



Gamma-glutamyl transpeptidase to platelet ratio index is a good noninvasive biomarker for predicting liver fibrosis in Chinese chronic hepatitis B patients

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Abstract

Objective: To evaluate whether gamma-glutamyl transpeptidase to platelet ratio index (GPRI) can diagnose the extent of liver fibrosis in Chinese patients with chronic hepatitis B (CHB) infection.

Methods: This prospective observational study used liver biopsy results as the gold standard to evaluate the ability of GPRI to predict hepatic fibrosis compared with two other markers, the aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis-4 score (FIB-4). The clinical and demographic factors that affected GPRI, independent of liver fibrosis, were assessed using multivariate linear regression analyses.

Results: This study enrolled 312 patients with CHB. GPRI had a significantly positive correlation with liver fibrosis stage and the correlation coefficient was higher than that for APRI and FIB-4. The areas under the receiver operating curves for GPRI for significant fibrosis, bridging fibrosis, and cirrhosis were 0.728, 0.836, and 0.842, respectively. Of the three indices, GPRI had the highest diagnostic accuracy for bridging fibrosis and cirrhosis. Age, elevated AST and elevated total bilirubin levels were independent determinants of increased GPRI.

Conclusion: GPRI was a more reliable laboratory marker than APRI and FIB-4 for predicting the stage of liver fibrosis in Chinese patients with CHB.

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Keywords

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Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). Worldwide it is estimated that more than 240 million people have suffered from chronic HBV infections and about 780 000 people die every year due to the complications of hepatitis B, including cirrhosis, hepatic failure and hepatocellular carcinoma.¹ Patients with significant hepatic inflammation and fibrosis are at the highest risk of these complications. With early diagnosis and the advent of effective antiviral therapies, the prognosis of chronic hepatitis B (CHB) can be improved significantly.² A precise definition of liver disease severity remains important in predicting prognosis and therapeutic outcomes in patients with CHB. At present, liver biopsy is still regarded as the gold standard for assessing the degree of hepatic inflammation and fibrosis.³ However, it has some limitations such as invasiveness, cost, sampling variability and associated risk for complications. Furthermore, a single biopsy does not measure the dynamic nature of liver fibrosis.⁴ Therefore, accurate, noninvasive, repeatable, and easily available alternative methods for identifying patients with CHB are needed urgently.

To address this unmet need, several serum marker panels thought to be indicators of liver fibrosis have been extensively studied, including the aspartate aminotransferase (AST) to platelet ratio index (APRI), the fibrosis-4 (FIB-4) score (based on AST, alanine aminotransferase [ALT], patient age, and platelet count), the AST/ALT ratio, and Forn's index.⁵ All of these markers have shown promise for the

detection of advanced fibrosis and cirrhosis, but they have been mostly studied within relatively small sets of patients with CHB under somewhat controlled conditions, making the results difficult to generalize to broader patient populations in real-world clinical settings and their ideal cut-offs are unclear.⁶⁻⁸ Thus, new modalities are needed to overcome these problems. Serum gamma-glutamyl transpeptidase (GGT) is a microsomal enzyme that can be isolated from hepatocytes and gall bladder epithelium.⁹ Its levels can increase in many diseases and conditions, for example, alcohol dependency, drug use, viral hepatitis and obesity.^{10,11} In patients with CHB, it was concluded that an increase in serum GGT was associated with high ALT and AST levels, low albumin levels, and advanced fibrosis.⁹ Therefore, it may be considered an indicator of significant fibrosis in CHB patients. Recently, a study found that the gamma-glutamyl transpeptidase to platelet ratio might be an accurate marker for staging liver fibrosis in patients with CHB in West Africa,¹² but further validation in non-African populations is still required. Based on these findings,^{9,12} this present study evaluated the noninvasive marker, the gamma-glutamyl transpeptidase to platelet ratio index (GPRI) in Chinese patients with CHB. The GPRI is calculated based on the serum GGT value (and the upper limit of normal [ULN] value for the laboratory) and platelet counts using the following formula: $[\text{GGT}/\text{ULN}]/\text{platelet counts} [\times 10^9/\text{l}] \times 100$.

The aims of this study were to: (i) investigate a reliable and routine indicator for determining the progression of fibrosis in Chinese patients with CHB, using liver

histology as the gold standard; (ii) compare GPRI with two other biomarker panels; (iii) explore the influencing factors on GPRI values.

Patients and methods

Patients

This prospective observational study enrolled consecutive patients with CHB at the Department of Traditional and Western Medical Hepatology, Third Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China between January 2008 and March 2015. The criterion for a diagnosis of CHB was having serum hepatitis B surface antigen positivity for > 6 months.¹³ All enrolled patients underwent liver biopsy. Patients meeting the following criteria were excluded: (i) co-infection with human immunodeficiency virus, hepatitis A, C or D virus; (ii) presence of decompensated cirrhosis, hepatocellular carcinoma, hepatic failure, and other causes of chronic liver disease. Written informed consent was obtained from all patients and the study was approved by the Third Hospital of Hebei Medical University Research Ethics Committee and carried out according to the guidelines of the 1975 Declaration of Helsinki.

Liver biopsy

Ultrasonography-guided percutaneous liver biopsy was performed using a 16 G disposable needle (Bard Biopsy Systems, Tempe, AZ, USA) under local anaesthesia. All liver biopsies had an adequate specimen of ≥ 1.5 cm in length and included at least eight complete portal tracts. The liver specimens were fixed in buffered formalin and embedded in paraffin. Fixed hepatic tissues were sectioned and routinely stained with haematoxylin and eosin, and Masson's trichrome. The tissue sections were blindly evaluated by one experienced hepatopathologist, who had no information about the clinical characteristics of the study

patients, in order to avoid inter-observer discrepancy. The degree of hepatic inflammation and fibrosis was assessed on the basis of the 2000 Xi'an Viral Hepatitis Management Guidelines recommended by the Chinese Society of Infectious Diseases and Parasitology and the Chinese Society of Hepatology of the Chinese Medical Association.¹⁴ Fibrosis was staged from F0 to F4: F0, no fibrosis; F1, mild fibrosis without fibrous septum; F2, fibrosis with a few fibrous septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Likewise, inflammatory activity was graded from G0 to G4:¹⁴ G0, no inflammation; G1, portal inflammation with rare lobular necrosis; G2, mild piecemeal portal necrosis, focal or spotty lobular necrosis; G3, moderate piecemeal portal necrosis, bridging necrosis in lobule; G4, severe piecemeal portal necrosis, multi-lobular necrosis. The increased numerical value indicated more severe disease.

Liver biochemistry tests

Venous blood samples (6 ml) were obtained from overnight fasted patients within 1 week before or after the liver biopsy. Laboratory tests were analysed within 2 h after obtaining the blood samples at room temperature. Serum ALT, AST, total bilirubin (TBIL) and GGT were measured using an enzymatic method with an automatic biochemistry analyser (Olympus AU2700; Olympus, Tokyo, Japan) according to the manufacturer's instructions. Blood platelet counts were determined using an automated haematology analyser (Sysmex K4500; Sysmex Corporation, Kobe, Japan). From these routine laboratory values, GPRI, APRI and FIB-4 were calculated using the following formulae:

$$\text{GPRI} = \frac{\text{GGT level}(\text{ULN}^*)}{\text{platelet count}(10^9/\text{l})} \times 100$$

(*where ULN = upper limit of normal for that laboratory)

$$\text{APRI} = \text{AST level}(\text{U/LN}^*) / \text{platelet count}(10^9/\text{l}) \times 100$$

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

Statistical analyses

All statistical analyses were performed using the SPSS[®] statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows[®]. Quantitative variables with a normal distribution were expressed as mean \pm SD, and those with an abnormal distribution as median (25th, 75th percentile). The relationship between the noninvasive biomarkers and liver histopathology was determined with Spearman's rank correlation coefficient analysis. The diagnostic performance of all noninvasive markers evaluated was assessed by receiver operating characteristic (ROC) curves using histology as a reference. Optimal cut-off values were chosen based on a maximum sum of sensitivity and specificity. Defining the effect of the clinical and laboratory parameters on GPRI in patients with CHB was undertaken using multivariate linear regression analyses. Qualitative and quantitative differences between subgroups were compared using Mann-Whitney *U*-test or Student's *t*-test, respectively. All *P*-values given are 2-sided and a *P*-value < 0.05 was considered statistically significant.

Results

From January 2008 to March 2015, 312 subjects who fulfilled the study criteria were enrolled. The mean \pm SD age was 35.26 ± 1.18 years (range 13 – 65 years). Of these patients, 227 (72.8%) patients were men and 85 (27.2%) were women. The clinical, biological and histological

characteristics of the patients are shown in Table 1. The biopsy fibrosis stage distribution was as follows: F0, $n = 17$ (5.4%); F1, $n = 126$ (40.4%); F2, $n = 76$ (24.4%); F3, $n = 39$ (12.5%); F4, $n = 54$ (17.3%). Significant hepatic fibrosis (F2–F4) was found in 169 (54.2%) patients and significant hepatic inflammatory activity (G3–G4) was found in 50 (16.0%) patients.

Box plots of GPRI, APRI and FIB-4 in relation to the fibrosis stage are presented in Figure 1. GPRI had a significant positive correlation with fibrosis stage in patients with CHB ($r = 0.516$, $P < 0.001$), with mean values of 0.23, 0.28, 0.33, 0.91, and 1.25 for F0, F1, F2, F3, and F4, respectively. The Spearman's correlation coefficient was

Table 1. Baseline clinical and demographic characteristics of the patients with chronic hepatitis B infection ($n = 312$) who participated in this study to evaluate a biomarker for the diagnosis of hepatic fibrosis.

	Patients with CHB $n = 312$
Age, years	35.26 ± 1.18
Sex, male/female	227/85
Alanine transaminase, U/l	102.46 (82.45–122.47)
Aspartate aminotransferase, U/l	69.25 (55.87–82.63)
Total bilirubin, $\mu\text{mol/l}$	21.19 (18.89–24.49)
Gamma-glutamyl transpeptidase, U/l	49.57 (44.12–55.03)
Platelet count, $\times 10^9/\text{l}$	197.14 ± 71.53
GPRI	0.82 (0.70–0.93)
APRI	1.06 (0.87–1.26)
FIB-4	1.52 (1.32–1.72)
Fibrosis stage, F0/F1/F2/F3/F4	17/126/76/39/54
Inflammatory activity grade, G0/G1/G2/G3/G4	0/119/143/47/3

Data presented as mean \pm SD, median (25th, 75th percentile) or *n* of patients.

GPRI, gamma-glutamyl transpeptidase to platelet ratio index; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 score.

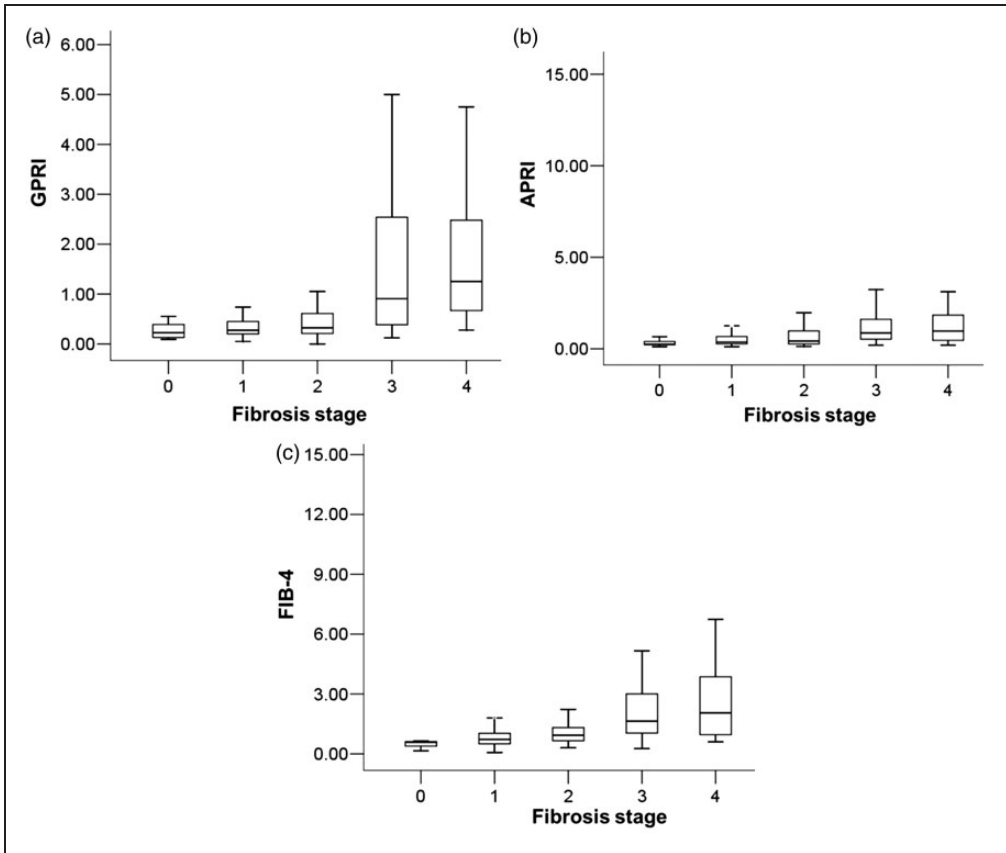


Figure 1. Box plots showing median and percentiles for (a) GPR, (b) APRI and (c) FIB-4 scores for diagnosing fibrosis stages in the Chinese patients with chronic hepatitis B infection ($n = 312$). The central horizontal lines in the boxes are the medians, the extremities of the boxes are the 25th and 75th percentiles, and the error bars represent the minimum and maximum outliers. GPR, gamma-glutamyl transpeptidase to platelet ratio index; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 score.

higher than for FIB-4 ($r = 0.508$, $P < 0.001$) or APRI ($r = 0.407$, $P < 0.001$).

The study analysed the data comparing the different biomarkers in relation to different stages of hepatic fibrosis using ROC curves (Table 2). In discriminating significant fibrosis (F0–F1 versus F2–F4), the area under ROC curve (AUROCs) of GPR, APRI and FIB-4 were 0.728 (sensitivity 59%, specificity 78%), 0.686 (sensitivity 70%, specificity 63%) and 0.742 (sensitivity 72%, specificity 67%), respectively

(Figure 2a). For predicting bridging fibrosis (F0–F2 versus F3–F4), the AUROCs of GPR, APRI and FIB-4 were 0.836 (sensitivity 76%, specificity 81%), 0.758 (sensitivity 85%, specificity 58%) and 0.803 (sensitivity 69%, specificity 77%), respectively (Figure 2b). For diagnosing cirrhosis (F0–F3 versus F4), the AUROCs of GPR, APRI and FIB-4 were 0.842 (sensitivity 82%, specificity 77%), 0.710 (sensitivity 85%, specificity 48%) and 0.776 (sensitivity 67%, specificity 76%), respectively (Figure 2c).

Table 2. Diagnostic accuracy of gamma-glutamyl transpeptidase to platelet ratio index (GPRI), aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 score (FIB-4) in the prediction of liver fibrosis and cirrhosis based on optimal cut-off values.

	Significant fibrosis (F0–F1 versus F2–F4)			Bridging fibrosis (F0–F2 versus F3–F4)			Cirrhosis (F0–F3 versus F4)		
	GPRI	APRI	FIB-4	GPRI	APRI	FIB-4	GPRI	APRI	FIB-4
AUROC	0.728	0.686	0.742	0.836	0.758	0.803	0.842	0.710	0.776
95% CI	0.67, 0.78	0.60, 0.75	0.69, 0.80	0.78, 0.89	0.70, 0.81	0.75, 0.86	0.79, 0.89	0.64, 0.78	0.71, 0.84
Cut-off values	0.46	0.42	0.86	0.53	0.43	1.19	0.65	0.41	1.34
Sensitivity	0.59	0.70	0.72	0.76	0.85	0.69	0.82	0.85	0.67
Specificity	0.78	0.63	0.67	0.81	0.58	0.77	0.77	0.48	0.76
PPV, %	76.34	69.00	71.86	61.02	46.20	56.14	42.31	25.58	36.08
NPV, %	61.88	63.83	66.21	89.18	90.07	85.35	95.19	92.86	91.16
Positive LR	2.73	1.89	2.18	4.00	2.02	3.00	3.57	1.63	2.79
Negative LR	0.52	0.48	0.42	0.29	0.26	0.40	0.23	0.31	0.43
DA, %	67.95	66.67	69.23	78.53	66.03	74.68	77.56	55.77	74.04

AUROC, area under receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; DA, diagnostic accuracy.

Thus, GPRI showed better performances for the diagnosis of bridging fibrosis and cirrhosis than the other two established noninvasive biomarkers in patients with CHB.

The demographic and clinical characteristics of age, ALT, AST, TBIL, fibrosis stage and inflammatory activity were studied to determine their correlation with GPRI in 312 patients with CHB. According to Spearman's rank correlation coefficient analysis, age, fibrosis stage, inflammatory activity, ALT, AST and TBIL were significantly correlated with GPRI ($P < 0.05$). Multivariate linear regression analyses were undertaken, which showed that in model summary (R multiple = 0.63, adjusted $R^2 = 0.40$, analysis of variance: $F = 32.15$, $P < 0.01$), regression analyses had statistical significance. As shown in Table 3, the items of age, AST, TBIL, fibrosis stage and inflammatory activity demonstrated positive correlations with GPRI ($P < 0.01$). ALT demonstrated no correlation with GPRI.

All patients were divided into two subgroups according to age (<40 years versus ≥ 40 years) as shown in Figure 3a. The GPRI values were significantly higher in patients ≥ 40 years of age when patients with all stages of fibrosis were compared ($P < 0.01$).

As shown in Figures 3b and 3c, the 312 patients with CHB were divided into three groups according to the AST and TBIL levels: <1 times ULN, 1–3 times ULN, and >3 times the ULN. The GPRI values progressively increased with increasing AST and TBIL levels, especially in the group with AST or TBIL levels > 3 times the ULN regardless of fibrosis stage ($P < 0.001$ compared with <1 times ULN for both).

Discussion

Chronic HBV infection is a prolonged inflammatory disease of the liver that may lead to the progressive development of fibrosis. Because fibrosis and its end-point

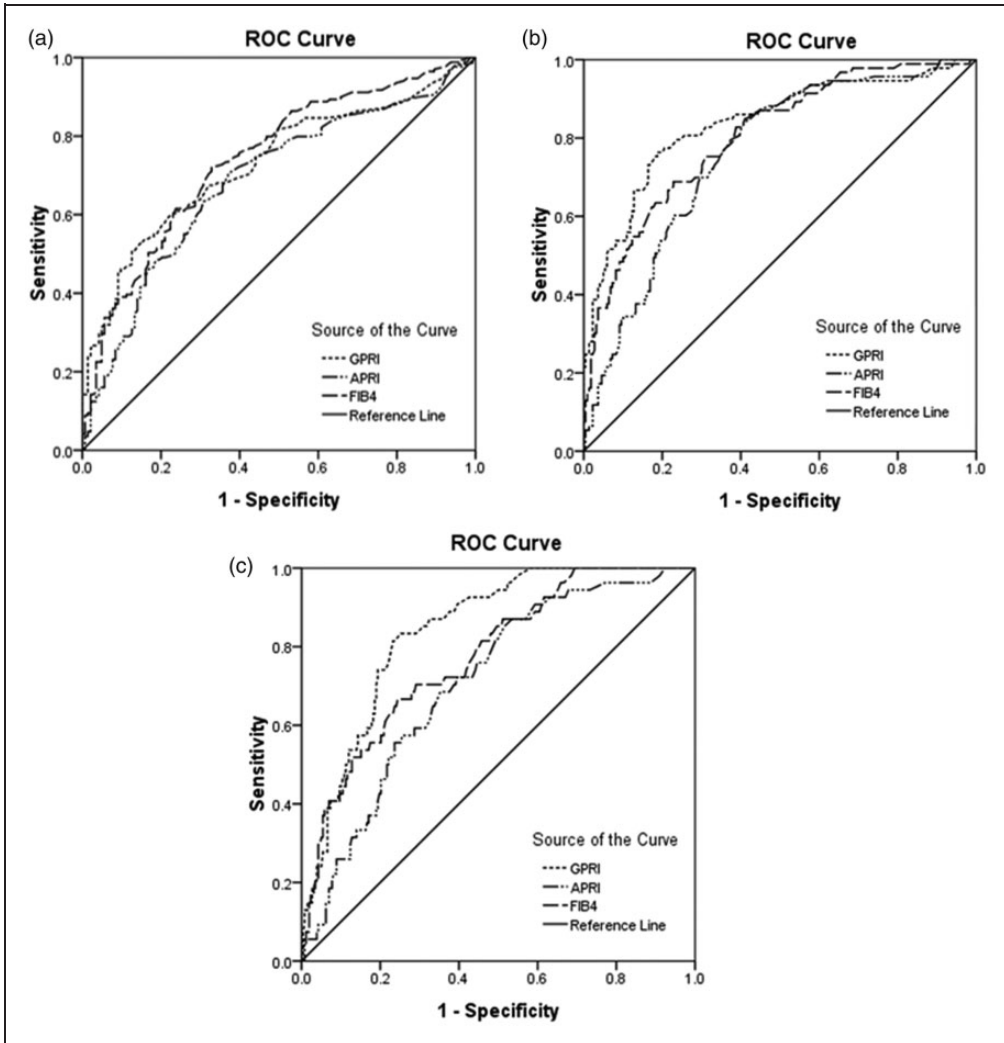


Figure 2. Area under receiver operating characteristic (ROC) curves of GPRi, APRI and FIB-4 for the diagnosis of various stages of liver fibrosis using liver biopsy as the reference. (a) Significant fibrosis: F0–F1 versus F2–F4); (b) bridging fibrosis: F0–F2 versus F3–F4); (c) cirrhosis: F0–F3 versus F4). GPRi, gamma-glutamyl transpeptidase to platelet ratio index; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 score.

cirrhosis are the main causes of morbidity and mortality, continued monitoring of fibrosis is a critical determinant for staging, prognosis, as well as therapeutic decision-making in CHB patients.¹⁵ Liver biopsy is the current gold standard for staging liver fibrosis, but has some disadvantages and

potential complications.¹⁶ Over the last decade, remarkable achievements have been made in the noninvasive diagnosis of fibrosis.¹⁷ However, sensitivity and specificity for diagnosis by these markers are limited, especially in differentiating between adjacent stages of fibrosis.¹⁸

Table 3. Multivariate linear regression analyses of clinical items and gamma-glutamyl transpeptidase to platelet ratio index in patients with chronic hepatitis B infection ($n = 312$).

Constants	Unstandardized coefficient		Standardized coefficients		P-value
	B	Standard error	Beta	t	
	-1.090	0.179	0.138	-6.089	$P < 0.001$
Age	0.020	0.004	0.220	4.887	$P < 0.001$
ALT	0.000	0.000	0.138	-0.938	NS
AST	0.002	0.001	0.298	2.624	$P = 0.009$
TBIL	0.015	0.003	0.229	5.724	$P < 0.001$
Fibrosis grade	0.318	0.078	-0.074	4.060	$P < 0.001$
Inflammatory activity grade	0.123	0.046	0.205	2.681	$P = 0.008$

ALT, alanine transaminase; AST, aspartate aminotransferase; TBIL, total bilirubin; NS, not significant ($P \geq 0.05$).

Recently, serum GGT was reported to be an important parameter in estimating the severity of liver fibrosis.^{19,20} It is present in several organs, most notably in the liver and is a commonly used diagnostic clinical test for liver function.^{18,21} GGT levels change in various conditions, such as inflammation, fibrosis, cholestasis and alcohol consumption.^{22–26} As a marker of oxidative stress, the major function of GGT is to enable the metabolism of glutathione (GSH) and glutathionylated xenobiotics.²³ It catalyses the transfer of a γ -glutamyl group from glutathione and other γ -glutamyl compounds to amino acids or dipeptides.²⁷ Catabolism of GSH by GGT results in pro-oxidant activity, which then leads to downstream cell, tissue, and DNA damage.^{25,28,29} In mild chronic hepatitis and inactive cirrhosis, GGT is usually not elevated.⁹ At the precirrhotic chronic hepatitis stage, GGT may increase up to 2-times above the normal range.⁹ Therefore, increased GGT activity is directly associated with liver injury and predicted fibrosis progression.³⁰ Previous studies have also shown that platelet count is a reflection of disease severity.^{31,32} There was a negative correlation between significant liver fibrosis and platelet count.³³ Worsening of fibrosis and increasing portal pressure are associated with the reduced

production of thrombopoietin by hepatocytes and increased platelet sequestration within the spleen.²⁵ Therefore, based on these two routine tests, GGT and platelet count, this present study evaluated the ability of a new serum marker, GGT-to-platelet ratio or GPRI, to determine the degree of fibrosis in chronic HBV-infected patients.

This present study measured the diagnostic accuracy of GPRI for the noninvasive identification of significant hepatic fibrosis, using liver biopsy as the gold standard reference, compared with two other biomarker indices, APRI and FIB-4. In the 312 Chinese patients with CHB, the GPRI increased with the progressive stages of liver fibrosis and the correlation coefficient ($r = 0.516$, $P < 0.001$) was higher than for APRI ($r = 0.407$, $P < 0.001$) and FIB-4 ($r = 0.508$, $P < 0.001$). These results confirmed that GPRI could predict the development of hepatic fibrosis.

Using ROC curves, the present study demonstrated the good performance of GPRI to diagnose significant fibrosis, bridging fibrosis and cirrhosis, with AUROCs of 0.728, 0.836 and 0.842, respectively. The AUROCs of APRI and Fib-4 to predict significant fibrosis, bridging fibrosis and cirrhosis were 0.686, 0.742, 0.758, 0.803 and 0.710, 0.776 respectively. Thus, for

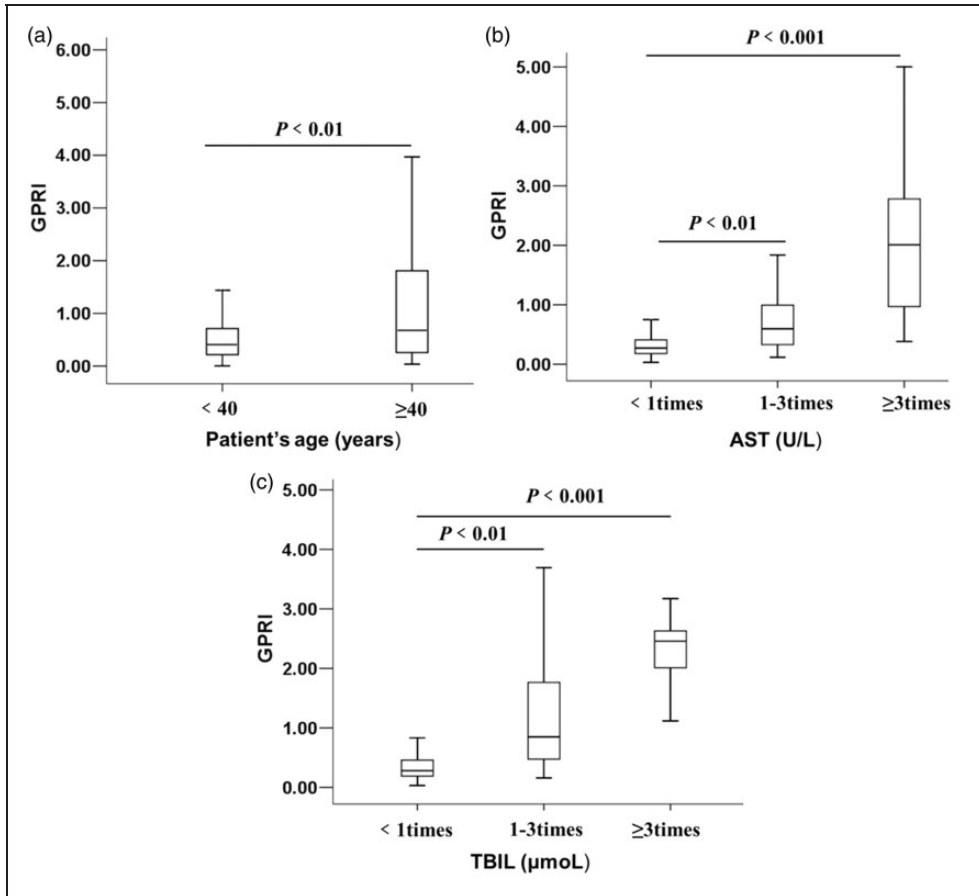


Figure 3. Box plots showing the effect of age, AST and TBIL levels on GPRI values in patients with chronic hepatitis B (CHB) infection ($n = 312$): (a) GPRI values in patients with CHB stratified according to age; (b) GPRI values in patients with CHB stratified according to AST levels; (c) GPRI values in patients with CHB stratified according to TBIL levels. The central horizontal lines in the boxes are the medians, the extremities of the boxes are the 25th and 75th percentiles, and the error bars represent the minimum and maximum outliers. GPRI, gamma-glutamyl transpeptidase to platelet ratio index; AST, aspartate aminotransferase; TBIL, total bilirubin.

advanced fibrosis (F3–F4), the GPRI yielded the highest AUROC. This matched with another study that showed that GPRI was an important predictor of either significant fibrosis or cirrhosis.¹²

Using optimized cut-off values of GPRI, significant fibrosis (cut-off value, 0.46) could be accurately diagnosed in 67.95% of patients with CHB and cirrhosis (cut-off value, 0.65) could be accurately diagnosed in

77.56% of patients with CHB. However, the diagnostic accuracy of APRI and FIB-4 for significant fibrosis and cirrhosis in accordance with liver biopsy were 66.67%, 69.23% and 55.77%, 74.04%, respectively (Table 3). The current findings indicated that GPRI showed a slightly better diagnostic accuracy than FIB-4 for the diagnosis of bridging fibrosis and cirrhosis; and APRI had the lowest diagnostic accuracy for predicting

significant fibrosis, bridging fibrosis and cirrhosis compared with GPRI and FIB-4. Therefore, although APRI and FIB-4 had previously been shown to be useful to stage liver fibrosis in patients with CHB,³⁴ these current results suggest that GPRI is superior to APRI and FIB-4 in Chinese patients with CHB as demonstrated by higher AUROCs and diagnostic accuracies.

The present study also evaluated whether individual patient demographic and clinical characteristics, such as age and biochemical parameters, might affect the application of GPRI in the measurement of hepatic fibrosis in patients with CHB. Multivariate linear regression analyses found that age, AST and TBIL were independent significant determinants of GPRI. Patients with more advanced age (≥ 40 years) had significantly higher GPRI values than younger patients (< 40 years) regardless of the stage of fibrosis. The best explanation of this result was that age might represent the long-term inflammatory and fibrotic processes taking place in many of the Chinese patients who had been infected with HBV at an earlier age.

It is noteworthy that a chronic inflammatory response drives the progression of liver fibrosis.³⁵ The role of liver enzymes in the assessment of CHB remains important for the majority of clinical indices estimating the degree of liver fibrosis.³ Studies have reported that the AST level was elevated in the patients with chronic viral hepatitis and the changes in TBIL had an impact on liver cirrhosis.^{36,37} The present study observed a clear association between the GPRI value and AST and TBIL levels in patients with CHB. The GPRI value increased as the AST and TBIL levels increased and it might be the significant extrinsic predictor of progressive liver fibrosis. Therefore, caution is advised when interpreting the diagnostic accuracy of GPRI when performed in patients with high AST and TBIL levels (i.e. $> 3 \times \text{ULN}$), as this might result in its overestimation of the severity of liver

fibrosis. In such patients, serial measurements of GPRI value are recommended after the resolution of the acute inflammatory phase of hepatitis.

In conclusion, this present study demonstrated that GPRI is a reliable method to evaluate the degree of liver fibrosis in Chinese patients with CHB. It showed significantly higher diagnostic accuracy compared with APRI and FIB-4. Age, and elevated AST and TBIL levels (i.e. $> 3 \times \text{ULN}$) might affect the diagnostic accuracy of GPRI. Further studies with larger patient populations are needed to corroborate these results.

Authors' contributions

Y.M.N. designed the study; R.Q.W., Q.S.Z., S.X.Z., X.M.N., J.H.D. and H.J.D. performed the experiments; R.Q.W. and Q.S.Z. analysed the data and wrote the paper.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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