6.2), 40 IU/L (IQR = 25–60), 33 IU/L (IQR = 24–55), 33 IU/L (IQR = 19–

TABLE 1. Baseline Characteristics of the Study Population

	Total (n = 372)	S0–S1 (n = 196)	S2–S4 (n = 176)	P Value
Man (n, %)	257 (69.1%)	140 (71.4%)	117 (66.5%)	0.54
Age (year)	39 ± 11	38 ± 11	40 ± 12	0.07
HBeAg positive, n (%)	214 (57.5%)	116 (59.2%)	98 (55.7%)	0.24
HBV DNA (log10 copies/mL)	5.4 (3.8–6.2)	5.5 (3.7–6.4)	5.3 (4.0–5.9)	0.069
ALT (IU/L)	40 (25–60)	39 (22–56)	42 (28–64)	0.08
AST (IU/L)	33 (24–55)	28 (21–43)	41 (27–63)	<0.001
GGT (IU/L)	33 (19–65)	23 (16–40)	45 (27–97)	<0.001
Platelet (10 ⁹ /L)	144 (109–179)	162 (132–194)	126 (91–161)	<0.001
GPR	0.67 (0.38–1.15)	0.45 (0.31–0.76)	0.89 (0.55–1.48)	<0.001
APRI	0.51 (0.29–1.24)	0.33 (0.20–0.55)	0.93 (0.44–2.06)	<0.001
Fib-4	1.47 (0.96–2.47)	1.16 (0.82–1.65)	1.89 (1.21–3.30)	<0.001
Median BMI (kg/m ²)	22.4 (20.5–24.9)			
Median size of liver biopsy (mm)	24 (19–28)			
Number of portal tracts	8 ± 2			
Inflammation stage (G0/G1/G2/G3/G4)	62 (16.7%)/137 (36.8%)/74 (19.9%)/57 (15.3%)/42 (11.3%)			
Fibrosis stage (S0/S1/S2/S3/S4)	43 (11.6%)/153 (41.1%)/47 (12.6%)/57 (15.3%)/72 (19.4%)			

ALT = alanine transaminase, APRI = AST to platelet ratio index, AST = aspartate transaminase, BMI = body mass index, Fib-4 = fibrosis index based on the four factors, GGT = gamma-glutamyl-transpeptidase, GPR = GGT to platelet ratio index, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, IU = international unit.

P < 0.05 indicates a significant difference between S0–S1 and S2–S4 group.

65), 22.4 kg/m² (IQR = 20.5–24.9), and 24 mm (IQR = 19–28), respectively; and mean number of portal tracts was 8. Median GPR, APRI, and Fib-4 were 0.67 (IQR = 0.38–1.15), 0.51 (IQR = 0.29–1.24), and 1.47 (IQR = 0.96–2.47). The liver fibrosis was distributed as follows: S0 = 43 (11.6%); S1 = 153 (41.1%); S2 = 47 (12.6%); S3 = 57 (15.3%); and S4 = 72 (19.4%). Of 372 patients, 176 (47.3%), 129 (34.7%), and 72 (19.4%) were classified as having significant fibrosis (≥ S2), severe fibrosis (≥ S3), and cirrhosis (S4), respectively.

The patients with significant fibrosis had higher AST (41 (27–63) vs. 28 (21–43) IU/L, *P* < 0.001), GGT (45 (27–97) vs. 23 (16–40) IU/L, *P* < 0.001), GPR (0.89 (0.55–1.48) vs. 0.45 (0.31–0.76), *P* < 0.001), APRI (0.93 (0.44–2.06) vs. 0.33 (0.20–0.55), *P* < 0.001), and Fib-4 (1.89 (1.21–3.30) vs. 1.16 (0.82–1.65), *P* < 0.001), but lower platelet count (126 (91–161) vs. 162 (132–194) × 10⁹/L, *P* < 0.001) compared with patients without significant fibrosis (Table 1). No significant differences were seen in sex, age, proportion of HBeAg positive, HBV DNA, and ALT between patients with and without significant fibrosis (Table 1).

Correlations Between Serum Models and Liver Fibrosis Stages

The correlations of serum models with liver fibrosis stages were analyzed using the Spearman test (Table 2). Liver fibrosis significantly correlated with APRI (Spearman’s *r* = 0.532, *P* < 0.001), GPR (Spearman’s *r* = 0.475, *P* < 0.001), and Fib-4 (Spearman’s *r* = 0.459, *P* < 0.001). As shown in Table 2, the APRI has the highest correlation coefficient, followed by GPR and Fib-4.

Diagnostic Performances of Serum Models for Liver Fibrosis and Cirrhosis

The ROC curves of APRI, GPR, and Fib-4 for diagnosing significant fibrosis (Figure 1A), severe fibrosis (Figure 1B), and cirrhosis (Figure 1C) are shown in Figure 1. The AUROCs of serum models for diagnosing liver fibrosis and cirrhosis are shown in Table 3. The AUROCs of GPR for significant fibrosis (0.72 vs. 0.78; *P* = 0.01), severe fibrosis (0.75 vs. 0.80; *P* = 0.04), and cirrhosis (0.78 vs. 0.83; *P* = 0.02) were lower

TABLE 2. Correlations Between Serum Models and Liver Fibrosis Stages

Variables	Spearman's <i>r</i>	<i>P</i> Value
APRI	0.532	<0.001
GPR	0.475	<0.001
Fib-4	0.459	<0.001

APRI = aspartate transaminase to platelet ratio index, Fib-4 = fibrosis index based on the 4 factors, GPR = gamma-glutamyl-transpeptidase to platelet ratio index.

Spearman's *r*, correlation coefficient.

than those of APRI. The AUROCs of GPR and Fib-4 for diagnosing significant fibrosis (0.72 vs. 0.70; *P* = 0.29), severe fibrosis (0.75 vs. 0.73; *P* = 0.33), and cirrhosis (0.78 vs. 0.75; *P* = 0.38) were comparable (Table 3).

Diagnostic Thresholds and Accuracies of Serum Models for Liver Fibrosis and Cirrhosis

Diagnostic thresholds and accuracies of serum models for liver fibrosis and cirrhosis are presented in Table 4. According to maximizing the sum of sensitivity and specificity, the optimal cut-off values of GPR were 0.61, 0.65, and 0.72, for diagnosing significant fibrosis (the corresponding sensitivity, specificity, PPV, NPV, and correct classified were 71%, 69%, 68%, 73%, and 70%, respectively), severe fibrosis (the corresponding sensitivity, specificity, PPV, NPV, and correct classified were 77%, 64%, 53%, 84%, and 69%, respectively), and cirrhosis (the corresponding sensitivity, specificity, PPV, NPV, and correct classified were 81%, 53%, 29%, 92%, and 58%, respectively) (Table 4).

The optimal cut-off values of APRI were 0.64, 0.68, and 0.77, for diagnosing significant fibrosis (the corresponding sensitivity, specificity, PPV, NPV, and correct classified were 62%, 82%, 75%, 70%, and 72%, respectively), severe fibrosis (the corresponding sensitivity, specificity, PPV, NPV, and correct classified were 74%, 74%, 60%, 84%, and 74%, respectively), and cirrhosis (the corresponding sensitivity, specificity, PPV, NPV, and correct classified were 76%, 71%, 39%, 93%, and 72%, respectively), respectively (Table 4). At the WHO cut-off value of APRI (2.0), the sensitivity, specificity, PPV, NPV, and correct classified were 18%, 95%, 48%, 70%, and 83%, respectively for diagnosing cirrhosis (Table 4).

DISCUSSION

Liver fibrosis is a common pathological process in various chronic liver diseases, including CHB. In patients with CHB, a pathological finding of significant fibrosis indicates the need for antiviral therapy.³ CHB patients with cirrhosis should not only potentially be treated for longer duration but also monitored for complications related to portal hypertension and regularly screened for HCC.¹³ Therefore, early detection of significant fibrosis and cirrhosis is an essential step in deciding treatment commencement, course of treatment, and prognosis of CHB patients. However, assessing the severity of liver fibrosis is still one of the main challenges in clinical practice, especially in resource-limited settings where liver biopsy and Fibroscan is impractical.

In June 2015, Lemoine et al developed a new fibrosis model, the GPR, to identify HBV-infected subjects with significant fibrosis or cirrhosis in West Africa.⁸ To date, GPR has been compared with APRI and Fib-4 in patients with CHB in three cohorts with conflicting results. Two cohorts (Gambia cohort and Senegal cohort in 135 and 80 CHB patients, respectively) suggested that GPR is more accurate than APRI and Fib-4 in diagnosis of significant fibrosis and cirrhosis, whereas another cohort from France in 63 CHB patients reported similar accuracy for significant fibrosis and cirrhosis. Further data are required to evaluate if GPR has superior accuracy for detecting significant fibrosis and cirrhosis as compared with APRI and Fib-4.⁸ In the large sample size retrospective study, we found that GPR does not show advantages than APRI and Fib-4 in identifying significant fibrosis, severe fibrosis, and cirrhosis in CHB patients in China. APRI, which has been recommended by the WHO guidelines, may be the best serum diagnostic model for liver fibrosis and cirrhosis in China.

Some reasons may be helpful to determine why the GPR, which shows application prospect in West Africa, is not useful in Chinese CHB patients. Firstly, these studies have been conducted in heterogeneous populations. Most of patients in our cohort are HBeAg seropositive (57.5%) and high HBV DNA levels (median, 5.4 log10 copies/mL), which is in line with the standard of "immune tolerant phase" or "immune clearance phase."⁹ However, in the Gambia (West African) cohort, most of patients are HBeAg seronegative (96%) and low HBV DNA levels (median, 2.6 log10 copies/mL), which is in line with the standard of "inactive phase" or "HBeAg-negative hepatitis."⁹ Secondly, HBV genotype may be one reason for why GPR is not useful in Chinese CHB patients. Although we didn't detect the HBV genotypes of 372 CHB patients in this

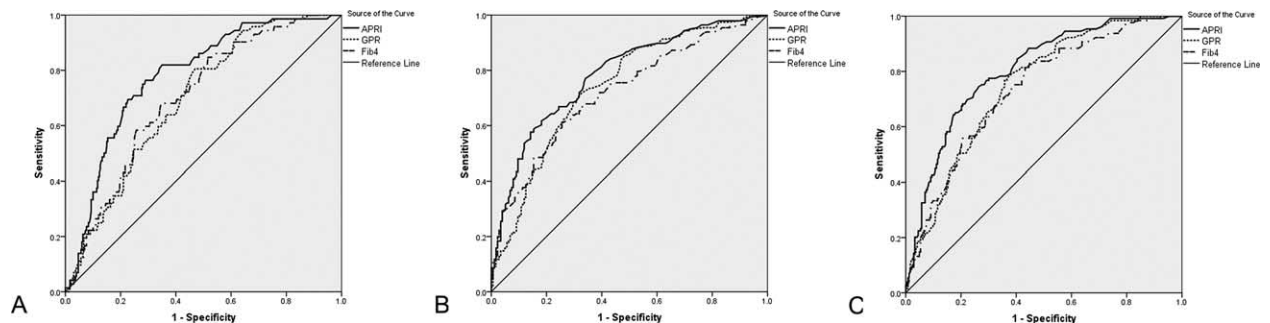


FIGURE 1. ROC curves of GPR, APRI, and Fib-4 for diagnosing significant fibrosis (A), severe fibrosis (B), and cirrhosis (C). APRI = AST to platelet ratio index, Fib-4 = fibrosis index based on the four factors, GPR = GGT to platelet ratio index, ROC = receiver operating characteristic.

TABLE 3. Diagnostic Performances of Serum Models for Liver Fibrosis and Cirrhosis

	Significant Liver Fibrosis (≥ S2)			Severe Liver Fibrosis (≥ S3)			Cirrhosis (S4)		
	AUROC	(95% CI)	P Value	AUROC	(95% CI)	P Value	AUROC	(95% CI)	P Value
APRI	0.78	(0.74–0.83)	<0.001	0.80	(0.76–0.85)	<0.001	0.83	(0.77–0.87)	<0.001
GPR	0.72	(0.69–0.77)	<0.001	0.75	(0.70–0.80)	<0.001	0.78	(0.72–0.83)	<0.001
Fib-4	0.70	(0.67–0.74)	<0.001	0.73	(0.68–0.79)	<0.001	0.75	(0.69–0.81)	<0.001
Comparison of AUROC									
GPR and APRI	P = 0.01			P = 0.04			P = 0.02		
GPR and Fib-4	P = 0.29			P = 0.33			P = 0.38		
APRI and Fib-4	P = 0.03			P = 0.02			P = 0.03		

APRI = aspartate transaminase to platelet ratio index, AUROC = the area under the receiver operating characteristic curve, CI = confidence interval, Fib-4 = fibrosis index based on the four factors, GPR = gamma-glutamyl-transpeptidase to platelet ratio index.

cohort, we have a reason to believe that there's a big difference in HBV genotypes between this cohort and the West African cohorts. On the basis of present epidemiological evidence, genotype A is highly prevalent in sub-Saharan Africa, Northern Europe, and Western Africa, and genotypes B and C are common in Asia, including China.^{14–17} Thirdly, the difference in sample size and spectrum bias of cirrhosis may lead to different results between this cohort and the Western Africa cohorts. The Gambia cohort (135 patients) and Senegal cohort (80 patients) in Western Africa are underpowered with small sample size and very few patients with cirrhosis (15% for Gambia cohort and 0 for Senegal cohort). Our cohort is more believable with large samples (372 patients) and sizable patients with cirrhosis (19%). Fourthly, the different histological scoring systems between this cohort (Scheuer scoring systems) and the Western Africa cohorts (Metavir scoring systems) might be another reason for the diametrically opposite conclusions.

According to the recent European Association For the Study of the Liver (EASL)-Asociación Latinoamericana para el Estudio del Hígado (ALEH) Clinical Practice Guidelines for noninvasive tests for evaluation of liver disease severity and

prognosis, the median AUROCs of APRI in diagnosis of significant fibrosis and cirrhosis were 0.77 and 0.84, respectively.¹⁸ The AUROCs of APRI in diagnosis of significant fibrosis and cirrhosis are 0.78 (95% CI = 0.74–0.83) and 0.83 (0.77–0.87) in our study. So, we think the performances of APRI were acceptable in our cohort. However, the performances of APRI were surprisingly low in West African cohort (AUROC = 0.62–0.66 for significant fibrosis; 0.70 for cirrhosis). Difference between performances may be related to difference in disease phenotype and HBV genotype between this cohort and the West African cohort. Difference in the prevalence of significant fibrosis and cirrhosis in the studied populations might be also one reason for the different performances of APRI between this cohort and the West African cohort, known as the spectrum bias.^{19,20}

The WHO guidelines recommend a single cut-off value of the APRI score (2.0) to diagnose cirrhosis in resource-limited countries.³ In this study, by applying the WHO cut-off value of APRI, the sensitivity and specificity for the diagnosis of cirrhosis was 18% and 95%, respectively. This implies that 82% of patients with cirrhosis might be erroneously categorized as patients without

TABLE 4. Diagnostic Thresholds and Accuracies of Serum Models for Liver Fibrosis and Cirrhosis

	Cut-off Value	Se (%)	Sp (%)	PPV (%)	NPV (%)	Correct Classified (%)
GPR						
≥ S2	0.61	71	69	68	73	70
≥ S3	0.65	77	64	53	84	69
= S4	0.72	81	53	29	92	58
APRI						
≥ S2	0.64	62	82	75	70	72
≥ S3	0.68	74	74	60	84	74
= S4	0.77	76	71	39	93	72
	2.0 (WHO threshold)	18	95	48	70	83
Fib-4						
≥ S2	1.1	61	74	68	68	68
≥ S3	1.3	81	57	50	85	65
= S4	1.6	85	50	29	93	56

Cut-off values were established by maximizing the sum of sensitivity and specificity; WHO threshold as recommended in the “Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection (March 2015).” Liver fibrosis staging was determined using Scheuer classification; significant fibrosis was defined as ≥ S2; severe fibrosis was defined as ≥ S3; cirrhosis was defined as S4.

APRI = aspartate transaminase to platelet ratio index, Fib-4 = fibrosis index based on the four factors, GPR = gamma-glutamyl-transpeptidase to platelet ratio index, NPV = negative predictive value, PPV = positive predictive value, Se = sensitivity, Sp = specificity, WHO = world health organization.

cirrhosis, but 95% of patients with APRI ≥ 2 have cirrhosis. The cut-off value of APRI proposed by the WHO guidelines provided high specificity for the diagnosis of cirrhosis, at a cost of very low sensitivity. This limits the usefulness of APRI as screening tests and selection of candidates for liver biopsy. In our study, by using the cut-off value derived from the maximum Youden index (sensitivity + specificity - 1), the cut-off value of APRI is 0.77 to diagnose cirrhosis, and the corresponding sensitivity, specificity, PPV, and NPV were 76%, 71%, 39%, and 93%, respectively. The cut-off value of APRI in this study (0.77) is more appropriate for screening cirrhosis and selection of candidates for liver biopsy, and the WHO cut-off value of APRI is more appropriate for diagnosing cirrhosis in Chinese CHB patients.

It is undeniable that this study has some biases. First, according to the Asian-Pacific consensus statement on the management of CHB,⁹ liver biopsy was mainly performed in patients with normal or mildly abnormal ALT level, and we could not invite all of the CHB patients for liver biopsy. As a result, the patients included in this study are not representative of the general population with CHB in China. This might have caused verification bias resulting in overestimated sensitivities and underestimated specificities of these serum models.²¹ Second, this study has been conducted in tertiary referral centers with a higher proportion of patients with significant fibrosis and cirrhosis than in the general population, making it difficult to extrapolate the performances of these models in detecting significant fibrosis and cirrhosis in general populations, known as the spectrum bias.^{19,20}

In conclusion, GPR, which shows application prospect in West Africa, does not show advantages than APRI and Fib-4 in identifying significant fibrosis, severe fibrosis, and cirrhosis in CHB patients in China. GPR may not be accurate enough to deserve to be popularized in Chinese CHB patients.

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