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Original Article

Gamma-glutamyl Transpeptidase to Platelet Ratio Predicts Liver Injury in Hepatitis B e Antigen-negative Chronic Hepatitis B Patients With Normal Alanine Aminotransferase

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Abstract

Background and Aims: Chronic hepatitis B virus (HBV) infection is a serious health problem worldwide. Evaluating liver injury in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) with detectable HBV DNA and normal alanine aminotransferase (ALT) is crucial to guide their clinical management. We aimed to investigate the stages of liver inflammation and fibrosis as well as the predictive accuracy of gamma-glutamyl transpeptidase-to-platelet ratio (GPR) in these patients. ***Methods:*** A total of 184 treatment-naïve HBeAg-negative CHB patients with detectable HBV DNA and normal ALT were enrolled. The Scheuer scoring system was used to classify liver inflammation and fibrosis. ***Results:*** The distribution of patients with different liver inflammation grades were as follows: G0, 0 (0%); G1, 97 (52.7%); G2, 68 (37.0%); G3, 12 (6.5%); and G4, 7 (3.8%). The distribution of patients with different liver fibrosis stages were as follows: S0, 22 (12.0%); S1, 72 (39.1%); S2, 42 (22.8%); S3, 19 (10.3%); and S4, 29 (15.8%). The areas under the receiver operating characteristic (AUROC) curves of GPR in predicting significant inflammation, severe inflammation, and advanced inflammation were 0.723, 0.895, and 0.952, respectively. The accuracy of GPR was significantly superior to that of ALT in predicting liver inflammation. The AUROCs of GPR in predicting significant fibrosis, severe fibrosis, and cirrhosis were 0.691, 0.780, and 0.803, respectively. The predictive accuracy of GPR was significantly higher than that of aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) in identifying advanced fibrosis and cirrhosis, and it was superior to FIB-4 but comparable to APRI in identifying significant fibrosis. ***Conclusions:*** Nearly half of the HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels had significant liver inflammation or fibrosis. GPR can serve as an accurate predictor of liver inflammation and fibrosis in these patients.

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Keywords: Chronic hepatitis B; Liver injury; Gamma-glutamyl transpeptidase; Platelet.

Abbreviations: ALT, alanine aminotransferase; APRI, aminotransferase-to-platelet ratio index; AUROC, areas under the receiver operating characteristic; CHB, chronic hepatitis B; CI, confidence interval; FIB-4, fibrosis index based on four factors; GGT, gamma-glutamyl transpeptidase; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LB, Liver biopsy; TE, Transient elastography; ULN, upper limit of normal.

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Introduction

Chronic hepatitis B virus (HBV) infection is a serious health problem worldwide, and it can cause a series of manifestations, including liver cirrhosis, liver failure, and hepatocellular carcinoma.[1] Antiviral therapy can prevent disease progression and reduce the risk of adverse events in patients with chronic hepatitis B (CHB).[2,3] Patients with either hepatitis B e antigen (HBeAg)-positive or -negative immune active phase are recommended antiviral treatment, according to current guidelines.[2,3] However, a substantial number of HBeAg-negative CHB patients with detectable HBV DNA and normal alanine aminotransferase (ALT) levels are not recommended antiviral treatment.[2,3] Previous studies have

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reported that normal ALT levels do not mean the absence of significant liver injury.[4–6] In addition, high HBV DNA levels were associated with significant liver inflammation and fibrosis in HBeAg-negative CHB patients with normal ALT levels.[7] A retrospective study that enrolled 286 patients with HBeAg-negative CHB showed that nearly a third of patients with normal ALT levels had significant liver inflammation or fibrosis.[8] Choi *et al*.[9] reported that untreated HBeAg-negative CHB patients with normal ALT and high HBV DNA levels had a higher risk of advanced events than treated immune-active CHB patients did. Thus, identifying the stages of liver inflammation and fibrosis in these patients is crucial to guide their clinical management.

Liver biopsy (LB) is considered the gold standard to evaluate liver injury in chronic liver diseases.[10] Nonetheless, LB cannot be widely used in clinical practice owing to limitations such as high cost, potential complications, and sampling errors.[10–13] Transient elastography (TE) was reported as a promising method to evaluate liver fibrosis in patients with CHB.[14–16] However, the accuracy of TE could be affected by various factors, including liver inflammatory activity, obesity, and operator skills.[17] In addition, noninvasive indexes have been established by simple serological markers to assess liver fibrosis and inflammation. The aspartate aminotransferase-to-platelet ratio index (APRI) and the fibrosis index based on the four factors (FIB-4) are widely used to assess fibrosis in viral hepatitis,[18–22] while ALT is generally regarded as an indicator of liver inflammation. However, numerous studies have demonstrated an inconsistency between liver inflammation grade and ALT levels in patients with CHB.[8,23]

Previous studies have reported that the gamma-glutamyl transpeptidase (GGT)-to-platelet ratio (GPR) serves as a simple and accurate index for predicting liver inflammation and fibrosis in patients with CHB.[24,25] Lemoine *et al*.[24] reported that GPR was more accurate than APRI and FIB-4 in distinguishing liver fibrosis among patients with CHB. Our previous study also reported that the accuracy of GPR in predicting significant liver inflammation was superior to that of ALT in patients with CHB.[25] However, the predictive value of GPR in HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels is unclear. Therefore, through this study, we investigated the stages of liver inflammation and fibrosis in HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels, and assess the diagnostic accuracy of GPR in liver inflammation and fibrosis in these patients.

Methods

Patients

Consecutive patients with CHB who underwent LB at Huai'an No. 4 People's Hospital (Huai'an, China) and Nanjing Drum Tower Hospital (Nanjing, China) between April 2004 and September 2020 were retrospectively enrolled. Patients who had CHB concurrent with other viral hepatitis, consumed a significant amount of alcohol (≥30 g of alcohol per day for men and ≥20 g of alcohol per day for women), had nonalcoholic fatty liver disease, primary biliary cirrhosis, autoimmune hepatitis, and other chronic liver diseases, had CHB concurrent with malignant tumors before and at the time of LB, and had undergone organ transplantation before enrollment were excluded.

Written informed consent was obtained from all patients prior to enrolment. The study was performed according to the Declaration of Helsinki and approved by the Ethics Committees of the Nanjing Drum Tower Hospital and Huai' No. 4 People's Hospital.

LB and laboratory test

Ultrasonographic-guided LB was routinely performed in patients with CHB. All the LB specimens were processed by formalin fixation, paraffin-embedded, and stained with hematoxylin and eosin. Histological specimens were reviewed by experienced pathologists who were blinded to the clinical characteristics of the patients according to the Scheuer scoring system.[26] The clinical and laboratory data were collected from the electronic medical charts of the above two centers. The upper limit of normal (ULN) of ALT in the study was 40 U/L. The cut-off value of detectable HBV DNA was 500 IU/mL in Huai'an No. 4 People's Hospital, while the cut-off value of detectable HBV DNA was 20 IU/mL in Nanjing Drum Tower Hospital. Autoantibody screening was routinely performed to exclude concomitant autoimmune liver diseases, including antinuclear antibody, anti-smooth muscle antibody, and antimitochondrial antibody.[27–29]

Noninvasive prediction indexes and calculation formulae

The calculation formulae of noninvasive prediction indexes were as follows: GPR = (GGT [U/L]/ULN of GGT)/platelet count (10^9/L) × 100;[24,30] APRI = (AST [U/L]/ULN of AST)/ platelet count (10^9/L) × 100;[31] FIB-4 = (age [years] × AST (U/L))/ (platelet count [10^9/L] × (ALT [U/L])$^{1/2}$).[31]

Statistical analyses

Continuous variables are presented as the median (interquartile range) and categorical variables as percentages. The predictive values of GPR for liver inflammation and fibrosis were evaluated using the area under the receiver operating characteristic curve (AUROC). Differences between the AUROCs were tested using the z-test. The cut-off values were determined by Youden's index, which was the optimal combination of sensitivity and specificity. Data were analyzed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) and SigmaPlot version 12.5 (Systat Software Inc., San Jose, CA, USA). A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

In total, 1,241 consecutive patients with CHB were included, of whom 1,057 were excluded according to the exclusion criteria (Fig. 1). Finally, a total of 184 HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels were included for analysis. The clinical characteristics of the patients are shown in Table 1. The median patient age was 43 years, and 52.2% of them were male. The median HBV DNA and hepatitis B surface antigen (HBsAg) levels were 3.7 $\log_{10}$ IU/mL and 2,567.6 IU/mL, respectively. The liver inflammation grades of the patients were distributed as follows: G0, 0 (0%); G1, 97 (52.7%); G2, 68 (37.0%); G3, 12 (6.5%); and G4, 7 (3.8%), respectively. The liver fibrosis stages of the patients were distributed as follows: S0, 22 (12.0%); S1, 72 (39.1%); S2, 42 (22.8%); S3, 19 (10.3%); and S4, 29 (15.8%) (Fig. 2). About 47.3% of patients had significant liver inflammation (≥G2) and 48.9% of patients had significant liver fibrosis (≥S2).

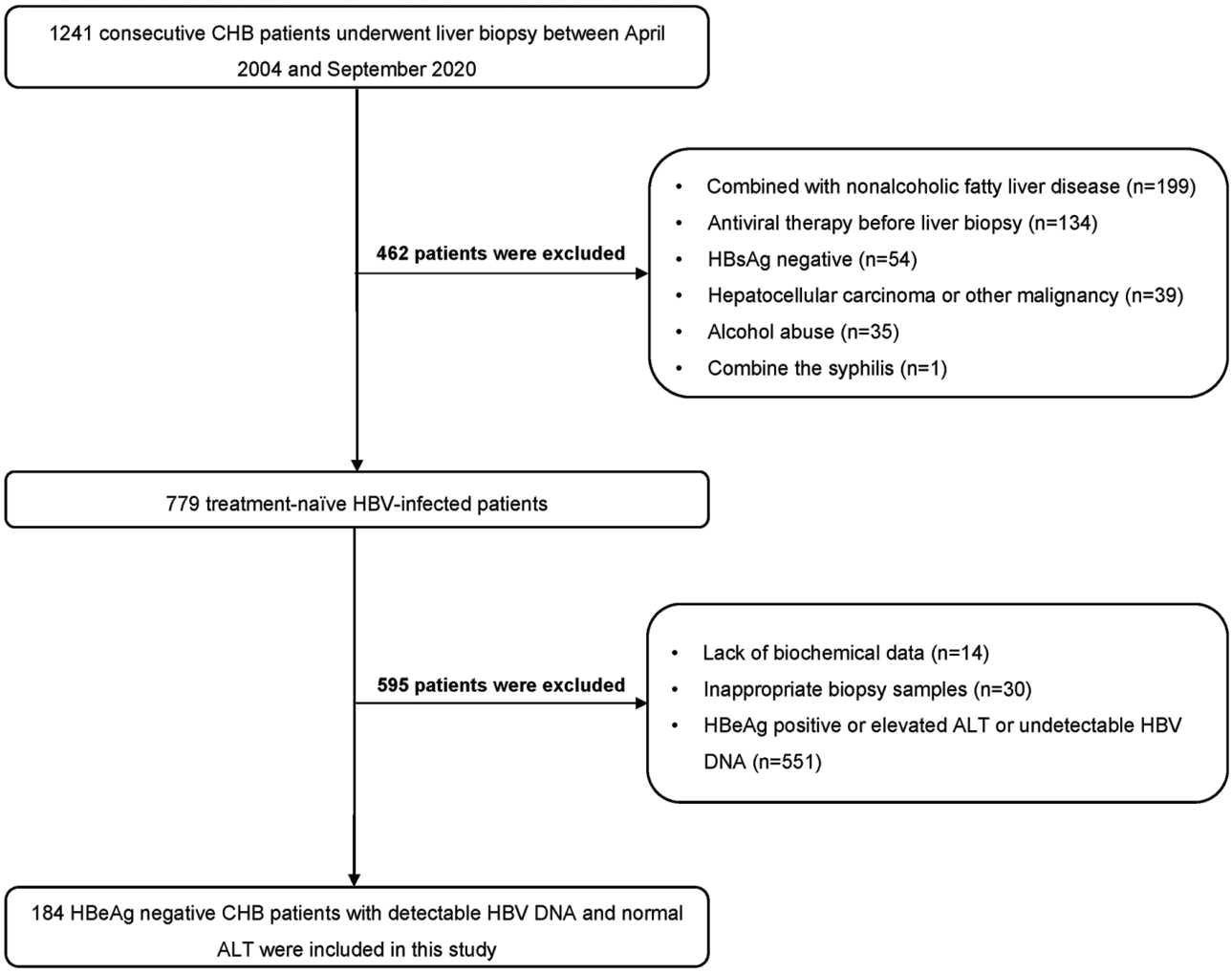

Fig. 1. Flow diagram describing the selection of the study population.

Table 1. Baseline characteristics of the study population

Characteristics	Patients with CHB, *n*=184
Age (years)	43.0 (36.0–50.0)
Male (%)	96 (52.2)
Hb (g/L)	136.4 (123.0–150.0)
PLT (× 10^9/L)	173.8 (135.0–208.5)
ALT (U/L)	23.7 (16.0–30.9)
AST (U/L)	23.2 (18.8–27.7)
GGT (U/L)	27.6 (12.5–28.0)
Tbil (μmol/L)	14.0 (9.1–17.0)
ALB (g/L)	43.4 (40.8–46.2)
HBsAg (IU/mL)	2,567.6 (191.2–3,494.4)
HBV DNA (log_{10} IU/mL)	3.7 (1.7–5.1)

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; GGT, gamma-glutamyl transferase; GLB, globulin; Hb, hemoglobin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PLT, platelet; Tbil, total bilirubin; PT, prothrombin time.

Comparisons of AUROCs for predicting liver inflammation grades between GPR and other indexes

The ROC curves of GPR and ALT for predicting significant liver inflammation (≥G2), severe liver inflammation (≥G3), and advanced liver inflammation (G4) are shown in Figure 3 (panels A, B, and C, respectively). The predictive accuracy of GPR was compared with that of ALT, as shown in Table 2. The AUROCs of GPR in predicting significant liver inflammation, severe liver inflammation, and advanced liver inflammation were 0.723 (95% confidence interval [CI]: 0.647 to 0.800, $p<0.001$), 0.895 (95% CI: 0.831 to 0.959, $p<0.001$), and 0.952 (95% CI: 0.915 to 0.988, $p<0.001$), with optimal cut-off values of 0.240, 0.534, and 0.671, respectively. The AUROCs of GPR were significantly higher than those of ALT in predicting significant liver inflammation ($p=0.042$), severe liver inflammation ($p=0.001$), and advanced liver inflammation ($p=0.026$).

Comparisons of AUROCs for predicting liver fibrosis stages between GPR and other indexes

The ROC curves of GPR, APRI, and FIB-4 for predicting sig-

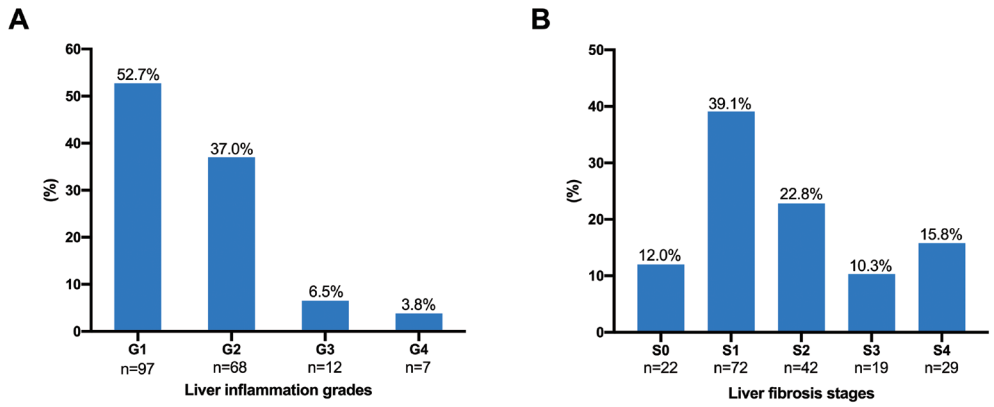

Fig. 2. Distribution of liver inflammation grades and fibrosis stages among the HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

nificant liver fibrosis (≥S2), advanced liver fibrosis (≥S3), and cirrhosis (S4) are shown in Figure 3 (panels D, E, and F, respectively). The predictive accuracy of GPR was compared with that of APRI and FIB-4, as shown in Table 3. The AUROCs of GPR in predicting significant liver fibrosis, advanced liver fibrosis, and cirrhosis were 0.691 (95% CI:

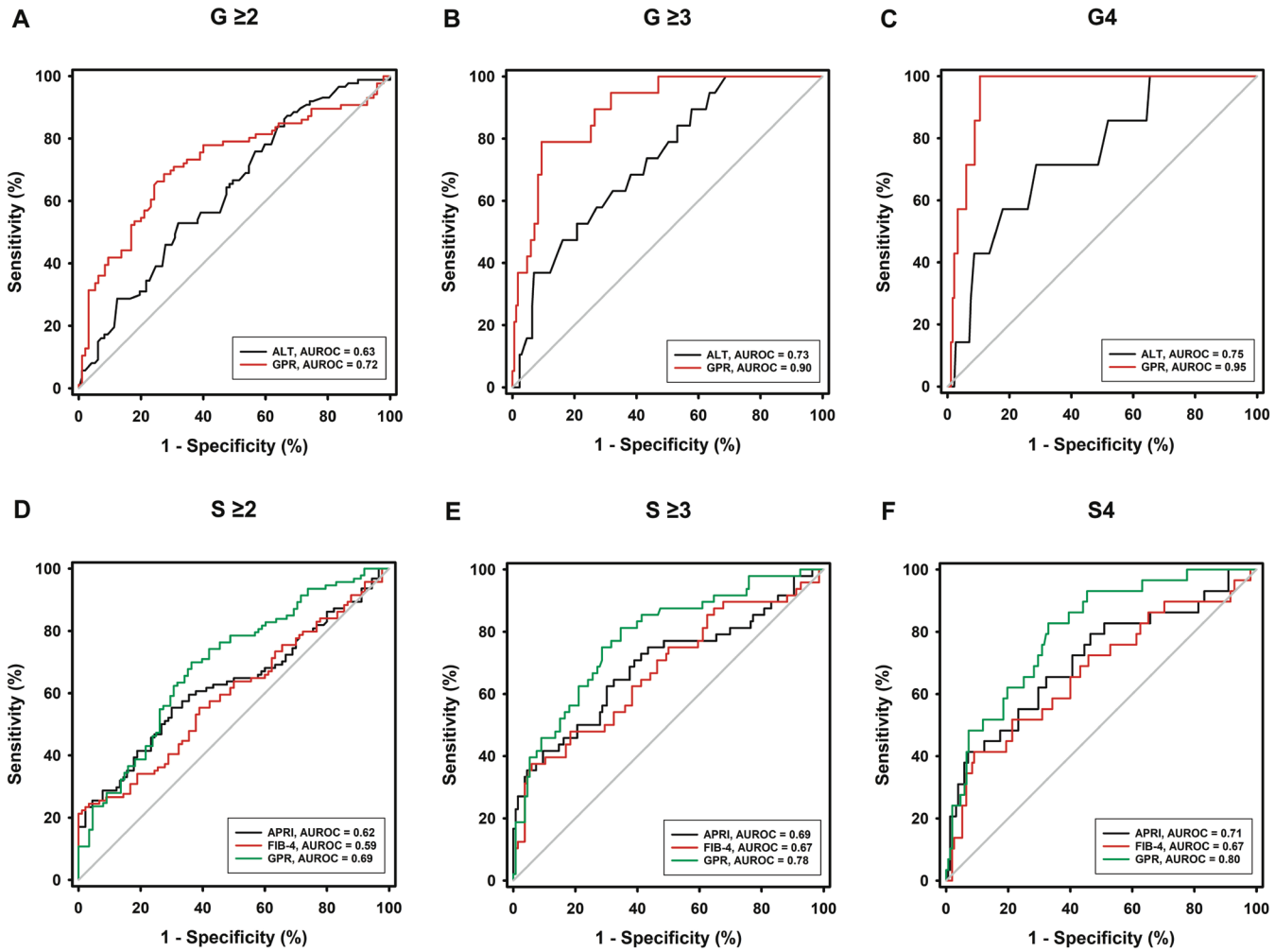

Fig. 3. ROC curves for predicting liver inflammation and fibrosis between GPR and other indexes in the HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels. ALT, alanine aminotransferase; CHB, chronic hepatitis B; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ROC, receiver operating characteristic.

Table 2. Diagnostic accuracy of different indexes for prediction of liver inflammation in HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels

	Optimized cutoff	Sensitivity (%)	Specificity (%)	AUC (95%CI)	*P*-value	*P*-value of ROC contrast test*
G≥2						
ALT (U/L)	25.9	52.87	68.04	0.630 (0.550, 0.710)	0.002	0.042
GPR	0.240	68.60	72.63	0.723 (0.647, 0.800)	<0.001	–
G≥3						
ALT (U/L)	30.9	52.63	79.19	0.732 (0.622, 0.841)	<0.001	0.001
GPR	0.534	78.95	90.59	0.895 (0.831, 0.959)	<0.001	–
G4						
ALT (U/L)	28.9	71.43	71.35	0.748 (0.567, 0.929)	0.025	0.026
GPR	0.671	100.00	89.56	0.952 (0.915, 0.988)	<0.001	–

*Compared with GPR. ALT, alanine aminotransferase; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; GPR, gamma-glutamyl transpeptidase-to-platelet ratio.

0.614 to 0.768, $p<0.001$), 0.780 (95% CI: 0.703 to 0.857, $p<0.001$), and 0.803 (95% CI: 0.721 to 0.884, $p<0.001$), with optimal cut-off values of 0.208, 0.240, and 0.277, respectively. GPR was significantly superior to APRI and FIB-4 in predicting advanced liver fibrosis ($p=0.022$ and $p=0.022$) and cirrhosis ($p=0.028$ and $p=0.010$), while it was superior to FIB-4 ($p=0.035$) but comparable to APRI ($p=0.088$) in predicting significant liver fibrosis.

Discussion

Current treatment guidelines do not recommend HBeAg-negative patients with CHB with normal ALT and detectable HBV DNA levels as candidates for antiviral therapy.[2,3] However, previous studies have reported that these patients present significant liver injury and are at a high risk of adverse events.[32] A retrospective study that enrolled 126 HBeAg-negative CHB patients with normal ALT and detectable HBV DNA levels showed that 23.1% of patients had significant liver inflammation and 10.8% of patients had significant liver fibrosis.[8] Another study reported that untreated HBeAg-negative patients with CHB with high HBV DNA levels and without significant ALT elevation had a higher risk of adverse clinical events than treated active-phase patients with elevated ALT did.[9] We also found that 47.3% of patients had significant liver inflammation and 48.9% of patients had significant liver fibrosis. The proportion of significant liver injury in our study was higher than that in the study by Alam *et al*.[8] A possible explanation is that the median age of patients (43.0 years) in our study was significantly higher than the median patient age in the previous study (26.8 years).[8] Thus, early assessment of liver inflammation and fibrosis plays an important role in the evaluation of disease severity and may help in deciding the antiviral therapy in these patients.

Although LB is the gold standard for detecting liver injury, it is not appropriate for all patients with CHB, owing to its invasiveness and lack of repeatability.[33] Given the shortcomings of LB, it is necessary to identify a simple noninvasive biomarker to estimate liver fibrosis and inflammation. Several noninvasive predicting indexes of liver fibrosis have

Table 3. Diagnostic accuracy of different indexes for prediction of liver fibrosis in HBeAg-negative CHB patients with detectable HBV DNA and normal ALT levels

	Optimized cutoff	Sensitivity (%)	Specificity (%)	AUC (95%CI)	*p*-value	*p*-value of ROC contrast test*
S≥2						
APRI	0.357	55.32	70.00	0.623 (0.542, 0.702)	0.003	0.088
FIB-4	2.486	21.28	1.000	0.593 (0.511, 0.676)	0.027	0.035
GPR	0.208	69.89	63.64	0.691 (0.614, 0.768)	<0.001	–
S≥3						
APRI	0.382	62.50	69.85	0.691 (0.595, 0.788)	<0.001	0.022
FIB-4	2.256	37.50	94.12	0.674 (0.579, 0.768)	<0.001	0.022
GPR	0.240	81.25	65.41	0.780 (0.703, 0.857)	<0.001	–
S4						
APRI	0.622	41.38	92.90	0.710 (0.597, 0.823)	<0.001	0.028
FIB-4	2.256	41.38	90.97	0.671 (0.554, 0.788)	0.003	0.010
GPR	0.277	82.76	67.11	0.803 (0.721, 0.884)	<0.001	–

*Compared with GPR. APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; FIB-4, fibrosis index based on the four factors; GPR, gamma-glutamyl transpeptidase-to-platelet ratio.

been reported during the past decade. APRI and FIB-4 are the most widely used surrogate indexes for predicting liver fibrosis in patients with CHB.[34,35] However, these two indexes showed only moderate accuracy for assessing liver fibrosis in these patients.[36,37] Although ALT is widely used to evaluate liver inflammation activity, its accuracy has always been controversial.[4,5] Thus, there has been a lack of effective markers to predict liver inflammation.

GPR was initially developed to predict liver fibrosis in patients with CHB with a higher accuracy than that of APRI and FIB-4.[24] Our previous study also demonstrated that the predictive performance of GPR was significantly superior to that of ALT in patients with CHB.[25,38] However, the predictive accuracy of GPR in predicting liver inflammation and fibrosis remains unclear in HBeAg-negative CHB patients with normal ALT and detectable HBV DNA levels. In this study, we demonstrated that the accuracy of GPR was superior to that of APRI and FIB-4 in predicting advanced fibrosis and cirrhosis, as well as to ALT in predicting significant inflammation, severe inflammation, and advanced inflammation. Our results suggested that GPR could not only predict liver fibrosis but also assess liver inflammation activity in HBeAg-negative patients with CHB with normal ALT and detectable HBV DNA levels.

GPR contains two simple serological markers of GGT and platelet count. GGT is a microsomal enzyme that is widely distributed in human tissues.[39] Serum GGT is mainly derived from hepatocytes and bile duct cell. Numerous hepatobiliary diseases that induce hepatocyte injury can cause GGT elevation, including viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease.[40,41] Ethanol intake is an independent predictor of LC in patients with chronic HCV infection and an independent predictor of death in patients with hepatitis C virus or HBV infection.[42] Platelet counts have been verified to be associated with the severity of liver diseases.[43,44] Numerous studies have reported that platelet counts were correlated with the degree of liver injury.[43,44]

Although our study demonstrated that GPR is a promising index for predicting liver inflammation and degree of fibrosis in HBeAg-negative CHB patients with normal ALT and detectable HBV DNA levels, it has several limitations that should be considered. First, this was a retrospective study, and all data were obtained from just two centers. Second, the sample size was relatively small. Third, the long-term prognosis of these patients was unclear. The predictive value of GPR for adverse clinical events in these patients needs to be evaluated in future studies. Fourth, the HBV genotypes were unavailable, which may have affected the results of our study. Fifth, the dynamic change of GPR was not observed continuously. Therefore, our results should be further validated by prospective and multicenter studies with a larger sample size. Sixth, the lower limit of normal HBV DNA was inconsistent between these two medical centers. Thus, potential selection bias might exist in this study. Last, although this study excluded patients with significant alcohol consumption, a few occasional-drinkers were enrolled. Bedogni *et al*.[42] reported that irrespective of the quantity or frequency, alcohol consumption is able to aggravate liver injury, which is a predictor of death in subjects with chronic HBV infection. Thus, our results need to be validated in future studies.

In summary, we observed that approximately half of the HBeAg-negative CHB patients with normal ALT and detectable HBV DNA levels presented significant liver inflammation or fibrosis. GPR showed a high diagnostic accuracy for liver inflammation and fibrosis in these patients. Thus, use of GPR as a predictive index may reduce the need for unnecessary LB and help assess liver injury in these patients to identify those who would benefit from antiviral therapy.

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Conflict of interest

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

Author contributions

Conception and design of the study (CW, RH), manuscript writing (XAZ, JW, JW), statistical analysis (XAZ, JW), data collection (JL, GC, LW, GW, JX, WW, SY, XT, XY, WD, XX), critical revision of the manuscript (CW, RH).

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Lee WM. Hepatitis B virus infection. New Engl J Med 1998;337:1733–1745. doi:10.1056/NEJM199712113372406.
[2] Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, *et al*. Asian-pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98. doi:10.1007/s12072-015-9675-4.
[3] Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283. doi:10.1002/hep.28156.
[4] Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. J Hepatol 2007;47:760–767. doi:10.1016/j.jhep.2007.07.022.
[5] Gui HL, Wang H, Yang YH, Wu YW, Zhou HJ, Guo SM, *et al*. Significant histopathology in Chinese chronic hepatitis B patients with persistently high–normal alanine aminotransferase. J Viral Hepatitis 2010;17(Suppl 1):44–50. doi:10.1111/j.1365-2893.2010.01270.x.
[6] Yuen MF, Yuan HJ, Wong DK, Yuen JC, Wong WM, Chan AO, *et al*. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. Gut 2005;54(11):1610–1614. doi:10.1136/gut.2005.065136.
[7] Chu CM, Chen YC, Tai DI, Liaw YF. Level of hepatitis B virus DNA in inactive carriers with persistently normal levels of alanine aminotransferase. Clin Gastroenterol Hepatol 2010;8(6):535–540. doi:10.1016/j.cgh.2010.03.006.
[8] Alam S, Ahmad N, Mustafa G, Shrestha A, Alam AK, Khan M. Evaluation of normal or minimally elevated alanine transaminase, age and DNA level in predicting liver histological changes in chronic hepatitis B. Liver Int 2011;31(6):824–830. doi:10.1111/j.1478-3231.2011.02491.x.
[9] Choi GH, Kim GA, Choi J, Han S, Lim YS. High risk of clinical events in untreated HBeAg-negative chronic hepatitis B patients with high viral load and no significant ALT elevation. Aliment Pharmacol Ther 2019;50(2):215–226. doi:10.1111/apt.15311.
[10] Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, *et al*. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. Hepatol Int 2017;11(1):1–30. doi:10.1007/s12072-016-9760-3.
[11] Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20(1 Pt 1):15–20.
[12] Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). Hepatology 2000;32(3):477–481. doi:10.1053/jhep.2000.16602.
[13] Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, *et al*. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97(10):2614–2618. doi:10.1111/j.1572-0241.2002.06038.x.

[14] Seo YS, Kim MY, Kim SU, Hyun BS, Jang JY, Lee JW, *et al*. Accuracy of transient elastography in assessing liver fibrosis in chronic viral hepatitis: a multicentre, retrospective study. Liver Int 2015;35(10):2246–2255. doi:10.1111/liv.12808.
[15] Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, *et al*. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53(6):1013–1021. doi:10.1016/j.jhep.2010.05.035.
[16] Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Lédinghen V, *et al*. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29(2):242–247. doi:10.1111/j.1478-3231.2008.01802.x.
[17] Kim DY, Kim SU, Ahn SH, Park JY, Lee JM, Park YN, *et al*. Usefulness of FibroScan for detection of early compensated liver cirrhosis in chronic hepatitis B. Dig Dis Sci 2009;54(8):1758–1763. doi:10.1007/s10620-008-0541-2.
[18] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al*. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2010;38(2):518–526. doi:10.1053/jhep.2003.50346.
[19] Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T, *et al*. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357(9262):1069–1075. doi:10.1016/S0140-6736(00)04258-6.
[20] Vallet-Pichard A, Mallet V, Pol S. FIB-4: a simple, inexpensive and accurate marker of fibrosis in HCV-infected patients. Hepatology 2006;44(3):769–770. doi:10.1002/hep.21334.
[21] Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015;61(1):292–302. doi:10.1002/hep.27382.
[22] Kim WR, Berg T, Asselah T, Flisiak R, Marcellin P. Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients. J Hepatol 2016;64(4):773–780. doi:10.1016/j.jhep.2015.11.012.
[23] Chao DT, Lim JK, Ayoub WS, Nguyen LH, Nguyen MH. Systematic review with meta-analysis: the proportion of chronic hepatitis B patients with normal alanine transaminase ≤40IU/L and significant hepatic fibrosis. Aliment Pharmacol Ther 2014;39(4):349–358. doi:10.1111/apt.12590.
[24] Lemoine M, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, *et al*. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut 2016;65(8):1369–1376. doi:10.1136/gutjnl-2015-309260.
[25] Wang J, Xia J, Zhang R, Yan X, Yang Y, Zhao X, *et al*. A novel index using routine clinical parameters for predicting significant liver inflammation in chronic hepatitis B. J Viral Hepatitis 2018;25(10):1151–1160. doi:10.1111/jvh.12925.
[26] Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13(3):372–374. doi:10.1016/0168-8278(91)90084-o.
[27] Granito A, Muratori P, Ferri S, Pappas G, Quarneti C, Lenzi M, *et al*. Diagnosis and therapy of autoimmune hepatitis. Mini Rev Med Chem 2009;9(7):847–860. doi:10.2174/138955709788452676.
[28] Granito A, Muratori P, Quarneti C, Pappas G, Cicola R, Muratori L. Antinuclear antibodies as ancillary markers in primary biliary cirrhosis. Expert Rev Mol Diagn 2012;12(1):65–74. doi:10.1586/erm.11.82.
[29] Granito A, Muratori P, Muratori L, Pappas G, Cassani F, Worthington J, *et al*. Antinuclear antibodies giving the 'multiple nuclear dots' or the 'rim-like/membranous' patterns: diagnostic accuracy for primary biliary cirrhosis. Aliment Pharmacol Ther 2006;24(11-12):1575–1583. doi:10.1111/j.1365-2036.2006.03172.x.
[30] Li Q, Song J, Huang Y, Li X, Zhuo Q, Li W, *et al*. The gamma-glutamyl-transpeptidase to platelet ratio does not show advantages than APRI and Fib-4 in diagnosing significant fibrosis and cirrhosis in patients with chronic hepatitis B: a retrospective cohort study in China. Medicine 2016;95(16):e3372. doi:10.1097/MD.0000000000003372.
[31] Organization WH. WHO | Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization 2015.
[32] Park JY, Park YN, Kim DY, Paik YH, Lee KS, Moon BS, *et al*. High prevalence of significant histology in asymptomatic chronic hepatitis B patients with genotype C and high serum HBV DNA levels. J Viral Hepatitis 2008;15(8):615–621. doi:10.1111/j.1365-2893.2008.00989.x.
[33] Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). Hepatology 2000;32(3):477–481. doi:10.1053/jhep.2000.16602.
[34] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, *et al*. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43(6):1317–1325. doi:10.1002/hep.21178.
[35] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al*. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38(2):518–526. doi:10.1053/jhep.2003.50346.
[36] Seto WK, Lee CF, Lai CL, Ip PP, Fong DY, Fung J, *et al*. A new model using routinely available clinical parameters to predict significant liver fibrosis in chronic hepatitis B. PLoS One 2011;6(8):e23077. doi:10.1371/journal.pone.0023077.
[37] Lin CL, Liu CH, Wang CC, Liang CC, Su TH, Liu CJ, *et al*. Serum biomarkers predictive of significant fibrosis and cirrhosis in chronic hepatitis B. J Clin Gastroenterol 2015;49(8):705–713. doi:10.1097/MCG.0000000000000250.
[38] Wang J, Xia J, Yan X, Yang Y, Wei J, Xiong Y, *et al*. The gamma-glutamyl transpeptidase to platelet ratio predicts liver inflammation in chronic hepatitis B with normal or mildly elevated alanine transaminase. Clin Res hepatol gastroenterol 2020;44(6):913–922. doi:10.1016/j.clinre.2020.01.011.
[39] Eminler AT, Irak K, Ayyildiz T, Keskin M, Kiyici M, Gurel S, *et al*. The relation between liver histopathology and GGT levels in viral hepatitis: more important in hepatitis B. Turk J Gastroenterol 2014;25(4):411–415. doi:10.5152/tjg.2014.3693.
[40] Myers RP, Tainturier MH, Ratziu V, Piton A, Thibault V, Imbert-Bismut 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.
[41] Schiavon L, Narciso-Schiavon J, Ferraz M, Silva A, Carvalho-Filho R. The γ-glutamyl transpeptidase to platelet ratio (GPR) in HBV patients: just adding up? Gut 2017;66(6):1169–1170. doi:10.1136/gutjnl-2016-312658.
[42] Bedogni G, Miglioli L, Masutti F, Ferri S, Castiglione A, Lenzi M, *et al*. Natural course of chronic HCV and HBV infection and role of alcohol in the general population: the Dionysos Study. Am J Gastroenterol 2008;103(9):2248–2253. doi:10.1111/j.1572-0241.2008.01948.x.
[43] Pan JJ, Yang CF, Chu CJ, Chang FY, Lee SD. Prediction of liver fibrosis in patients with chronic hepatitis B by serum markers. Hepato-gastroenterology 2007;54:1503–1506.
[44] Zeng MD, Lu LG, Mao YM, Qiu DK, Li JQ, Wan MB, *et al*. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. Hepatology 2005;42(6):1437–1445. doi:10.1002/hep.20960.