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Original Article

Advantages of a Novel Model for Predicting Hepatic Fibrosis in Chronic Hepatitis B Virus Carriers Compared with APRI and FIB-4 Scores

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Abstract

Background and Aims: Aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) are widely used to assess liver fibrosis in chronic hepatitis B virus (HBV) infection. Currently, the definition of normal alanine aminotransferase (ALT) is controversial. We aimed to examine the diagnostic value of APRI and FIB-4 in chronic HBV carriers with different upper limits of normal (ULNs) for ALT. ***Methods:*** 581 chronic HBV carriers were divided into the following four groups based on different ULNs for ALT: chronic HBV carriers I, II, III, and IV. Furthermore, 106 chronic HBV carriers formed an external validation group. Predictive values of APRI and FIB-4 were elucidated using the area under the curve (AUC). A liver fibrosis-predictive model-GPSA (named for its measure of gamma glutamyl transpeptidase, platelet count, HBsAg and albumin) was developed using multivariate logistic regression analysis. ***Results:*** In chronic HBV carriers I, the AUCs of APRI and FIB-4 were 0.680 and 0.609 for significant fibrosis and 0.678 and 0.661 for cirrhosis, respectively. The AUCs of GPSA for significant fibrosis in the training group, internal group, and external validation group were 0.877, 0.837, and 0.871, respectively. The diagnostic value of GPSA differed among chronic HBV carriers I, II, III, and IV, with AUCs for significant fibrosis being 0.857, 0.853, 0.868, and 0.905 and AUCs for cirrhosis being 0.901, 0.905, 0.886, and 0.913, respectively. GPSA showed a higher diagnostic value than APRI and FIB-4 for predicting significant fibrosis in the four groups. ***Conclusions:*** The GPSA model allows for accurate diagnosis of liver fibrosis in chronic HBV carriers with different ULN for ALT.

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Introduction

In chronic hepatitis B virus (HBV) carriers with normal alanine aminotransferase (ALT) levels, liver histopathology is usually normal or minimally affected, and even under such conditions, the antiviral treatment may still not be effective.[1] However, chronic HBV carriers with normal ALT levels can also present with severe histopathology, which may progress into liver cirrhosis or hepatocellular carcinoma (HCC).[2–5] Therefore, early diagnosis of hepatic fibrosis followed by timely administration of antiviral therapy is critical to controlling disease progression and possibly even reversing early liver cirrhosis.[6]

The upper limit of normal (ULN) for ALT levels has long been defined as ≤40 U/L, and the European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend this ULN for ALT as the traditional threshold.[7,8] However, the American Association for the Study of Liver Diseases hepatitis B guidlines define the ULN for ALT as ≤35 U/L for men

Keywords: APRI; FIB-4; Liver fibrosis; Chronic HBV carriers; HBV.
Abbreviations: ALT, alanine aminotransferase; APRI, Aspartate aminotransferase-to-platelet ratio index; AUC, area under the curve; CHB, chronic hepatitis B; CHE, cholinesterase; FIB-4, fibrosis-4 index; GGT, glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; PLT, platelet count; TCHO, total cholesterol; ULN, upper limits of normal; WBC, white blood cell count.
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and ≤25 U/L for women,[9] and the World Health Organization (WHO) guidelines define it as <30 U/L for men and <19 U/L for women.[10] Duan *et al*.[11] found ALT >20 U/L to be an ideal marker to predict moderate liver injury in HBeAg-negative chronic hepatitis B (CHB) patients with normal ALT levels. Several specialists have suggested that chronic HBV-infected patients should undergo invasive or noninvasive liver fibrosis assessment to allow for timely administration of antiviral treatment based on these new ALT standards.[12]

Liver biopsy is the gold standard to assess hepatic fibrosis; however, most chronic HBV-infected patients are extremely reluctant to undergo this invasive procedure. Therefore, aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) are extensively used for this assessment; these are based on routine laboratory tests[8] and are recommended in the WHO and APASL HBV guidelines.[7,10] However, Li *et al*.[13] found the WHO-recommended cutoffs of APRI and FIB-4 to have poor diagnostic value for significant fibrosis and cirrhosis in HBeAg-negative CHB patients with ALT ≤2 ULN. Tan *et al*.[14] found APRI and FIB-4 to have poor accuracy for diagnosing significant fibrosis in a small sample of CHB patients with persistently normal ALT. Recent studies have suggested that APRI and FIB-4 are not optimal noninvasive panels for assessing fibrosis in chronic hepatitis C or CHB patients during long-term antiviral treatment.[15,16] In summary, APRI and FIB-4 are controversial for assessing hepatic fibrosis in CHB patients.

To the best of our knowledge, no study has explored the diagnostic value of APRI and FIB-4 for assessing hepatic fibrosis in chronic HBV carriers with different ULN for ALT. In this study, we referred to multicenter and cross-sectional research and retrospectively analyzed the predictive value of APRI and FIB-4 for diagnosing different stages of fibrosis in chronic HBV carriers. Furthermore, we constructed a noninvasive gamma glutamyl transpeptidase, platelet count, hepatitis B surface antigen (HBsAg), and albumin (GPSA) panel to diagnose liver fibrosis in chronic HBV carriers with different ULN for ALT, and then, we compared the predictive performance of GPSA with that of APRI and FIB-4.

Methods

Patients

We retrospectively assessed 581 chronic HBV carriers who underwent liver biopsies from three affiliated hospitals of Fujian Medical University (First Affiliated Hospital, Meng Chao Hepatobiliary Hospital, and The First Hospital of Quanzhou), the Affiliated Hospital of Putian University, and the Xiamen Hospital of Traditional Chinese Medicine between June 2010 and June 2018. We also collected data from 106 chronic HBV carriers from Huashan Hospital Affiliated to Fudan University between October 2008 and December 2015. The patients represented our external validation group. Chronic HBV carriers in our study were defined as patients in the phase of HBeAg-positive chronic HBV infection (immune tolerant) and HBeAg-negative chronic HBV infection (inactive carrier) according to the 2017 European Association for the Study of the Liver guidelines, 2018 American Association for the Study of Liver Diseases hepatitis B guidelines, and the 2019 guidelines of prevention and treatment for chronic hepatitis B.[8,9,17] The inclusion criteria were: (1) patients having been positive for HBsAg for ≥6 months; (2) HBV DNA≥500 IU/mL; (3) ALT≤ULN; and (4) antiviral treatment-naïve patients, i.e. patients having never received antiviral therapy before the liver biopsy. The exclusion criteria were: (1) HCC; (2) human immunodeficiency virus, hepatitis A virus, hepatitis C virus, or hepatitis E virus infection; (3) autoimmune liver disease; (4) hepatolenticular degeneration; (5) drug-induced liver injury; or (6) nonalcoholic fatty liver disease or alcoholic liver disease. To account for differences in the ALT ULN criteria, chronic HBV carriers were defined as: chronic HBV carriers I (the ULN was 40 U/L, *n*=581), chronic HBV carriers II (the ULN was ≤35 U/L for men and ≤25 U/L for women), *n*=448), chronic HBV carriers III (the ULN was ≤30 U/L for men and ≤19 U/L for women, *n*=323], and chronic HBV carriers IV (the ULN was 20 U/L, *n*=167; Supplementary Fig. 1). The study was approved by the institutional review board of Fujian Medical University. Given the retrospective design of the study, the need for informed consent was waived.

Liver biopsy

Liver tissues were obtained with a disposable 16 gauge aspiration needle (TSK Laboratory, Tochigi, Japan). Liver tissues (length ≥1.5 cm with more than six portal tracts) were obtained, fixed in 4% formalin, embedded in paraffin, and stained with hematoxylin–eosin–saffron and Masson's trichrome. Pathologists were blinded to patient data and used the METAVIR scoring system to diagnose liver fibrosis. Significant fibrosis was defined as F≥2, advanced fibrosis as F≥3, and cirrhosis as F=4, as previously reported.[18]

Serum markers

Routine biochemical parameters were quantified by routine automated analyzers. The HBsAg level was tested using an Elecsys HBsAg II quant assay (Roche Diagnostics, Mannheim, Germany) or an Abbott Architect assay (Abbott Laboratories, Chicago, IL, USA). HBV DNA level was assayed by real-time polymerase chain reaction (PG Company, Shenzhen, China).

Statistical analysis

Student's *t*-test was used with normally distributed data and homogeneity of variance. The Mann–Whitney test was used with continuous data with a non-normal distribution. The Spearman test was used to assess correlations of APRI and FIB-4 with liver fibrosis. Univariate or multivariate analysis was used to select predictors linked with F≥2. Predictive accuracy was evaluated using the area under the curve (AUC). Difference between advanced and non-advanced fibrosis stages (DANA) was applied to standard AUCs of fibrosis markers according to the prevalence of fibrosis stages. The Obuchowski index was used to take into account all pairwise comparisons between different stages of liver fibrosis to reduce the spectrum effect and minimize the need for multiple testing. The Z test was used to compare the AUC of GPSA with those of APRI and FIB-4. The statistical analysis was performed with SPSS v. 23.0 (IBM Corp., Armonk, NY, USA) and MedCalc v. 9.38 for Windows.

Results

Clinical data

The patient characteristics are shown in Table 1. Herein, 581 patients were classified as chronic HBV carriers I, 448 as chronic HBV carriers II, 323 as HBV carriers III, and 167 as HBV carriers IV. We found that the differences in total bilirubin, albumin, ALT, AST, gamma glutamyl transpeptidase (GGT), white blood cells (WBCs), and HBsAg levels, platelet count (PLT), and APRI were statistically significant ($p<0.05$) among the four groups. No significant differences were found

Table 1. Clinical characteristics of the four groups of chronic HBV carriers

	Chronic HBV carriers I (*n*=581)	Chronic HBV carriers II (*n*=448)	Chronic HBV carriers III (*n*=323)	Chronic HBV carriers IV (*n*=167)	*p*-value
Age (years)	37.95±10.58	37.49±10.51	37.40±10.62	38.34±10.18	0.714
Sex					
Male	368 (63.3%)	314 (70.4%)	239 (74.0%)	74 (44.3%)	<0.001
Female	213 (36.7%)	134 (29.9%)	84 (26.0%)	93 (55.7%)	
Total bilirubin (mmol/L)	13.95±10.02	14.99±8.44	15.15±8.36	14.81±8.43	<0.001
Albumin (g/L)	41.94±5.13	42.66±5.06	42.67±4.96	42.27±4.58	<0.001
Globulin (g/L)	25.53±8.00	25.61±10.98	25.50±8.97	26.21±7.57	0.975
ALT (U/L)	26.84±7.62	23.62±6.46	21.59±5.07	17.40±3.96	<0.001
AST (U/L)	24.86±6.51	22.18±5.79	25.52±5.86	19.91±5.16	<0.001
GGT (U/L)	23.43±14.91	23.09±5.57	22.84±14.60	21.65±15.05	<0.001
TCHO (mmol/L)	4.70±1.08	4.73±1.16	4.72±1.26	4.82±1.56	0.945
CHE (LogU/L)	3.90±0.11	3.90±0.11	3.90±0.10	3.88±0.11	0.487
WBC (10^9/L)	5.76±1.51	5.77±1.53	5.69±1.55	5.38±1.37	0.025
PLT (10^9/L)	208.32± 55.27	209.77±55.11	207.39±57.90	218.20±62.77	<0.001
HBsAg (log IU/mL)	3.39±1.02	3.40±1.03	3.35±1.06	3.24±1.12	<0.001
HBV DNA (log IU/mL)	5.52±2.04	5.45±2.03	5.38±2.03	5.18±2.07	0.537
PT (s)	12.82±4.40	12.92±4.96	12.77±1.04	12.73±1.02	0.933
INR	1.02±0.07	1.02±0.07	1.02±0.07	1.02±0.07	0.969
APRI	0.31±0.15	0.29±0.13	0.29±0.14	0.26±0.12	<0.001
FIB-4	0.95±0.56	0.92±0.55	0.95±0.59	0.96±0.61	0.808
Fibrosis stage, *n* (%) 0.582					
F0	77 (13.3)	64 (14.3)	40 (12.4)	26 (15.6)	
F1	314 (54.0)	249 (55.6)	184 (56.9)	91 (54.5)	
F2	125 (21.5)	91 (20.3)	59 (18.3)	23 (13.7)	
F3	45 (7.8)	31 (6.9)	29 (9.0)	19 (11.4)	
F4	20 (3.4)	13 (2.9)	11 (3.4)	8 (4.8)	

Data are *n* (%) or mean±SEM. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHE, cholinesterase; GGT, gamma glutamyl transpeptidase; HBV, hepatitis B virus; INR, international normalized ratio PLT, platelet count; PT, prothrombin time; TCHO, total cholesterol; WBC, white blood cell count.

in age, globulin levels, total cholesterol levels, cholinesterase levels, HBV DNA levels, prothrombin time, international normalized ratio (INR), and FIB-4. The proportions of patients with significant fibrosis in chronic HBV carriers I, II, III, and IV were 32.7% (190/581), 30.1% (135/448), 30.7% (99/323), and 29.9% (50/167), respectively. Similarly, the prevalence of liver cirrhosis in the four groups was 3.4% (20/581), 2.9% (13/448), 3.4% (11/323), and 4.8% (8/167), respectively.

Correlation of APRI and FIB-4 with fibrosis stages

APRI and FIB-4 revealed a weak positive correlation with hepatic fibrosis in the four groups of chronic HBV carriers with different ULN for ALT (Table 2).

Predictive value of APRI and FIB-4 for significant fibrosis and cirrhosis at cutoffs recommended by the WHO

Table 3 shows that no patients were correctly diagnosed when an APRI of >1.5 and a FIB-4 of >3.25 were used to predict significant fibrosis. In chronic HBV carriers I, only 67.2% and 56.4% of patients with nonsignificant fibrosis were correctly predicted with an APRI of <0.5 and a FIB-4 of <1.45. Patients were not correctly diagnosed even when an APRI of >2.0 was used to predict liver cirrhosis. In summary, significant fibrosis and cirrhosis in chronic HBV carriers I and III were correctly predicted using the cutoff values recommended in the WHO HBV guidelines. Furthermore, a large proportion of nonsignificant fibrosis was correctly predicted.

Predictive value of APRI and FIB-4 for the assessment of significant fibrosis, advanced fibrosis, and cirrhosis

We analyzed the diagnostic value of APRI and FIB-4 models for detecting significant fibrosis, advanced fibrosis, and cirrhosis in the four chronic HBV carrier groups with different ULN of ALT (Table 4). The AUCs of APRI vs. FIB-4 to assess significant fibrosis were: chronic HBV carriers I, 0.680

Table 2. Correlation of APRI and FIB-4 with liver fibrosis in the four groups of chronic HBV carriers with different ULN for ALT

Score	Chronic HBV carriers I (*n*=581)	Chronic HBV carriers II (*n*=448)	Chronic HBV carriers III (*n*=323)	Chronic HBV carriers IV (*n*=167)
APRI				
Spearman	0.313	0.301	0.357	0.333
p-value	<0.001	<0.001	<0.001	<0.001
FIB-4				
Spearman	0.208	0.191	0.238	0.186
p-value	<0.001	0.001	<0.001	0.017

APRI, Aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; HBV, hepatitis B virus.

vs. 0.609 (p=0.060); chronic HBV carriers II, 0.680 vs. 0.602 (p=0.070); chronic HBV carriers III, 0.682 vs. 0.609 (p=0.140); and chronic HBV carriers IV, 0.736 vs. 0.647 (p=0.176). The AUCs of APRI vs. FIB-4 to assess advanced fibrosis were: chronic HBV carriers I, 0.757 vs. 0.698 (p=0.228); chronic HBV carriers II, 0.759 vs. 0.702 (p=0.332); chronic HBV carriers III, 0.788 vs. 0.718 (p=0.240); and chronic HBV carriers IV, 0.852 vs. 0.727 (p=0.062). Similarly, the AUCs of APRI vs. FIB-4 to assess cirrhosis were: chronic HBV carriers I, 0.678 vs. 0.661 (p=0.841); chronic HBV carriers II, 0.692 vs. 0.655 (p=0.692); chronic HBV carriers III, 0.756 vs. 0.709 (p=0.580); and chronic HBV carriers IV, 0.767 vs. 0.628 (p=0.256).

Development of a novel model for predicting significant fibrosis

First, we randomly divided chronic HBV carriers into training and internal validation groups and assessed 106 chronic HBV carriers who underwent liver biopsies at Huashan Hospital Affiliated to Fudan University as an external validation group. The clinical characteristics of these three groups are shown in Supplementary Table 1. Second, we analyzed the relationship between clinical data and significant fibrosis (Supplementary Table 2). Using univariate analysis, it was found that PLT, HBV DNA levels, HBsAg levels, GGT levels, AST levels, INR, and albumin levels were different in patients with nonsignificant and significant fibrosis (p<0.05). A novel noninvasive predictive panel named GPSA was constructed to assess significant fibrosis in chronic HBV carriers using multivariate regression: 7.987 + 0.087 × GGT (U/L) − 0.013 × PLT (10^9/L) − 0.422 × log HBsAg (IU/mL) − 0.159× ALB (g/L). Finally, we evaluated the predictive value of GPSA for assessing significant fibrosis (Table 5). The AUC of GPSA for assessing significant fibrosis was 0.877.

Poynard *et al*.[19] showed that the AUC of liver fibrosis markers should be standardized according to the prevalence of fibrosis stages in a large-scale cohort. Therefore, we adopted a similar method to minimize the bias of statistical analyses. In the training group, the adjusted uniform AUC (AduAUC) for GPSA was 0.968. In the internal validation group, the AduAUC for GPSA was 0.927. In the external validation group, the AduAUC for GPSA was 0.885. The training group showed no significant differences in the AUCs compared with internal validation group and external validation group (Z=1.201, p=0.230 and Z=0.158, p=0.875, respectively).

Table 3. Diagnostic value of APRI and FIB-4 for diagnosing liver fibrosis in chronic HBV carriers I and chronic HBV carriers III at cutoff values recommended by the WHO HBV guidelines

Criteria	Score	Cutoff	Predicted fibrosis stage	Sensitivity %	Specificity %	PPV %	NPV %
Chronic HBV carriers I (*n*=581)							
Significant fibrosis	APRI	>1.5	F2–F4	0 (0/190)	100 (391/391)	0 (0/0)	67.3 (391/581)
		<0.5	F0–F1	94.9 (371/391)	21.6 (41/190)	71.4 (371/520)	67.2 (41/61)
	FIB-4	>3.25	F2–F4	0 (0/190)	100 (391/391)	0 (0/0)	67.3 (391/581)
		<1.45	F0–F1	89.3 (349/391)	27.7 (53/190)	71.8 (349/486)	56.4 (53/94)
Cirrhosis	APRI	>2.0	F4	0 (0/20)	100 (561/561)	0 (0/0)	96.6 (561/581)
		<1.0	F0–F3	100 (561/561)	0 (0/561)	96.6 (561/581)	0 (0/0)
Chronic HBV carriers III (*n*=323)							
Significant fibrosis	APRI	>1.5	F2–F4	0 (0/99)	100 (224/224)	0 (0/0)	69.3 (224/323)
		<0.5	F0–F1	95.1 (213/224)	15.2 (15/99)	71.7 (213/297)	57.7 (15/26)
	FIB-4	>3.25	F2–F4	0 (0/99)	100 (224/224)	0 (0/0)	69.3 (224/323)
		<1.45	F0–F1	89.7 (201/224)	22.2 (22/99)	72.3 (201/278)	48.9 (22/45)
Cirrhosis	APRI	>2.0	F4	0 (0/11)	100 (312/312)	0 (0/0)	96.6 (312/323)
		<1.0	F0–F3	100 (312/312)	0 (0/11)	96.6 (312/323)	0 (0/0)

PPV, positive predictive value; NPV, negative predictive value.

Table 4. AUCs of APRI and FIB-4 to assess significant fibrosis, advanced fibrosis, and cirrhosis

Criteria	Score	Chronic HBV carriers I (*n*=581)	Chronic HBV carriers II (*n*=448)	Chronic HBV carriers III (*n*=323)	Chronic HBV carriers IV (*n*=167)
		AUROC 95% CI			
Significant fibrosis	APRI	0.680 (0.631–0.729)	0.680 (0.623–0.737)	0.682 (0.615–0.748)	0.736 (0.648–0.824)
	FIB-4	0.609 (0.557–0.661)	0.602 (0.541–0.663)	0.609 (0.539–0.679)	0.647 (0.553–0.741)
	p-value	0.060	0.070	0.140	0.176
Advanced fibrosis	APRI	0.757 (0.694–0.819)	0.759 (0.683–0.835)	0.788 (0.711–0.865)	0.852 (0.777–0.927)
	FIB-4	0.698 (0.627–0.770)	0.702 (0.616–0.787)	0.718 (0.629–0.807)	0.727 (0.620–0.833)
	p-value	0.228	0.332	0.240	0.062
Cirrhosis	APRI	0.678 (0.560–0.796)	0.692 (0.569–0.815)	0.756 (0.645–0.868)	0.767 (0.631–0.902)
	FIB-4	0.661 (0.543–0.783)	0.655 (0.519–0.790)	0.709 (0.586–0.832)	0.628 (0.431–0.825)
	p-value	0.841	0.692	0.580	0.256

APRI, Aspartate aminotransferase-to-platelet ratio index; AUC, area under the curve; FIB-4, fibrosis-4 index; HBV, hepatitis B virus.

Performance of the new panel to predict F≥2, F≥3, and F4

The respective AUCs of GPSA for the prediction of liver fibrosis in chronic HBV carriers I, II, III, and IV were as follows: for F≥2, 0.857, 0.853, 0.868, and 0.905; for F≥3, 0.902, 0.896, 0.892, and 0.926; and for F=4, 0.901, 0.905, 0.886, and 0.913, respectively. There were no significant differences in the AUCs for predicting F≥2, F≥3, and F4 in chronic HBV carriers I, II, III, and IV (all $p>0.5$; Table 6).

Comparisons of GPSA with APRI and FIB-4 models for assessing significant fibrosis

The GPSA model showed the highest predictive value among GPSA, APRI, and FIB-4 models (all $p<0.001$); therefore, GPSA was superior to APRI and FIB-4 in predicting significant fibrosis in the four chronic HBV carrier groups (Fig. 1). To avoid the spectrum effect and the risk of multiple testing, we performed comparisons of diagnostic accuracy of GPSA, APRI, and FIB-4 models for significant fibrosis using the Obuchowski index[20,21] (Table 7). The Obuchowski index of GPSA was also significantly higher than that of APRI and FIB-4 in the four chronic HBV carrier groups (all $p<0.001$).

Discussion

Several studies have shown that inactive carriers can still have significant liver disease.[22,23] The major novel findings of this retrospective study of chronic HBV carriers with different ULN for ALT from multiple centers were: (1) The prevalence of significant fibrosis was 29.9–32.7%. (2) APRI and FIB-4 had a weak positive correlations with hepatic fibrosis and had poor diagnostic value in predicting significant liver fibrosis. (3) In this specific chronic HBV-infected population, the WHO-recommended cutoffs were higher than what are required to predict significant fibrosis and cirrhosis, which may lead to an underestimation of the proportion of patients with significant fibrosis and cirrhosis. (4) Finally, the GPSA model had significantly better predictive accuracy than APRI and FIB-4 in diagnosing significant fibrosis. To our knowledge, this is the first effort to construct a novel panel (GPSA) and validate and compare the abilities of GPSA, APRI, and FIB-4 models in assessing significant fibrosis in chronic HBV carriers with different ULN for ALT.

A meta-analysis reported the AUCs of APRI and FIB-4 for diagnosing significant fibrosis as 0.7407 and 0.7844 and for as 0.7268 and 0.8448 for diagnosing cirrhosis in CHB patients.[6] Tan *et al*.[14] found that the AUCs of APRI and FIB-4 to predict significant fibrosis were lower in patients with persistently normal ALT than in patients with ALT within 1–2×ULN and in those with ALT >2×ULN. The results indicate that APRI and FIB-4 had poor predictive value for liver fibrosis in CHB patients with normal ALT when compared with those with abnormal ALT.

When the WHO-recommended cutoffs of an APRI >1.5 and a FIB-4 of >3.25 were used to predict significant fibrosis in chronic HBV carriers I, all chronic HBV carriers I having significant fibrosis were misclassified as not having significant fibrosis, which limits the use of APRI and FIB-4 models for predicting significant liver fibrosis in chronic HBV carriers I before liver biopsy, thus affecting antiviral therapy. PPV was 0 when an APRI >2.0 was used for predicting cirrhosis in chronic HBV carriers I, which means that the APRI score of all patients with cirrhosis was <2. Therefore,

Table 5. GPSA validity in internal and external validation groups

	AUC (95% CI)	Adu-AUC	Cutoff	Sensitivity %	Specificity %	Youden's index	PPV %	NPV %
Training group (*n*=290)	0.877 (0.834–0.920)	0.968	−0.6129	75.3 (61/81)	85.4 (158/185)	0.607	69.3 (61/88)	88.8 (158/178)
Internal validation group (*n*=291)	0.837 (0.787–0.886)	0.927	−0.8607	75.8 (75/99)	84.2 (154/183)	0.599	72.1 (75/104)	86.5 (154/178)
External validation group (*n*=106)	0.871 (0.799–0.944)	0.885	−1.9845	90.9 (30/33)	76.7 (56/73)	0.676	63.8 (30/47)	94.9 (56/59)

PPV, positive predictive value; NPV, negative predictive value.

Table 6. Diagnostic value of GPSA in the four groups of chronic HBV carriers

	AUC (95% CI)	Cutoff	Sensitivity %	Specificity %	Youden's index	PPV %	NPV %
Chronic HBV carriers I (*n*=581)							
F≥2	0.857 (0.824–0.890)	−0.8582	76.1	83.2	0.596	68.8	87.7
F≥3	0.902 (0.873–0.932)	−0.5664	92.2	77.0	0.692	34.7	98.7
F=4	0.901 (0.853–0.949)	−0.2352	85.0	76.7	0.617	12.1	99.3
Chronic HBV carriers II (*n*=448)							
F≥2	0.853 (0.815–0.891)	−0.8635	74.4	83.2	0.576	65.3	88.0
F≥3	0.896 (0.860–0.933)	−0.6373	93.0	76.9	0.699	31.5	99.0
F=4	0.905 (0.846–0.946)	−0.4306	92.3	74.2	0.665	10.3	99.7
Chronic HBV carriers III (*n*=323)							
F≥2	0.868 (0.827–0.908)	−0.8930	77.9	89.2	0.671	67.3	89.2
F≥3	0.892 (0.850–0.993)	−0.6718	92.3	76.5	0.688	36.7	98.5
F=4	0.886 (0.814–0.957)	−0.4276	90.9	72.7	0.636	11.1	99.5
Chronic HBV carriers IV (*n*=167)							
F≥2	0.905 (0.858–0.952)	−1.0354	91.7	82.3	0.740	68.8	95.9
F≥3	0.926 (0.885–0.967)	−0.5846	88.5	80.6	0.691	46.9	97.3
F=4	0.913 (0.830–0.995)	−0.2076	87.5	77.8	0.653	17.1	99.2

PPV, positive predictive value; NPV, negative predictive value.

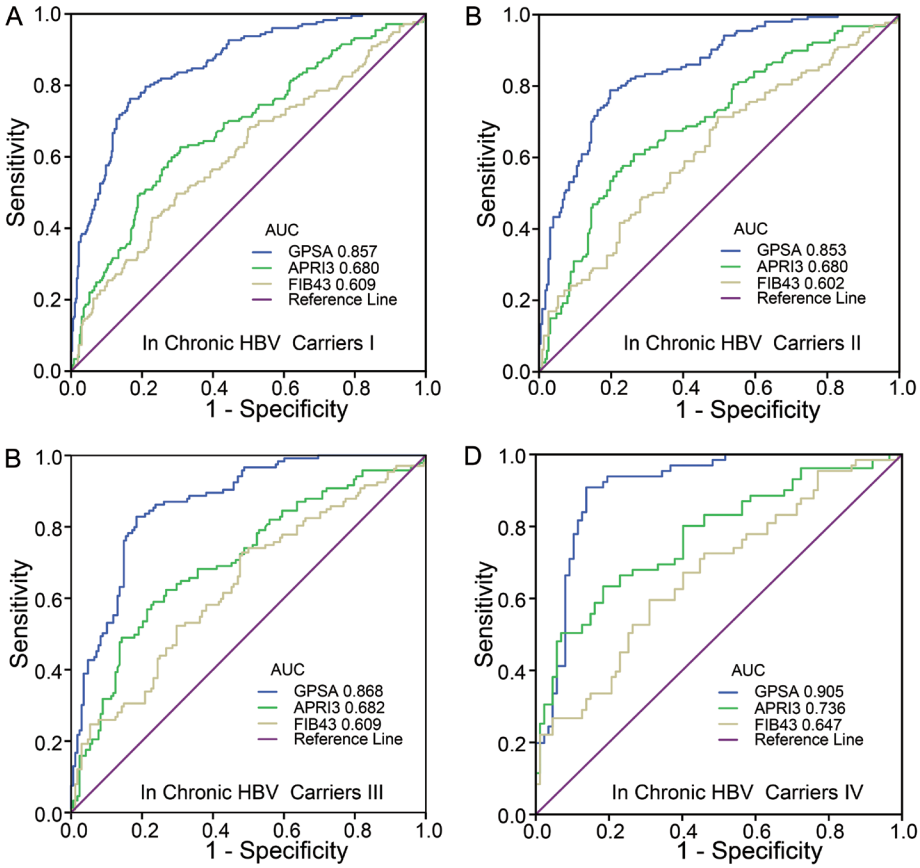

Fig. 1. ROC curves of the noninvasive models (GPSA, APRI, and FIB-4) in the four groups of chronic HBV carriers. APRI, Aspartate aminotransferase-to-platelet ratio index; AUC, area under the curve; FIB-4, fibrosis-4 index; HBV, hepatitis B virus; ROC, receiver operating characteristic curve.

Table 7. Diagnostic value and Obuchowski Indexes of GPSA, APRI, and FIB-4 in the four groups of chronic HBV carriers

	GPSA	APRI	FIB-4
Chronic HBV carriers I (*n*=581)			
AUC (95% CI)	0.857 (0.824–0.890)	0.680 (0.631–0.729)	0.609 (0.557–0.669)
Obuchowski index	0.858 (0.831–0.885)	0.698 (0.660–0.736)	0.634 (0.593–0.674)
Chronic HBV carriers II (*n*=448)			
AUC (95% CI)	0.853 (0.815–0.891)	0.680 (0.623–0.737)	0.602 (0.541–0.663)
Obuchowski index	0.850 (0.818–0.882)	0.699 (0.655–0.744)	0.625 (0.578–0.672)
Chronic HBV carriers III (*n*=323)			
AUC (95% CI)	0.868 (0.827–0.908)	0.682 (0.615–0.748)	0.609 (0.539–0.679)
Obuchowski index	0.866 (0.830–0.902)	0.705 (0.655–0.756)	0.636 (0.582–0.690)
Chronic HBV carriers IV (*n*=167)			
AUC (95% CI)	0.905 (0.858–0.952)	0.736 (0.648–0.824)	0.647 (0.553–0.741)
Obuchowski index	0.910 (0.865–0.954)	0.773 (0.711–0.834)	0.670 (0.598–0.741)

APRI, Aspartate aminotransferase-to-platelet ratio index; AUC, area under the curve; FIB-4, fibrosis-4 index; HBV, hepatitis B virus.

if these patients with cirrhosis cannot be diagnosed in time, the risk of their cirrhosis progressing into HCC is likely to increase. We considered the cutoff values recommended by the WHO as mainly suitable for CHB patients with abnormal ALTs.

We herein developed GPSA, which is a novel panel that combines GGT, HBsAg, PLT, and albumin for assessing hepatic fibrosis in chronic HBV carriers. Low serum albumin is common in decompensated cirrhosis and is associated with an adverse prognosis.[24,25] Decreased liver synthesis of albumin and progression of liver disease both lead to hypoalbuminemia.[26] GGT is reportedly related to hepatocyte growth factor and HBV-related fibrosis.[27] Early cholestasis increases the production of epidermal growth factor, which may explain the correlation between the increase in GGT levels and the severity of liver fibrosis.[28] Because of decreased production of thrombopoietin by the liver in the presence of liver fibrosis or cirrhosis,[29] PLT can be used as a potential noninvasive marker to assess liver fibrosis. Zeng *et al*.[30,31] found a significantly negative correlation between serum HBsAg and liver fibrosis. HBsAg is modulated by both virus and host immunity; it is speculated that the immune-mediated response to HBV infection results in liver damage and that the retention of HBsAg within hepatocytes results in the reduction of HBsAg levels. In this study, all AUC values were found to be >0.8 when GPSA was used to assess different liver fibrosis stages in chronic HBV carriers. GPSA was also found to have good predictive value on external validation. On further comparison of the AUC of the GPSA model with APRI and FIB-4 models, the GPSA model had a significantly higher AUC value. We demonstrated that GPSA would be a better non-invasive tool to facilitate clinicians' decision-making regarding antiviral treatment.

Several studies have recommended revision of the ULN for ALT. Thus, based on different standards of ALT levels,[11,32,33] we divided chronic HBV carriers into chronic HBV carriers I, II, III, and IV. Our analyses showed that APRI and FIB-4 had poor predictive value in assessing significant fibrosis in the four chronic HBV carrier groups. All AUCs of GPSA for predicting F≥2, F≥3, and F4 were >0.8, and GPSA was more accurate than APRI and FIB-4 in predicting significant fibrosis in the four chronic HBV carrier groups according to the Obuchowski index. We demonstrated that the GPSA model has good diagnostic value in identifying different liver fibrosis stages in chronic HBV carriers with different ULN for normal ALT.

Our study has several limitations. First, several studies have shown that liver stiffness measurement (LSM) can accurately diagnose liver fibrosis in CHB patients with normal ALTs.[34,35] Our study was a multicenter, cross-sectional study. Unfortunately, as we have insufficient valid data because of the lack of LSM in some centers, we could not compare the performance of GPSA with LSM, such as transient elastography or shear wave elastography, in detecting fibrosis. In the future, we will cooperate with centers that can perform LSM to expand the sample size for the next research. Second, few patients with advanced fibrosis (45, 7.8%) and cirrhosis (20, 3.4%) were included, which could have led to a statistical bias. Although we used the AduAUC to standardize the prevalence of different fibrosis stages in our study patients to minimize the bias in statistical analysis, large, multicenter cohort studies including patients with more advanced fibrosis and cirrhosis are needed for further investigation.

In summary, when compared with APRI and FIB-4, the GPSA model had increased diagnostic value for assessing liver fibrosis in chronic HBV carriers with different ULN for ALT, which can be beneficial for accurate and timely assessment of liver fibrosis and for reducing disease progression of chronic HBV infection.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (DWZ, NLK, QFR, DSZ, XPY), acquisition of data (NLK, QFR, DSZ, XPY, ZTH, LYW), analysis and interpretation of data (YRL, ZML, MXL, ZXH), adminis-

trative, technical, or material support (DWZ, JJJ, NLK, YRL, RCM), drafting of the manuscript (DWZ, NLK, QFR, DSZ), and study supervision (RCM, DWZ). All authors reviewed and commented on the manuscript and approved the final version.

Ethical statement

The study was approved by the institutional review board of Fujian Medical University. Given the retrospective design of the study, the need for informed consent was waived.

Data sharing statement

All data are available upon request.

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