Comparison and evaluation of non-invasive models in predicting liver inflammation and fibrosis of chronic hepatitis B virus-infected patients with high hepatitis B virus DNA and normal or mildly elevated alanine transaminase levels

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Abstract

Few studies have paid attention to the performances of non-invasive models in diagnosing stages of liver fibrosis and inflammation, which are critical for early and accurate assessment of prognostication and decisions on antiviral treatment in chronic hepatitis B infection patients with high hepatitis B virus DNA and normal or mildly elevated alanine transaminase levels ($\leq$2 times upper limit of normal (ULN)). This study aimed to investigate the value of routine serum markers in evaluation of liver inflammation and fibrosis in these patients.

A total of 370 consecutive chronic hepatitis B virus-infected patients who underwent liver biopsy were retrospectively analyzed. The Scheuer scoring system was adopted as the pathological standard for diagnosing liver inflammation and fibrosis. The receiver-operating characteristic curves (ROC) and the area under the ROC curves (AUROCs) were used to analyze the performances of the models, including aspartate transaminase to platelet ratio index (APRI), fibrosis index based on the 4 factors (FIB-4), red cell volume distribution width-to-platelet ratio (RPR), globulin-platelet model (GP), and gamma-glutamyl transpeptidase to platelet ratio index (GPR).

To predict significant inflammation (G $\geq$2), the AUROC of APRI was higher than that of FIB-4 (0.705 vs 0.629, $P = .001$), RPR (0.705 vs 0.593, $P < .001$) and GP (0.705 vs 0.620, $P = .002$), equivalent to that of GPR (0.705 vs 0.690, $P = .606$). As for severe inflammation ($\geq$G3) and significant fibrosis ($\geq$S2), there was no statistic difference among them. To predict severe fibrosis ($\geq$ S3), the AUROC of FIB-4 was higher than that of RPR (0.805 vs 0.750, $P = .006$) and GP (0.805 vs 0.755, $P = .046$), comparable to that of APRI (0.805 vs 0.785, $P = .550$) and GPR (0.805 vs 0.818, $P = .694$). As for significant liver histological changes (G $\geq$ 2 or/and S $\geq$ 2), the performance of APRI was higher than that of RPR (0.717 vs 0.652, P = .006), GP (0.717 vs 0.659, p = .011), equivalent to that of FIB-4 (0.717 vs 0.692, $P = .254$) and GPR (0.717 vs 0.680, $P = .166$).

We found that APRI, GPR, and FIB-4 were more effective than RPR and GP for diagnosing liver inflammation and fibrosis.

Abbreviations: ALT = alanine transaminase, APRI = aspartate transaminase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on the four factors, GGT = gamma-glutamyl transpeptidase, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index, HBV = hepatitis B virus, RPR = red cell volume distribution width-to-platelet ratio, ULN = upper limit of normal.

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1. Introduction

Hepatitis B virus (HBV) infection is still a major public health problem worldwide, which may cause hepatocellular necrosis and inflammation, even serious complications including cirrhosis with end-stage liver disease and hepatocellular carcinoma.[1] At present, it is estimated that there are about 70 million chronic carriers of HBV surface antigen (5% to 6% prevalence) and 0.5 million newly diagnosed cancer cases annually in China.[2–4]

To reduce the burden of HBV infection, the early and accurate diagnosis of liver inflammation and fibrosis, as well as the treatment with antiviral therapy may be critical. Although liver biopsy has been recommended as the gold standard method to assess the degree of fibrosis, it was limited because of its high cost and invasive procedure, which might cause the risks of bleeding and pneumothorax.[5] Recently, serum biomarkers including the aspartate aminotransferase-to-platelet ratio index (APRI), the fibrosis index based on the four factors (FIB-4), and Fibroscan have been recommended by the WHO as alternatives for liver biopsy.[6] Compared with the Fibroscan requiring the high cost of the equipment and trained operator, blood or serum indices are more available, simple and practical for the most public particularly in resource-limited settings. In addition, the innovative non-invasive models based on serum markers have been developed, including the red cell volume distribution width-to-platelet ratio (RPR),[7–9] globulin-platelet model (GP),[10–12] and the gamma-glutamyl transpeptidase-to-platelet ratio (GPR),[13–15] which are still under controversy in HBV-infected patients.

Liver fibrosis is a compensatory repair process involved hepatic inflammation. The serum alanine transaminase (ALT), a cytoplasmic enzyme in hepatocytes, is usually used to identify liver cell injury and its level $\geq$2 ULN is adopted as 1 of the criterions for antiviral treatment in CHB patients.[16] However, some recent studies suggested that patients with "normal" ALT might still suffer from liver histological changes even need antiviral therapy.[17] Given the spectrum of disease and natural history of chronic HBV infection diverse, according to the WHO guidelines[6] the non-invasive fibrosis models should be used alongside the clinical criteria and other laboratory criteria (ALT and HBV DNA levels). Therefore, we evaluated the clinical significances of the above five non-invasive models in diagnosing liver inflammation and fibrosis, as well as significant liver histological changes in chronic HBV-infected patients with high HBV DNA and normal or mildly elevated ALT levels.

2. Materials and methods

2.1. Patients

The electronic medical records of chronic HBV-infected patients who underwent liver biopsy at a university-based hospital (the Second Hospital of Anhui Medical University), from January 2012 to April 2019 were retrospectively reviewed. According to the guidelines, [6,18] chronic HBV infection is defined as having an HBsAg seropositive status for 6 months or beyond. The inclusion criteria were as follows:

(1) age $\geq$18 years;
(2) the persistent presence of HBsAg for more than 6 months;
(3) HBV DNA $\geq$ 20 000 IU/mL;
(4) ALT $\leq$ 2 ULN (the ULN of ALT is 50 U/L);
(5) with liver biopsy and routine laboratory tests.

The exclusion criteria were as follows:

(1) coinfection with HCV, HDV or HIV;
(2) a history of alcohol consumption (>20 g/d);
(3) concomitant other chronic liver diseases, such as nonalcoholic fatty liver disease, autoimmune liver disease;
(4) antiviral therapy within 1 year;
(5) with liver cirrhosis, decompensated liver disease, hepatocellular carcinoma, or any other type of cancer.

Finally, 370 HBV-infected patients were included in this study. This study was approved by our institutional review board (approval number: 20190251) and all patients have signed informed consent that their clinical data can be used in clinical studies before admission.

2.2. Liver histological examination

Liver biopsies were performed via percutaneous echo-assisted method and a minimum of 6 portal tracts is needed. Slides were viewed and read by pathologists (D.C.), who were unaware of patients' identity and history. Biopsies were classified into stages according to the Scheuer scoring system[19]: G 0-4 and S 0-4. In this study, significant fibrosis and severe fibrosis were defined as pathological stage $\geq$ S2 and $\geq$ S3, respectively. Significant inflammation and severe inflammation were defined as pathological stage $\geq$ G2 and $\geq$ G3, respectively.

2.3. Routine laboratory tests

All patients had routine laboratory blood tests about a week before biopsy based on the manufacturer's instructions. The liver function tests including albumin, globulin, ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) were detected by full-automated biochemistry analyser AU5800 (Beckman Coulter, California). Blood routine tests including platelet count, and red cell distribution width were measured by using automated hematology analyser Sysmex XT-2000i (Sysmex, Kobe, Japan). HBV DNA level was quantified by real-time PCR (ABI 7500, Applied Biosystems, Foster City, CA). The lower limit of the assay was 500 IU/mL. Hepatitis B surface antigen and e antigen HBeAg were tested by the Architect i2000 analyser (Abbott Diagnostics, Chicago). The non-invasive models were calculated in accordance with the following formulas:

$$APRI = (AST/ULN) \times 100)/\text{platelet count } (10^9/L)$$

$$FIB-4 = (age(y) \times AST\ (IU/L))/(\text{platelet count } (10^9/L) \times [ALT(IU/L)^{1/2}])$$

$$RPR = RDW\ (\%)/PLT\ (10^9/L);$$

$$GP = Globulin\ (g/dL) \times 100/\text{platelet count } (10^9/L);$$

$$GPR = (GGT/ULN)/\text{platelet count } (10^9/L) \times 100;$$

Table 1

Demographic and biochemical characteristics of the study participants.

	All Patients (n=370)	Inflammatory activity			Fibrosis stage		
		G0- 1 (n=272)	G2- 4 (n=98)	P value	S0- 1 (n=249)	S2- 4 (n=121)	P value
Male,n(%)	247 (66.8%)	182 (66.9%)	65 (66.3%)	.916	158 (63.5%)	89 (73.6%)	.053
HBeAg + (%)	273 (73.8%)	205 (75.4%)	68 (69.4%)	.248	200 (80.3%)	73 (60.3%)	<.001
Age (y)	34.5 (28.0,42.0)	34.0 (27.0,42.0)	35.5 (28.0,43.3)	.375	33.0 (27.0,41.0)	37.0 (30.0,44.5)	.001
Albumin (g/L)	40.8 (38.1,43.4)	40.5 (37.9,43.1)	41.7 (38.4,44.6)	.032	40.7 (38.1,43.2)	40.8 (37.7,44.1)	.773
Globulin (g/L)	26.3 (23.9,29.5)	26.0 (23.7,29.4)	27.8 (24.3,29.9)	.071	26.2 (24.0,29.4)	26.7 (23.6,29.7)	.920
ALT (U/L)	44.5 (27.0,62.3)	41.0 (25.0,57.8)	56.0 (39.0,74.5)	<.001	42.0 (25.0,62.0)	48.0 (36.0,63.0)	.015
AST (U/L)	31.5 (24.0,42.0)	28.0 (23.0,38.8)	40.0 (30.5,53.0)	<.001	28.0 (22.0,40.0)	37.0 (28.0,47.0)	<.001
GGT (U/L)	20.0 (14.8,30.0)	19.0 (14.0,26.8)	26.0 (17.8,41.2)	<.001	19.0 (14.0,27.0)	25.0 (17.0,40.0)	<.001
RDW (%)	12.9 (12.5,13.4)	12.9 (12.5,13.4)	13.0 (12.6,13.6)	<.239	12.9 (12.5,13.4)	13.0 (12.7,13.4)	.136
PLT (10⁹/L)	175±54	179±53	162±54	.006	184 (154,218)	144 (107,185)	<.001
HBV DNA (lg IU/mL)	6.94 (5.58,7.73)	7.17 (5.65,7.81)	6.49 (5.44,7.42)	.006	7.32 (6.22,7.87)	5.90 (5.07,7.08)	<.001

ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma- glutamyl transpeptidase, HbeAg = hepatitis B e antigen, PLT = platelet count, RDW = red cell distribution width.

2.4. Statistical analysis

The SPSS software version 22.0 (IBM Corp, Armonk, NY) and MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium) were used to analyze all the data. Data in normal distribution were showed as mean value±standard deviation, and median (interquartile range) in non-normal distribution. The comparison between groups was conducted by using Student t-test and Mann-Whitney U-test. The performances of APRI, FIB- 4, RPR, GP, and GPR for the diagnosis of liver inflammation and fibrosis were estimated by the area under the ROC curves (AUROCs), and the optimal cut-offs were obtained by maximizing Youden's index. Diagnostic performances were evaluated by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR). P-value of less than .05 (2-tailed) was considered statistically significant.

3. Results

3.1. Baseline characteristics of enrolled patients

The baseline characteristics of patients were showed in Table 1. The majority of patients were male (66.8%), HBeAg positive (73.8%). Of 370 patients, 98 (26.5%) had G ≥ 2, and 121 (32.7%) had S ≥2. Compared with patients with G0-1, patients with G2-4 had higher albumin, ALT, AST, and GGT, lower PLT and HBV DNA. As for liver fibrosis, patients with S2-4 had higher ALT, AST, and GGT, lower percentage of HBeAg positive, PLT and HBV DNA compared with patients with S0-1.

3.2. Correlations between serum markers and liver Scheuer score

The Spearman test (Table 2) was used to analyze the correlations of serum markers with liver inflammation grades and fibrosis stages. The inflammation stages, as well as the liver fibrosis were strongly positive correlated with ALT, APRI, FIB-4, RPR, GP, and GPR.

3.3. Performances of serum markers for the diagnosis of liver inflammation

ALT is a marker of cytolysis and it is usually used as a traditional marker for the evaluation of the liver inflammatory activity.[20] The diagnostic performances of different NITs were presented in Table 3 and Figure 1. Not all indexes could predict liver inflammation. Compared with FIB-4, the AUROC of APRI was superior in predicting patients with G ≥ 2 inflammation (0.705 vs 0.629, P=.001), but no difference compared with GPR (0.705 vs 0.690, P=.606), ALT (0.705 vs 0.672, P=.289). The optimal cut-off values for diagnosing G ≥2 inflammation were 0.65 for APRI, 1.22 for FIB-4, 0.07 for RPR, 1.5 for GP, 0.18 for GPR, and 44 for ALT, respectively.

As for severe inflammation (G ≥3), APRI and GPR could predict liver inflammation, but there was no statistic difference between them.

3.4. Performances of non-invasive fibrosis models for the diagnosis of liver fibrosis

All indexes could predict liver fibrosis (Table 4 and Fig. 2). To diagnose S ≥ 2 liver fibrosis, the AUROCs were 0.729 for APRI, 0.722 for FIB-4, 0.690 for RPR, 0.686 for GP, and 0.688 for GPR, respectively. However, there was no difference among them to predict significant fibrosis. By maximizing Youden's index, the optimal cut-off values for the prediction of significant fibrosis were 0.54 for APRI, 1.35 for FIB-4, 0.09 for RPR, 1.5 for GP, and 0.42 for GPR, respectively.

To predict severe fibrosis (S ≥3), the AUROCs for non-invasive fibrosis models were increased greatly with different degrees. Among them, FIB-4 was superior to RPR (0.805 vs 0.750,

Table 2

Correlations between noninvasive fibrosis models and liver Scheuer score.

	Inflammatory activity		Fibrosis stage	
	Spearman's r	P value	Spearman's r	P value
ALT	0.262	<.001	0.136	.009
APRI	0.313	<.001	0.396	<.001
FIB-4	0.194	<.001	0.391	<.001
RPR	0.146	.005	0.339	<.001
GP	0.186	<.001	0.332	<.001
GPR	0.293	<.001	0.339	<.001

ALT = alanine aminotransferase, APRI = aspartate transaminase to platelet ratio index, FIB-4 = fibrosis index based on the 4 factors, RPR = red cell volume distribution width-to-platelet ratio, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index.

Table 3

The diagnostic performance of serum markers for predicting liver inflammatory.

	AUROC(95%CI)	Cut-off	Se (%)	Sp (%)	PLR	NLR	PPV (%)	NPV (%)	*P* value	*P* value*
≥G2										
APRI	0.705 (0.656–0.751)	0.65	56.1	77.2	2.5	0.6	47.0	83.0	<.001	–
FIB-4	0.629 (0.577–0.678)	1.22	51.0	71.7	1.8	0.7	39.4	80.2	<.001	.001
RPR	0.593 (0.541–0.644)	0.07	61.2	53.3	1.3	0.7	32.1	79.2	.006	<.001
GP	0.620 (0.569–0.670)	1.5	70.4	50.4	1.4	0.6	33.8	82.5	<.001	.002
GPR	0.690 (0.640–0.737)	0.18	82.7	48.2	1.6	0.4	36.5	88.5	<.001	.606
ALT	0.672 (0.622–0.720)	44	72.5	58.1	1.7	0.5	38.4	85.4	<.001	.289
≥G3										
APRI	0.668 (0.618–0.716)	0.54	73.3	59.1	1.8	0.4	7.1	98.1	.013	-
FIB-4	0.581 (0.529–0.632)	1.05	60.0	56.6	1.4	0.7	5.5	97.1	.290	.095
RPR	0.603 (0.551–0.653)	0.09	46.7	74.9	1.9	0.7	7.3	97.1	.198	.260
GP	0.624 (0.572–0.673)	1.25	100.0	24.8	1.3	0.0	5.3	100	.060	.335
GPR	0.703 (0.654–0.749)	0.18	93.3	41.4	1.6	0.2	6.3	99.3	.001	.584
ALT	0.635 (0.584–0.684)	69	40.0	83.1	2.4	0.7	9.1	97.0	.065	.509

ALT = alanine aminotransferase, APRI = aspartate transaminase to platelet ratio index, AUROC = area under the receiver operating characteristic curve, FIB-4 = fibrosis index based on the four factors, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, RPR = red cell volume distribution width-to-platelet ratio, Se = sensitivity, Sp = specificity.
* Compared with APRI.

P = .006) and GP (0.805 vs 0.755, *P* = .046), but comparable to APRI (0.805 vs 0.785, *P* = .550) and GPR (0.805 vs 0.818, *P* = .694). Maximizing Youden's index for the prediction of severe fibrosis, the cut-off values were 0.54 for APRI, 1.5 for FIB-4, 0.09 for RPR, 2.24 for GP, and 0.45 for GPR, respectively.

3.5. Performances of non-invasive fibrosis models for the diagnosis of significant liver histological changes

The presence of significant liver injury especially fibrosis suggests the need for immediate antiviral therapy even if ALT ≤ 2 ULN, therefore, ≥ S2 or/and ≥ G2 were put into 1 group as significant liver histological changes. The AUROCs of them were all slightly decreased compared with that in the single evaluation of liver fibrosis, while increased compared with that in the single evaluation of liver inflammation. As for the estimation the AUROCs to predict significant histological changes, the performance of APRI was higher than that of RPR (0.717 vs 0.652, *P* = .006) and GP (0.717 vs 0.659, *P* = .011), equal to that of FIB-4

(0.717 vs 0.692, *P* = .254) and GPR (0.717 vs 0.680, *P* = .166). Maximizing Youden's index for predicting significant histological changes, the optional cut-off values were 0.65 for APRI, 1.28 for FIB-4, 0.09 for RPR, 1.5 for GP, and 0.18 for GPR. (Table 5 and Fig. 3)

4. Discussion

The natural history of chronic HBV infection is dynamic and complex. What is more, it may cause a markedly increased risk of hepatocellular carcinoma in chronic hepatitis patients while antiviral therapy has been shown to reduce the risk.[21,22] Therefore, it is important to identify patients with liver inflammation and fibrosis in the clinical practice so that the treatment and hepatocellular carcinoma surveillance can be started. However, the lack of simple and convenient evaluations remains a major problem in clinical practice especially in resource-limited area. Recently, although several indexes have been supposed to be the substitute for biopsy, the measurement

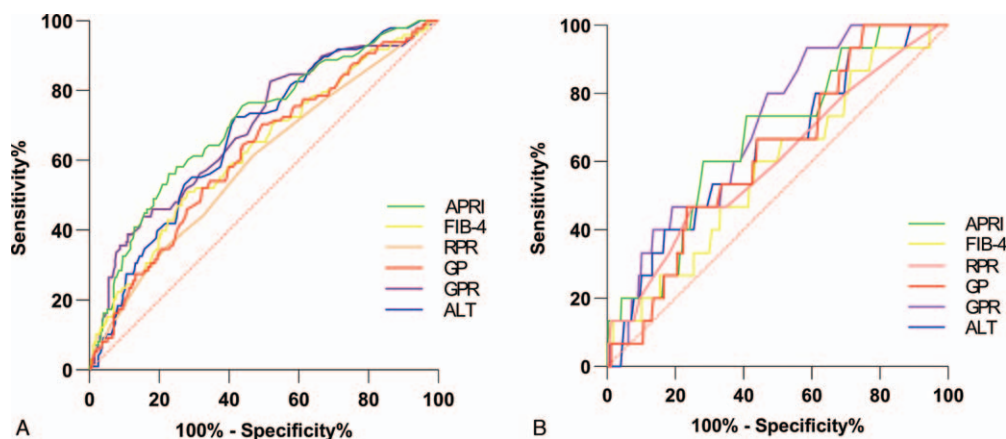**Figure 1.** ROC curves of serum marks for diagnosing G ≥2(A) and G≥3(B). APRI = aspartate transaminase-to-platelet ratio index, FIB4 = fibrosis index based on the four factors, RPR = red cell volume distribution width-to-platelet ratio, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index, ALT = alanine aminotransferase.

Table 4

The diagnostic performance of markers for predicting liver fibrosis.

	AUROC(95%CI)	Cut-off	Se (%)	Sp (%)	PLR	NLR	PPV (%)	NPV (%)	P value	P value [*]
≥S2										
APRI	0.729 (0.681–0.774)	0.54	66.9	69.9	2.2	0.5	51.9	81.3	<.001	.765
		0.5	69.4	63.9	1.9	0.5	48.3	81.1		
		1.5	5.8	98.4	3.6	1.0	63.6	68.2		
FIB-4	0.722 (0.674–0.767)	1.35	57.9	83.5	3.5	0.5	63.1	80.3	<.001	-
		1.45	55.4	85.9	3.9	0.5	65.7	79.9		
		3.25	7.4	98.4	4.6	0.9	69.2	68.6		
RPR	0.690 (0.640–0.737)	0.09	47.9	84.7	3.1	0.6	60.4	77.0	<.001	.107
GP	0.686 (0.636–0.733)	1.5	75.2	54.6	1.7	0.5	44.6	81.9	<.001	.124
GPR	0.688 (0.638–0.735)	0.42	38.0	91.2	4.3	0.7	67.6	75.2	<.001	.230
≥S3										
APRI	0.785 (0.740–0.826)	0.54	84.2	62.7	2.3	0.3	20.5	97.2	<.001	.550
FIB-4	0.805 (0.761–0.844)	1.5	73.7	79.2	3.6	0.3	28.9	96.3	<.001	-
RPR	0.750 (0.702–0.793)	0.09	63.2	78.1	2.9	0.5	25.0	94.9	<.001	.006
GP	0.755 (0.708–0.798)	2.24	55.3	87.4	4.4	0.5	33.3	94.5	<.001	.046
GPR	0.818 (0.775–0.856)	0.45	65.8	88.3	5.6	0.4	39.1	95.8	<.001	.694

APRI = aspartate transaminase to platelet ratio index, AUROC = area under the receiver operating characteristic curve, FIB-4 = fibrosis index based on the four factors, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, RPR = red cell volume distribution width-to-platelet ratio, Se = sensitivity, Sp = specificity.
[*] Compared with FIB-4.

accuracy of liver fibrosis and liver inflammation was controversial. Therefore, this study aimed to evaluate the diagnostic performances of indexes for liver fibrosis and inflammation in chronic HBV-infected patients with high HBV DNA and normal or mildly elevated ALT levels.

In the present study, of 370 HBV-infected patients, 26.5% (98/370) of the patients had significant hepatic inflammation (G2–4) and 32.7% (121/370) had significant liver fibrosis (S2–4). On the whole, 40.5% (150/370) indicated significant liver histological changes (G ≥ 2 or/and S ≥2). Meanwhile, in those patients with "normal" ALT, ≥G2 and ≥G3 were 36/208(17.3%) and 6/208 (2.9%), ≥S2 and ≥S3 were 59/208(28.3%) and 20/208(9.6%), respectively, which, reflected that patients with "normal" ALT did not mean exclusion of histological disease to some extent.[23] Using ALT alone seems likely not enough to predict liver inflammation. However, compared with FIB-4, RPR and GP, the AUROCs of APRI was significantly higher in patients with G ≥2,

but not superior to ALT and GPR. In this way, the results indicated that those non-invasive models did not show distinct advantage over ALT to predict significant inflammation (G ≥2). However, when it came to G ≥3, there was only 15 cases enrolled, which did not present remarkable differences between APRI and GPR. Overall, these non-invasive fibrosis models did not show much advantage like Wu's study.[24]

GPR, firstly reported in 2015, showed more accuracy than classical biomarkers APRI and FIB-4 to stage liver fibrosis in patients with chronic HBV infection in West Africa and China.[13,25] However, it did show controversial advantage in some Chinese cohorts later.[14,24,26] Though based on the large sample over 1000 patients regardless of e antigen status and viral load, the accuracy of GPR to diagnose fibrosis and cirrhosis was different from that of APRI and FIB-4.[14,15] Ming-Jian Lian revealed that the AUROC of GPR for the prediction of significant fibrosis, severe fibrosis, and cirrhosis were 0.733, 0.777, and
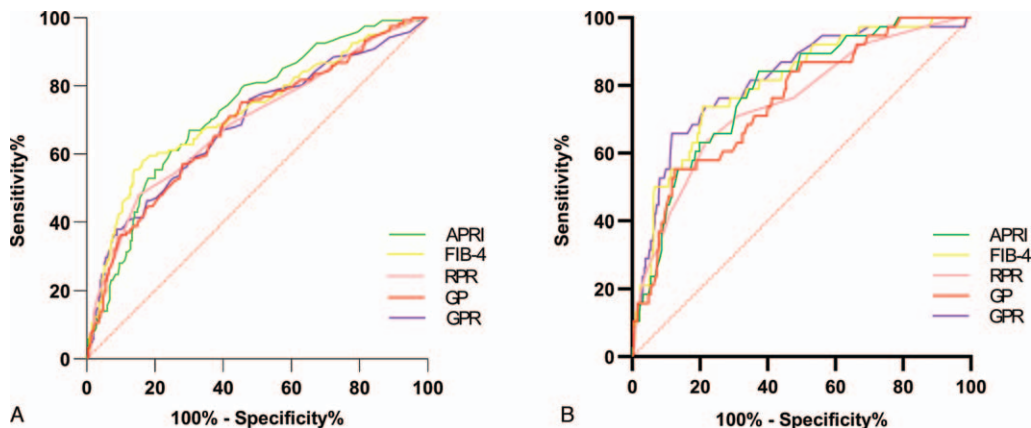

Figure 2. ROC curves of noninvasive models for diagnosing S ≥ 2(A) and S≥ 3(B). APRI = aspartate transaminase-to-platelet ratio index, FIB4 = fibrosis index based on the four factors, RPR = red cell volume distribution width-to-platelet ratio, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index.

Table 5

The diagnostic performance of markers for predicting significant liver histological changes.

	AUROC (95%CI)	Cut-off	Se (%)	Sp (%)	PLR	NLR	PPV (%)	NPV (%)	*P* value	*P* value[*]
APRI	0.717 (0.668–0.762)	0.65	52.0	82.3	2.9	0.6	66.7	71.5	<.001	–
FIB-4	0.692 (0.642–0.739)	1.28	54.0	82.3	3.1	0.6	67.5	72.4	<.001	.254
RPR	0.652 (0.601–0.701)	0.09	41.3	84.6	2.7	0.7	64.6	67.9	<.001	.006
GP	0.659 (0.608–0.707)	1.5	71.3	55.9	1.6	0.5	52.5	74.1	<.001	.011
GPR	0.680 (0.629–0.727)	0.18	77.3	51.8	1.6	0.4	52.3	77.0	<.001	.166

APRI = aspartate transaminase to platelet ratio index, AUROC = area under the receiver operating characteristic curve, FIB-4 = fibrosis index based on the four factors, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, RPR = red cell volume distribution width-to-platelet ratio, Se = sensitivity, Sp = specificity.
* Compared with APRI.

0.796, respectively, by the analysis of 10 studies including 5882 patients with HBV infection. Meanwhile, it suggested that GPR had moderate diagnostic accuracy but did not compare the difference between classical serum models and itself.[27] In the present study, GPR was comparable to other serum markers in the diagnosis of significant fibrosis (S ≥2), advanced fibrosis (S ≥3), and advanced inflammation (G ≥3), while superior to RPR and GP for the prediction of significant inflammation (G ≥ 2). The GPR cut-off valves obtained by maximizing the sum of sensitivity and specificity in this study (≥S2, 0.42; ≥S3, 0.45) were higher than those obtained by Lemoine (≥F2, 0.32; ≥F3, 0.32).[13] In addition, the specificity of the GPR to predict significant fibrosis (S ≥2) and advanced fibrosis (S ≥3) was higher (ranging 88.3–91.2%) than that obtained by Lemoine (ranging 49%–83%), which suggested GPR is likely useful in excluding significant and advanced fibrosis.

As for GP, Xu-Dong Liu first pointed out its value in identifying minimal fibrosis and cirrhosis in chronic HBV-infected patients.[11] Recently, Qiang Li et al reported that it was superior to APRI and FIB-4 in predicting significant fibrosis and cirrhosis in CHB patients with high HBV DNA and mildly elevated ALT levels.[12] In the present study, GP did not show any

Figure 3. ROC curves of noninvasive models for the diagnosis of significant liver histological changes. APRI = aspartate transaminase-to-platelet ratio index, FIB4 = fibrosis index based on the four factors, RPR = red cell volume distribution width-to-platelet ratio, GP = globulin-platelet model, GPR = gamma-glutamyl transpeptidase to platelet ratio index.

advantage on the diagnosis of liver fibrosis and inflammation, which was also in accordance with other reports.[28,29]

For RPR, more than one study suggested that it was a strong predictor of the degree of fibrosis and cirrhosis in CHB patients.[7–9] Similarly, Chen et al proposed that RPR could predict significant fibrosis and cirrhosis in CHB patients with relatively high accuracy than FIB-4 and APRI, suggesting the application of this index may reduce the need for liver biopsy in CHB patients.[30] However, in this study, RPR was inferior to APRI and FIB-4 in diagnosing hepatic inflammation and fibrosis, which was in consistent with Xiaojuan Wu's study.[24] This was further confirmed by Minhui Dong's investigations,[28] which compared the diagnostic accuracy of 17 models in treatment-naïve CHB patients. Some researchers recommended stepwise applying RPR and other markers to free proportion of HBV-related patients from liver biopsies in detecting significant fibrosis and cirrhosis.[31,32]

APRI and FIB-4, recommended by WHO as alternatives for liver biopsy, have faced challenges after new innovative models continuously proposed.[10,13,15,25,28,30] The results indicated that the 2 formulas had similar diagnostic accuracy in predicting fibrosis, while APRI was superior to FIB-4 in predicting inflammation. Their performances were not inferior to others in the diagnosis of fibrosis by the observation of continuous articles.[11,12,14,24,26] The cut-off values of APRI and FIB-4 obtained by maximizing the sum of sensitivity for the diagnosis of significant fibrosis were 0.54 and 1.35, which were close to the low cut-off values (0.5 and 1.45) recommended by WHO guidelines. When chose the high cut-off (1.5) to predict significant fibrosis recommended by WHO guidelines, the sensitivity decreased and specificity increased. Of note, when we put ≥S2 or/and ≥G2 into 1 group as significant liver histological changes, the emerging models did not show any advantages over the classical APRI and FIB-4 in the measurement of significant histological changes which may be the primary indication for treatment initiation in patients with HBV-infected.[6]

The discrepancies among the 5 non-invasive models for the diagnosis of liver diseases could be due to the specific inclusion and exclusion criteria, different pathological scoring systems, individual variation, and genetic factors. There were also some defects in the present study. First, the retrospective design might have caused selective bias, which may result in misestimated sensitivity and specificity of indexes. Second, the relatively small number of patients with G ≥3 (15 patients, 4.1%) unavoidably led to statistical bias when evaluating and comparing the performances of serum models. Third, FibroScan result was not included although many studies reported it had a good performance in the identification of liver fibrosis.
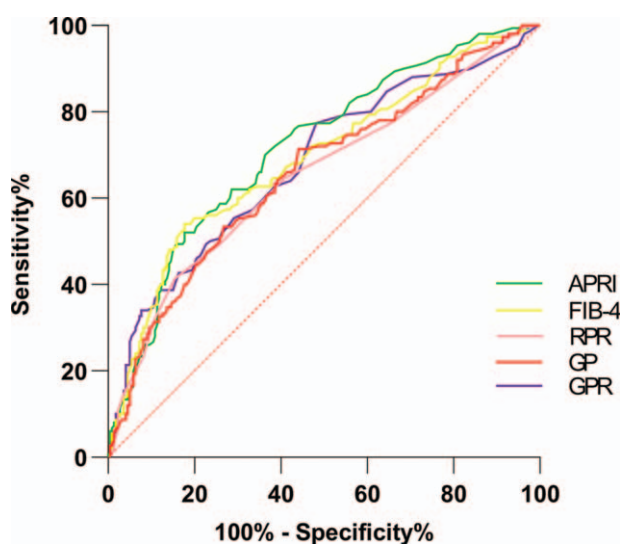
In conclusion, the study showed that serum ALT was not inferior to APRI and GPR in diagnosis of liver moderate inflammation (G ≥2) for chronic HBV infection patients with HBV DNA ≥ 20000 IU/mL and ALT ≤ 2ULN. APRI and GPR were more effective than FIB-4, RPR and GP for diagnosing liver significant inflammation (G ≥2), equal to others in diagnosing severe inflammation (G ≥ 3) and significant fibrosis (S ≥2). As for the diagnosis of advanced fibrosis (S ≥3) and significant liver histological changes, the APRI, FIB-4 and GPR showed advantage over the others. From this study, it appears that GPR, APRI and FIB-4 might be the most useful models to evaluate liver disease progression and to decide on the treatment in patients for the specific population. Further study is required to validate these non-invasive models in a clinical practice.

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Author contributions

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