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 measures 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 and cirrhosis 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 guidelines 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, cholestasis; 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, and the World Health Organization (WHO) guidelines define it as <30 U/L for men and <19 U/L for women. Duan et al. 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.

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 and are recommended in the WHO and APASL HBV guidelines. However, Li et al. found that WHO-recommended cutoffs of APRI and FIB-4 have poor diagnostic value for significant fibrosis and cirrhosis in HBeAg-negative CHB patients with ALT ≤2 ULN. Tan et al. 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. 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, Miang 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. 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) hepatocellular degeneration; and (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=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 META VIR 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.

**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.
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.

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; PT, prothrombin time; TCHO, total cholesterol; WBC, white blood cell count.
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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 |                               | 0.208                         | 0.191                         | 0.238                         | 0.186                         |
|       | p-value                        | <0.001                        | <0.001                        | <0.001                        | <0.001                        |

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

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.
The Obuchowski index (Table 7). The Obuchowski index compares the diagnostic accuracy of the GPSA, APRI, and FIB-4 models for significant fibrosis using the risk of multiple testing. To avoid the spectrum effect and the risk of multiple testing, we performed comparisons of diagnostic accuracy of the GPSA, APRI, and FIB-4 models (all \( p < 0.001 \)); therefore, the prevalence of significant fibrosis was 29.9–32.7%. (2) APRI and FIB-4 had a weak positive correlation 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 APRI, 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.14 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, 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) 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 (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 \( p < 0.001 \)). 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\( \geq 2 \), 0.857, 0.853, 0.868, and 0.905; for F\( \geq 3 \), 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\( \geq 2 \), F\( \geq 3 \), and F=4 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 correlation 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.

**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                        | AUROC | 95% CI                        | AUROC | 95% CI                        | 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; PPV, positive predictive value; NPV, negative predictive value.

**Table 5. GPSA validity in internal and external validation groups**

| Criteria             | AUC (95% CI) | Adjuvant AUC | Cutoff | Sensitivity % | Specificity % | Youden’s index | PPV % | NPV % |
|----------------------|--------------|--------------|--------|---------------|---------------|---------------|-------|-------|
| Training group       | 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  | 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  | 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 (0.850–0.933) | −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.
for assessing hepatic fibrosis in chronic HBV carriers. Serum albumin is common in decompensated cirrhosis and is associated with an adverse prognosis. Decreased liver synthesis of albumin and progression of liver disease both lead to hypoalbuminemia. GGT is reportedly related to hepatocyte growth factor and HBV-related fibrosis. 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. Because of decreased production of thrombopoietin by the liver in the presence of liver fibrosis or cirrhosis, PLT can be used as a potential noninvasive marker to assess liver fibrosis. Zeng et al. 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 immunemediated 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, 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. 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), administr-
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.

**References**

[1] Tseng KC, Chen CY, Tsai HW, Chang TT, Chuang WL, Hsu PI, et al. Efficacy of entecavir in chronic hepatitis B patients with persistently normal alanine aminotransferase: a randomized, double-blind, placebo-controlled study. J Investig Ther 2014;19(8):755–764. doi:10.3851/IMP2754, PMID:24583911.

[2] Weemhoff JL, Woolbright BL, Jenkins RE, McGill MR, Sharpe MR, Olson JC, et al. Plasma Biomarkers to Study Mechanisms of Liver Injury in Patients with Hypoxic Liver. Hepatol Int 2017;11(3):377–384. doi:10.1111/hil.13202, PMID:27429052.

[3] Gong Y, Liu Z, Lao Y, Mai C, Chen T, Tang H, et al. Effectiveness of ω-3 Polysaturated Fatty Acids Based Lipid Emulsions for Treatment of Patients after Hepatectomy: A Prospective Clinical Trial. Nutrients 2016;8(6):357. doi:10.3390/nu8060357, PMID:27322311.

[4] Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295(1):65–73. doi:10.1001/jama.295.1.65, PMID:16391218.

[5] Kelleni MT, Ibrahim SA, Abdelrahman AM. Effect of captopril and telmisartan on liver histological lesions and risk factors for liver injury following bone marrow transplantation. J Clin Gastroenterol 2003;36(5):421–426. doi:10.1097/01.MDG.000008436-200305000-00003, PMID:12702986.

[6] Peck-Radosavljevic M. Thrombocytopathy in chronic liver disease. Liver Int 2017;37(6):778–783. doi:10.1111/liv.13137, PMID:27860293.

[7] Zeng DW, Zhang JM, Liu YR, Dong J, Jiang JJ, Zhu YY. A Retrospective Study on the Significance of Liver Biopsy and Hepatitis B Surface Antigen in Chronic Hepatitis B Patients. Medicine (Baltimore) 2016;95(8):e2503. doi:10.1097/MD.0000000000000236, PMID:27482813.

[8] Li Q, Ren X, Lu C, Li W, Huang Y, Chen L. Evaluation of APRI and FIB-4 for noninvasive assessment of significant fibrosis and cirrhosis in HBeAg-negative CHB patients with ALT <2 times the upper limit of normal. World J Gastroenterol 2008;14(12):1315–1341. doi:10.3748/wjg.v14.i12.1315, PMID:18845489.

[9] Tan YW, Zhou XB, Ye Y, He C, Ge GH. Diagnostic value of FIB-4, aspartate aminotransferase-to-platelet ratio index and liver stiffness measurement in hepatitis B virus-infected patients with persistently normal alanine transaminase. World J Gastroenterol 2017;23(31):5746–5754. doi:10.3748/wjg.v23.i31.5746, PMID:28883700.

[10] Kim WR, Berg T, Asselah T, Flissak R, Fung S, Gordon SC, et al. Evaluation of APRI and FIB-4 scoring systems for non-invasive prediction of hepatofibrosis in chronic hepatitis B patients. J Hepatol 2016;64(4):773–780. doi:10.1016/j.jhep.2015.11.012, PMID:26626497.

[11] Ibukura J, Kurokashi M, Setoyama H, Sirmak S, Oza N, Korenaga M, et al. Applicability of APRI and FIB-4 as a transition indicator of liver fibrosis in patients with chronic viral hepatitis. J Gastroenterol 2015;50(9):227–242. doi:10.1007/s00535-017-0922-2, PMID:27337182.

[12] European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009;50(2):227–242. doi:10.1016/j.jhep.2008.10.001, PMID:19005488.

[13] Li Q, Ren X, Lu C, Huang Y, Chen L. Evaluation of APRI and FIB-4 for noninvasive assessment of significant fibrosis and cirrhosis in HBeAg-negative CHB patients with ALT ≥2 times the upper limit of normal and those with HBV DNA >20000 IU/mL and normal ALT. World J Gastroenterol 2011;17(6):658–674. doi:10.3748/wjg.v17.i6.658, PMID:21474964.

[14] Maden N, Asselah T, Asselah T, Fung S, Yilmaz F, Yilmaz F, et al. Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. J Hepatol. 2003;39(2):222–230. doi:10.1016/s0168-8278(03)00171-5, PMID:12873819.

[15] Zeng DW, Zhang JM, Liu YR, Dong J, Jiang JJ, Zhu YY. A Retrospective Study on the Significance of Liver Biopsy and Hepatitis B Surface Antigen in Chronic Hepatitis B Patients. Medicine (Baltimore) 2016;95(8):e2503. doi:10.1097/MD.0000000000000236, PMID:27482813.

[16] Zeng DW, Huang ZX, Lin MX, Kang NA, Lin X, Li YN, et al. A novel HBV-NA-based model for predicting significant liver fibrosis among Chinese patients with immune-tolerant phase chronic hepatitis B: a multicenter retrospective study. Ther Adv Gastroenterol 2016;9(10):507–515. doi:10.1177/1756284816640167, PMID:27308796.

[17] Lee JK, Shim JH, Lee JC, Lee SH, Kim KM, Lim YS, et al. Estimation of the healthy upper limits for serum alanine aminotransferase in Asian populations with normal liver histology. Hepatology 2010;51(5):1577–1583. doi:10.1002/201505. PMID:21627370.

[18] Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Defined health-related ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137(1):1–10. doi:10.7326/0003-4819-137-1-200207020-00006, PMID:12093239.

[19] Danis N, Salih Akarca U, Taran I, Karasu Z, Eroğlu G, Yılmaz F, et al. Prevalence of FibroScan in Patients with Chronic Hepatitis B Who Have HBV DNA 2000-20000 IU/mL and normal ALT. Panmin Clin Infect Dis 2011;60(6):568–574. doi:10.14744/pcid.2011.35545, PMID:23528476.

[20] Tan YW, Zhou XB, Ye Y, He C, Ge GH. Diagnostic value of FIB-4, aspartate aminotransferase-to-platelet ratio index and liver stiffness measurement in hepatitis B virus-infected patients with persistently normal alanine transaminase. World J Gastroenterol 2017;23(31):5746–5754. doi:10.3748/wjg.v23.i31.5746, PMID:28883700.