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# Evaluation and comparison of the diagnostic performance of routine blood tests in predicting liver fibrosis in chronic hepatitis B infection

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**ABSTRACT**

**Background & aims**: Biopsy is the gold standard for staging liver fibrosis, but it may be accompanied by complications. As an alternative, non-invasive markers such as transient elastography (for liver fibrosis) and certain combinations of routine blood markers (liver function tests, full blood count) have been developed although their clinical significance remains controversial. Here, we compare the diagnostic values of non-invasive markers for liver fibrosis in patients with chronic hepatitis B infection.

**Methods**: Transient elastography and routine laboratory tests were performed in 196 patients. Diagnostic performances were compared and were assessed based on the area under the curve (AUC) of a receiver operating characteristic (ROC) analysis.

**Results**: Elevated GGT to platelet ratio (GPR), the fibrosis index FIB-4 [based on age, AST, platelets and ALT], platelet to lymphocyte ratio (PLR) and total bilirubin were independent predictors of liver stiffness defined by transient elastography (all $P < 0.001$). The AUCs of GPR in predicting both advanced fibrosis and cirrhosis were significantly larger than that of FIB-4 ($P = 0.037$ and $P = 0.008$, respectively) and AST-to-platelet ratio index (APRI) ($P = 0.008$ and $P = 0.005$). FIB-4, APRI and red cell volume distribution width-to-platelet ratio (RPR) had similar diagnostic values in discriminating different levels of liver fibrosis.

**Conclusions**: GPR showed the best diagnostic value and RPR and PLR are easily available and inexpensive markers in evaluating fibrosis and cirrhosis. The diagnostic values of these laboratory markers are useful in diagnosing advanced fibrosis or cirrhosis, and in confirming the different levels of liver fibrosis.

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Chronic hepatitis B infection; liver fibrosis; transient elastography; non-invasive marker

## Introduction

Hepatitis B virus (HBV) is a serious global pathogen as it is estimated that more than 240 million are chronically infected worldwide. Active HBV replication is the main cause of liver injury and chronic infection may progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) without antiviral therapy. Around 650,000 people die from the complications of chronic HBV infection (CHBVI) each year [1].

Liver fibrosis presents in varying degrees, and accurate assessment is of great importance in deciding optimal treatment time, monitoring dynamic changes of chronic viral hepatitis and predicting disease prognosis [2]. Liver biopsy is the gold standard method for staging liver fibrosis, but sampling error, cost, potential risk of complications and inter-observer variability have limited its clinical application [3,4]. Moreover, sequential biopsies to monitor the dynamic changes of liver fibrosis and assess the long-term prognosis of disease are not practical. Serum biomarkers and transient elastography are recommended by the World Health Organization as non-invasive tests for CHBVI patients [1]. However, some drawbacks including expensive equipment and lack of experienced operators have limited the clinical application of transient elastography in resource-limited regions. Therefore, many studies focus on developing simpler, more available and cheaper non-invasive markers for staging liver fibrosis [5,6].

Fibrosis index FIB-4 [based on age, AST, platelets and ALT] [7] and aspartate transaminase-to-platelet ratio index (APRI) [8], developed in patients with chronic hepatitis C virus infection, display good diagnostic values in assessing fibrosis and cirrhosis [9,10]. Nevertheless, their values in evaluating the extent of liver fibrosis in CHBVI are controversial [11–13]. Although the gamma-glutamyl-transpeptidase to platelet ratio (GPR) is more accurate than APRI and FIB-4 in predicting significant fibrosis, advanced fibrosis and cirrhosis [14], diagnostic values vary among other studies [15,16]. Chen et al. [17] demonstrated that red cell distribution width-to-platelet ratio (RPR) was

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superior to APRI and FIB-4 in evaluating significant fibrosis and cirrhosis. However, in another study, the area under curve of a receiver operating characteristic analysis of RPR was similar to FIB-4 in predicting significant fibrosis and severe fibrosis, but was lower to APRI in diagnosing significant fibrosis and severe fibrosis [13]. Accordingly, confirmation as to whether RPR is better than APRI or FIB-4 in diagnosing HBV-related liver diseases is sought. A recent study indicated that the platelet to lymphocyte ratio (PLR) was related to the severity of CHBVI-related liver diseases, and that the PLR and neutrophil to lymphocyte ratio (NLR) provide a supplementary means for effectively managing CHBVI and associated disease [18]. However, PLR trend changes at various stages of liver fibrosis have not been investigated. The aspartate aminotransferase to alanine aminotransferase ratio (AAR) predicts hepatocellular carcinoma prognosis after transarterial embolization, so may also be useful in CHBVI [19]. Thus, as to which of these laboratory markers performs better in diagnosing liver fibrosis, there is no consensus.

Therefore, our aim was to determine which of a panel of several laboratory markers is best at defining the extent of liver fibrosis as defined by transient elastography.

## Methods

We conducted a cross-sectional retrospective study in the Second Affiliated Hospital of Xi'an Jiao Tong University between May 2017 and June 2018. The protocol was approved by the Hospital Ethics Committee. Inclusion criteria were serum hepatitis B surface antigen (HBsAg) positive for at least six months, ALT level < twice the upper limit of normal, body mass index <25 Kg/m$^2$, and time between transient elastography and other clinical assays <7 days. Exclusion criteria were other diseases, hepatitis C virus infection, hepatic decompensation, alcoholic liver disease, autoimmune hepatitis, non-alcoholic fatty liver disease, drug-induced toxicity, hepatic carcinoma, cholestatic liver disease, abnormal liver function, development of hepatic flares, incomplete routine blood testing, hepatomegaly and acute liver failure. By these criteria, we recruited 196 patients (126 females, 70 males).

Age, height and weight were recorded when transient elastography was performed. Serum biochemical parameters alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, bilirubin, albumin and globulin were detected by biochemistry analyser AU5800 (Beckman Coulter, California, USA). For females, the normal reference ranges of ALT, AST and GGT were 9–50 IU/L, 15–40 IU/L, 7–45 IU/L, respectively, and for male, these were 7–40 IU/L, 13–35 IU/L and 10–60 IU/L, respectively. The white blood cell count (WBC), red blood cell count (RBC), platelet count, lymphocyte count, neutrophil count and red cell distribution width were measured using hematology analyser Sysmex XT-2000i (Kobe, Japan). HBV DNA levels were quantified by real-time PCR (ABI 7500, Applied Biosystems, Foster City, CA, USA). The lower limit of the assay was 100 IU/mL. Hepatitis B surface antigen (HBsAg) and e antigen (HBeAg) were tested by an Architect i2000 analyser (Abbott Diagnostics, Chicago, USA) using Chemiluminescent Microparticle ImmunoAssay.

The formulas for FIB-4, APRI, GPR, NLR, AAR, RPR and PLR are as follows: FIB-4 = [Age (years) × AST (IU/L)]/{platelets ($10^9$/L) × [ALT (IU/L)]$^{1/2}$}; APRI = [AST (IU/L)/upper limit of normal (ULN) of AST]/[platelets ($10^9$/L)] × 100; GPR = [GGT (IU/L)/ULN of GGT]/platelets ($10^9$/L) ×100; NLR = neutrophils ($10^9$/L)/lymphocytes ($10^9$/L); AAR = ALT (IU/L)/AST (IU/L); PLR = platelets ($10^9$/L)/lymphocytes ($10^9$/L); RPR = red cell distribution width (%)/platelets ($10^9$/L).

Liver stiffness was measured using transient elastography (FibroTouch, Wuxi, China) with units of kilopascals (kPa), and was considered to be reliable only when (a) there were at least 10 valid measurements, (b) the ratio of interquartile range to median was <0.3, and (c) success rate >60%. Metavir fibrosis was staged based on the transient elastography results and was defined as significant fibrosis (SF, Metavir fibrosis score ≥2), advanced fibrosis (AF, Metavir fibrosis score ≥3) and cirrhosis (Metavir fibrosis score = 4). The transient elastography cut-off values [20,21] were 0–<5.3 kPa (F0: normal), 5.3–<7.2 kPa (F1: mild fibrosis), 7.2–<9.4 kPa (F2: significant fibrosis), 9.4–<12.2 kPa (F3: advanced fibrosis), ≥12.2 kPa (F4: cirrhosis).

Statistical analyses were performed by SPSS 20.0 (Chicago, USA) and MedCalc (Ostend, Belgium) software. Normality was defined by the Kolmogorov–Smirnov test. Continuous normally distribution data are expressed as mean with standard deviation (SD) and non-normally distribution continuous data are expressed as median with interquartile range. Spearman's rank correlation coefficient analysis was used to assess the relationship between liver stiffness and blood markers. Linear trend analysis was used to analyse the data in groups of different levels of liver fibrosis. Categorical variables were presented as numbers or percentages and analysed using Chi-square test. Multivariate linear regression analyses determined independent parameters of liver fibrosis. Receiver operating characteristic (ROC) curves were plotted to explore the diagnostic values of blood markers for fibrosis. A *P*-value <0.05 was considered statistically significant.

## Results

Characteristics of the 196 patients and their correlations with liver stiffness are shown in Table 1. The liver stiffness of the entire cohort was 7.4 (5.7–11.2) kPa, and correlations with laboratory markers are shown in

Table 1. Clinical and laboratory characteristics of study participants.

| Parameters | Data | Correlation with Liver stiffness |
|---|---|---|
| Age (years) | 44. 8 ± 11.7 | 0.35, $P < 0.001$ |
| BMI (Kg/m$^2$) | 23.5 ± 3.3 | 0.22, $P = 0.003$ |
| ALT (U/L) | 22 (15–33) | 0.38, $P < 0.001$ |
| AST (U/L) | 28 ± 11 | 0.45, $P < 0.001$ |
| Total bilirubin (μmol/L) | 16 ± 8 | 0.39, $P < 0.001$ |
| Direct bilirubin (μmol/L) | 4 (3–5) | 0.42, $P < 0.001$ |
| Bilirubin (μmol/L) | 11 ± 5 | 0.30, $P < 0.001$ |
| Albumin (g/L) | 47 ± 4 | −0.13, $P = 0.075$ |
| Globulin (g/L) | 28 ± 5 | 0.07, $P = 0.319$ |
| GGT (U/L) | 21 (14–29) | 0.56, $P < 0.001$ |
| ALP (IU/L) | 87 ± 28 | 0.09, $P = 0.215$ |
| Platelets (10$^9$/L) | 169 ± 58 | −0.45, $P < 0.001$ |
| Neutrophils (10$^9$/L) | 3 ± 1 | −0.08, $P = 0.272$ |
| Lymphocytes (10$^9$/L) | 2 (1–2) | −0.05, $P = 0.511$ |
| FIB-4 | 1.41 (0.95–2.18) | 0.49, $P < 0.001$ |
| APRI | 0.39 (0.28–0.59) | 0.52, $P < 0.001$ |
| GPR | 0.23 (0.14–0.40) | 0.65, $P < 0.001$ |
| AAR | 1.23 ± 0.53 | −0.14, $P = 0.053$ |
| NLR | 2.16 ± 1.11 | −0.06, $P = 0.440$ |
| RPR | 0.10 ± 0.06 | 0.44, $P < 0.001$ |
| PLR | 102 ± 38 | −0.35, $P < 0.001$ |

Data are expressed as mean ± SD or median (25th, 75th percentile). BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; FIB-4, fibrosis index; APRI, aspartate aminotransferase-to-platelet ratio index; GPR, gamma-glutamyl transpeptidase to platelet ratio; AAR, alanine aminotransferase to aspartate aminotransferase ratio; NLR, neutrophil to lymphocyte ratio; RPR, red cell volume distribution width-to-platelet ratio; PLR, platelet to lymphocyte ratio.

Table 1. Analysis according to category of liver stiffness F1 median 5.62 kPa (IQR 4.58–6.32), F2 8.15 (7.63–8.64), F3 10.9 (9.97–11.32), and F4 18.91 (14.67–21.80) are shown in Table 2, and were linked to age, male sex, AST, total and direct bilirubin, GGT, platelet count, FIB-4, APRI, GPR, RPR, PLR. To determine which of these were independent predictors of liver stiffness (as dependent variable), a multivariate analysis was performed. This showed that total bilirubin, FIB-4 and GPR each had a significant independent effect on hepatic fibrosis (all $p < 0.001$: $\beta = 0.18$, 1.02, 7.34, respectively).

Diagnostic performance of FIB-4, APRI, GPR, RPR and PLR are shown in Table 3 and the ROC curves of five markers in identifying significant liver fibrosis, advanced liver fibrosis and cirrhosis in Figure 1(a), 1(b) and 1(c). The AUC of GPR was the superior predictor of significant fibrosis, and was significantly larger than those of FIB-4 ($P = 0.037$ and $P = 0.008$) and APRI ($P = 0.008$ and $P = 0.005$) in predicting both advanced fibrosis and cirrhosis. There were no differences in the ability of FIB-4 and APRI to differentiate significant fibrosis ($p = 0.895$), advanced fibrosis ($p = 0.746$) or cirrhosis ($P = 0.829$). Although the AUCs of RPR were lower than that of FIB-4 and APRI, the diagnostic values of RPR were similar to FIB-4 and APRI in discriminating different levels of liver fibrosis. The diagnostic accuracy of PLR for the diagnosis of cirrhosis was comparable to FIB-4 ($p = 0.180$) and APRI ($p = 0.115$).

## Discussion

Non-invasive markers, including APRI, FIB-4 and transient elastography have been proposed as predictors the histologic severity of liver fibrosis [1–18]. Transient elastography is an accurate and reproducible method for measuring liver stiffness and has a higher diagnostic value than some serological markers [22,23]. We used transient elastography as a reference method to compare the diagnostic values of established markers in patients with CHBVI. Our primary result was that total bilirubin, FIB-4 and GPR are predictors of liver stiffness, and suggests these indices should be considered in clinical practice.

The predictive values of these non-invasive markers were further explored by ROC curve analysis. FIB-4 and APRI are commonly seen as predictive markers for liver fibrosis, but there is no consensus on their diagnostic values in determining the levels of liver fibrosis in CHBVI [11,13]. Our results indicated that FIB-4 and APRI had similar diagnostic accuracy in assessing significant fibrosis, advanced fibrosis and cirrhosis.

GPR is a new non-invasive marker to assess liver fibrosis in CHBVI, although diagnostic values of GPR are inconsistent [14,16,24–26]. Our finding that GPR showed prominent diagnostic performance than FIB-4 and APRI in assessing liver significant fibrosis,

Table 2. Values of study variables at different liver stiffness measurement levels.

| Variables | Fibrosis stage F0-1 (n = 93) | F2 (n = 40) | F3 (n = 23) | F4 (n = 40) |
|---|---|---|---|---|
| Age (years) | 40.9 ± 10.3 | 45.3 ± 12.3 | 48.3 ± 8.4 | 51.2 ± 12.4 |
| Male (n, %) | 51, 54.8 | 27, 67.5 | 18, 78.3 | 30, 75 |
| AST (U/L) | 24 ± 6 | 28 ± 11 | 31 ± 13 | 35 ± 14 |
| Tbil (μmol/L) | 14 ± 5 | 15 ± 6 | 19 ± 10 | 20 ± 9 |
| Dbil (μmol/L) | 3.3 (2.4–4.3) | 4.0 (2.6–5.6) | 4.9 (3.5–6.9) | 5.6 (4.3–9.1) |
| GGT (U/L) | 16 (11–23) | 19 (13–24) | 24 (20–29) | 37 (24–68) |
| Platelets (10$^9$/L) | 192 ± 43 | 171 ± 60 | 134 ± 58 | 133 ± 61 |
| FIB-4 | 1.10 (0.80–1.58) | 1.48 (0.91–2.31) | 2.17 (1.32–3.63) | 2.61 (1.47–4.08) |
| APRI | 0.32 (0.25–0.42) | 0.40 (0.29–0.54) | 0.54 (0.41–0.93) | 0.72 (0.45–1.08) |
| GPR | 0.16 (0.11–0.23) | 0.22 (0.16–0.30) | 0.30 (0.24–0.63) | 0.60 (0.40–1.08) |
| RPR | 0.07 ± 0.02 | 0.09 ± 0.04 | 0.13 ± 0.07 | 0.13 ± 0.07 |
| PLR | 114 ± 34 | 105±40 | 88 ± 39 | 80 ± 35 |

Notes: By linear trend analysis and χ2 test. Data are expressed as mean ± SD, median (25th, 75th percentile) or absolute numbers. See Table 1 for abbreviations. All $p < 0.001$ except male sex $p = 0.01$.

**Table 3.** Diagnostic performance of laboratory markers and their optimal cut-off values.

| Model | ROC AUC (95% CI) | Cut-off | Sen (%) | Spe (%) | PPV (%) | NPV (%) | Acc |
|---|---|---|---|---|---|---|---|
| Significant fibrosis | | | | | | | |
| FIB-4 | 0.76 (0.69–0.82) | 1.40 | 69.90 | 69.90 | 72.00 | 67.71 | 69.90 |
| | | 1.45a | 65.05 | 70.97 | 71.28 | 64.71 | 67.86 |
| APRI | 0.76 (0.70–0.82) | 0.47 | 58.26 | 88.17 | 84.51 | 65.60 | 72.45 |
| | | 0.50a | 53.40 | 90.32 | 85.94 | 63.64 | 70.92 |
| GPR | 0.80 (0.74–0.86) | 0.23 | 69.90 | 78.42 | 77.42 | 69.90 | 73.47 |
| RPR | 0.73 (0.66–0.79) | 0.08 | 60.19 | 78.49 | 75.61 | 64.04 | 68.88 |
| PLR | 0.66 (0.59–0.73) | 75.39 | 38.83 | 91.40 | 83.33 | 57.43 | 63.78 |
| Advanced fibrosis | | | | | | | |
| FIB-4 | 0.80 (0.74–0.85) | 1.40 | 80.95 | 63.16 | 51.00 | 87.50 | 68.88 |
| APRI | 0.79 (0.73–0.85) | 0.43 | 77.78 | 73.68 | 58.33 | 87.50 | 75.00 |
| GPR | 0.87 (0.82–0.92) | 0.24 | 85.71 | 75.76 | 62.80 | 91.82 | 79.08 |
| RPR | 0.77 (0.70–0.82) | 0.09 | 60.32 | 84.21 | 64.41 | 81.75 | 76.53 |
| PLR | 0.70 (0.63–0.76) | 73.27 | 44.44 | 90.23 | 68.29 | 77.42 | 75.51 |
| Cirrhosis | | | | | | | |
| FIB-4 | 0.78 (0.72–0.84) | 1.35 | 87.50 | 55.77 | 33.71 | 94.57 | 62.24 |
| APRI | 0.78 (0.71–0.83) | 0.57 | 67.50 | 83.97 | 51.92 | 90.97 | 80.61 |
| GPR | 0.88 (0.83–0.93) | 0.39 | 77.50 | 87.10 | 60.78 | 93.79 | 85.20 |
| RPR | 0.74 (0.67–0.80) | 0.09 | 65.00 | 78.85 | 44.07 | 89.78 | 76.02 |
| PLR | 0.70 (0.63–0.77) | 73.27 | 50.00 | 86.54 | 48.78 | 87.10 | 79.08 |

Predetermined cut-off values recommended by WHO guidelines. AUC, area under the curve; ROC, receiver operating characteristics; CI, confidence interval. Sen = sensitivity; Spe = specificity; PPV, NPV = positive and negative predictive value. See Table 1 for other abbreviations.

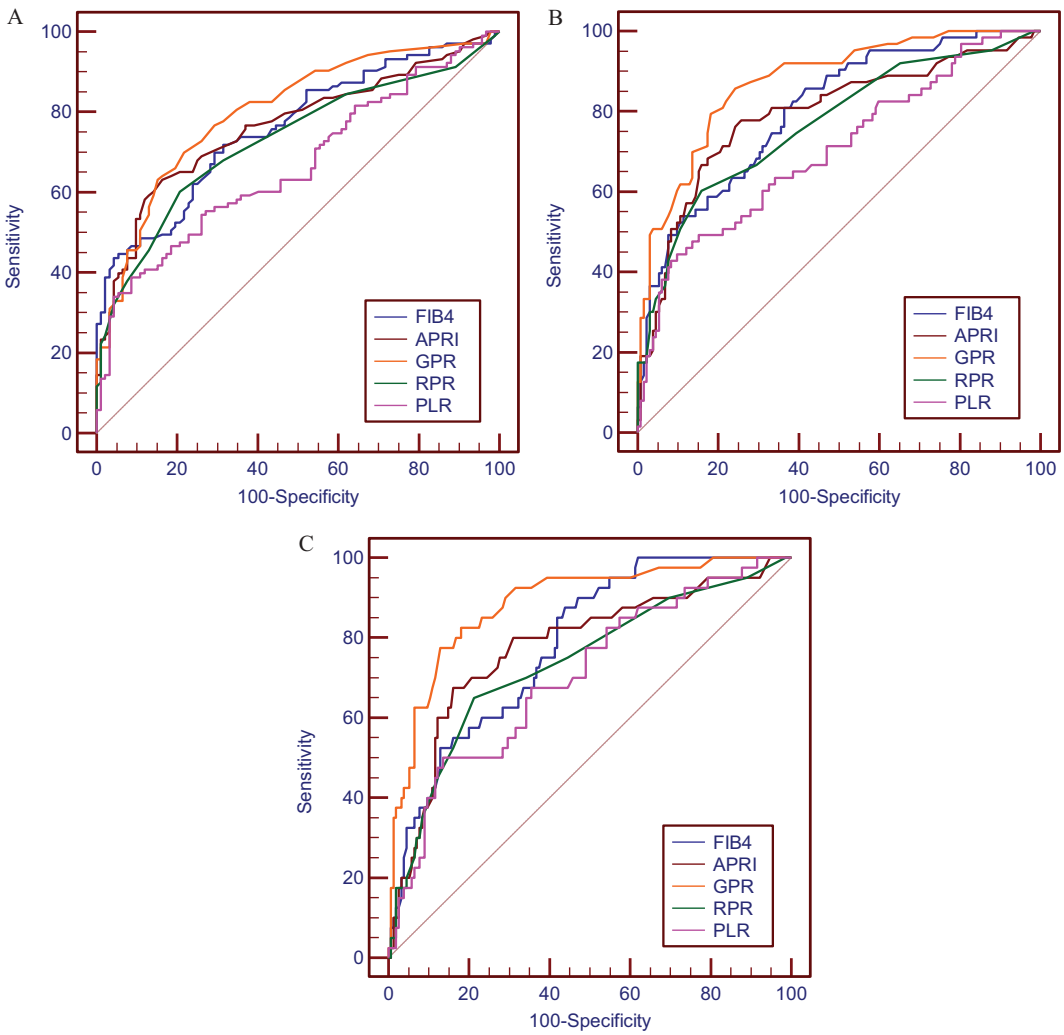


**Figure 1.** ROC curves of FIB-4, APRI, GPR, RPR and PLR in predicting significant fibrosis (A), advanced fibrosis (B) and cirrhosis (C). FIB-4, fibrosis index based on the 4 factor; APRI, aspartate aminotransferase-to-platelet ratio index; GPR, gamma-glutamyl transpeptidase to platelet ratio; RPR, red cell volume distribution width-to-platelet ratio; PLR, platelet to lymphocyte ratio.

advanced fibrosis and cirrhosis is consistent with some [14] but not all other studies [24,27]. To explore this discrepancy, we compared and analysed the baseline characteristics of these studies, finding differences in the HBeAg status of patients. Most of the patients were HBeAg seronegative and had low levels of viral load, as in the study by Lemoine et al. [14] and our studies. Most or all patients were HBeAg seropositive and had high HBV DNA levels in the studies of Ren et al. [24] and Li et al. [27]. Further studies [6,28] analysed the diagnostic accuracy of GPR according to the HBeAg status. For HBeAg positive CHBVI, GPR performed better than APRI in evaluating advanced fibrosis and cirrhosis, but was comparable to FIB-4 in identifying significant fibrosis, advanced fibrosis and cirrhosis [6,28]. However, in HBeAg negative CHB, the diagnostic performance of GPR were similar to FIB-4 and APRI in assessing significant fibrosis, advanced fibrosis and cirrhosis [6,28]. Therefore, the HBeAg status is not the main factor for the discrepancies. We consider that differences in basic characteristics, sample size, spectrum bias of the fibrosis distribution, HBV genotypes and different histological scoring systems lead to the result discrepancies.

Chen et al. [17] first demonstrated that RPR was superior to FIB-4 and APRI in estimating significant fibrosis and cirrhosis. However, Wu et al. [13] reported the performance of RPR was worse than FIB-4 and APRI in diagnosing S ≥ 2 and S ≥ 3. In our study, although the ROC AUCs of RPR were lower than FIB-4 and APRI in identifying fibrosis and cirrhosis, no major differences were found. Zhao et al. [18] reported that the mean value of PLR value was lower in patients with liver cirrhosis than HBV-Active-Carriers patients. In this study, we found the mean value of PLR was significantly lower in the liver fibrosis stage ≥3 than those in fibrosis stage ≤2 ($P < 0.001$).

AAR and NLR are also proposed as predictors of the degree of liver fibrosis [19]. However, consistent with previous studies [5,6,28–30] we could not confirm this assertion.

We acknowledged several limitations in our analysis. We used transient elastography as the reference method instead of the liver biopsy. However, previous studies have found good consistency between transient elastography and liver biopsy in CHBVI [19,31,32]. As some factors may lead to overestimation of transient elastography values (such as hepatic flares, obesity and ascites), we minimised these problems by setting strict inclusion criteria. Treatment-naive and treated CHBVI patients were not strictly distinguished and this study was a single-centre retrospective study with a related small sample size, so findings needed to be validated in prospective and multicentre clinical trials.

It seems that a common weakness of simple non-invasive markers based on routine parameters is the inability to accurately diagnose fibrosis and cirrhosis in a proportion of patients. However, we found the negative predictive values of FIB-4, APRI and GPR to be>0.85 for advanced fibrosis and cirrhosis. Hence, the diagnostic values of these non-invasive markers are better at excluding advanced fibrosis or cirrhosis, and these conclusions are also confirmed in the guidelines [2,33].

This work represents an advance in biomedical science because it shows that GPR has best diagnostic performance and FIB-4, APRI and RPR have similar diagnostic values in predicting fibrosis and cirrhosis, whilst PLR, FIB-4 and APRI are comparable for the diagnosis of cirrhosis.

## Summary table

*What is known about this subject:*

- Development simpler, more available and cheaper non-invasive markers for staging liver fibrosis is an important issue in CHB patients.
- Serum biomarkers, certain blood cell counts and transient elastography have been used to assess fibrosis and cirrhosis.
- The main values of these non-invasive markers lie in excluding advanced fibrosis and cirrhosis.

*What this paper adds*:

- The diagnostic values of PLR were inferior to FIB-4 and APRI in assessing significant fibrosis and advanced fibrosis.
- Although the AUROCs of PLR were lower to that of PRP, PLR was comparable to RPR in predicting fibrosis and cirrhosis.
- AAR and NLR were not predictive factors of liver fibrosis.

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Lu W and Zhang YP made the equal contributions to this paper.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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