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The gamma-glutamyl transferase to platelet ratio and the FIB-4 score are noninvasive markers to determine the severity of liver fibrosis in chronic hepatitis B infection

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ABSTRACT

Objective: Noninvasive liver fibrosis evaluation is an important issue in chronic hepatitis B infection, and may be assessed using transient elastography (Fibroscan) or with blood markers. We compared the value of Fibroscan with that of a panel of routine serum markers.

Materials and methods: We recruited 278 chronic hepatitis B patients who underwent Fibroscan and HBV DNA testing. Fibroscan assessments were made, and blood taken for the measurement of the gamma-glutamyl transferase (GGT) to platelet ratio (GPR), platelet count, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), international normalised ratio (INR), total cholesterol, trigylcerides, bilirubin, mean platelet volume (MPV), AST to platelet ratio index (APRI) and neutrophil to lymphocyte ratio.

Results: A fibrosis index based on four factors (FIB-4) and GPR were higher and platelets were lower in mild liver fibrosis than in non-liver fibrosis. GGT, AST, ALT, INR, MPV, APRI, FIB-4, GPR, and NLR were higher, and platelet and cholesterol were lower in severe liver fibrosis than in mild liver fibrosis. Elevated GPR (Odds ratio 95% CI 9.1 [1.66–50.0] $p = 0.011$) and FIB-4 (2.3 [1.2–4.2], $p = 0.01$) were associated with greater risk of liver fibrosis. The areas under the curve (AUC) were for GPR 0.84 at a cut-off of 0.299 and for FIB-4 0.82 at cut-off 1.571.

Conclusions: FIB-4 and GPR may be useful blood markers for evaluating the severity of liver fibrosis in chronic hepatitis B patients. Further prospective study is required to validate these noninvasive blood markers in a clinical practice.

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Introduction

Liver fibrosis is an important characteristic of chronic hepatitis B virus (HBV) infection. HBV is a potentially oncogenic virus and its prevalence is highest in sub-Saharan Africa and East Asia, in which 5–10% of the adult population are chronically infected [1]. The evaluation of liver fibrosis is crucial for the management of chronic hepatitis B infection. Although liver biopsy is the gold standard and the most specific test for assessing the nature and severity of liver fibrosis, but it is invasive, requires considerable experiences, and has associated clinical complications [2]. The noninvasive assessment of liver fibrosis is an important issue in chronic HBV infection, and many noninvasive methods to diagnose various liver diseases have been introduced, such as transient elastography (TE, Fibroscan) and blood biomarkers [3,4].

Several studies have examined the role of routine blood markers in liver disease. Wai et al. [5] reported the value of the aspartate aminotransferase (AST) to platelet ratio index (APRI) in chronic hepatitis C infection (HCV), damage being defined by liver biopsy. Sterling et al. [6] reported the development of the FIB-4 score (age [yr] x AST [U/L] / (platelet count [10^9/L] x alanine aminotransferase (ALT) [U/L]$^{1/2}$)) in HCV/HIV infection, wherein liver damage was assessed by the Ishak score. Shah et al. [7] confirmed the value of FIB-4 in biopsy-defined non-alcoholic fatty liver disease, and Lemoine et al. [8] reported a comparison of the gamma-glutamyl transferase (GGT) to platelet count ratio and FIB-4 in chronic HBV infection in West Africa: liver damage was defined by biopsy. Zhao et al. [9] reported that the platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) are associated with chronic HBV infection in China, and Giannini et al. reported the value of the AST/ALT ratio and platelet count in HCV related chronic liver disease as defined by monoethyl glycinexylidide testing [10]. Chronic HBV infection is a major public health issue in China [1,11].

Accordingly, we hypothesised that certain routine blood markers, alone and in combination, would be linked to the degree of liver damage as defined by fibroscan elastography. We tested our hypothesis in a modest cohort of patients with chronic HBV infection.

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Material and methods

We recruited 278 patients who had transient elastography (TE) using a Fibroscan device (FS502, Echosens, France), providing a liver stiffness measurement (LSM), and a quantified HBV DNA test from April 2009 to June 2017. TE was considered a valid test when the following three conditions were satisfied; Firstly, valid TE measurements count, secondly, a ratio of interquartile range to median LSM <0.3, and finally, a TE success rate >60%. The TE cut-off value was defined by the studies of Li et al. and of Kim et al. [12,13]. TE cut-off value for a diagnosis of severe liver fibrosis in chronic HBV patients was 7.2 kPa. TE values were interpreted to present following liver fibrosis status; normal < 5.3 kPa; mild fibrosis 5.3–<7.2 kPa; significant fibrosis; 7.2–<9.4 kPa; severe fibrosis; 9.4–<12.2 kPa; liver cirrhosis ≥ 12.2 kPa.

Venous blood was obtained for routine markers by standard pathology techniques. In the haematology laboratory, these were platelet count (local reference range 165–360 × 10^9/L), mean platelet volume (6.4–9.7 fL) and INR (0.92–1.13). In the biochemistry laboratory, these were GGT (male, <60; female, <40 U/L), total cholesterol (<5.2 mmol/L), triglycerides (<2.26 mmol/L), AST (<40 U/L), ALT (<40 U/L) and bilirubin (<22 µmol/L). From these, secondary indices were calculated: AST/ALT ratio, AST to platelet ratio index (APRI) [100 × AST (U/L) / upper limit of normal for that laboratory (40 (U/L) if male, 35 (U/L) if female) / platelet count (10^9/L)], GGT to platelet ratio (GPR) [100 × GGT (U/L) / upper limit of normal for that laboratory (60 (U/L) if male, 40 (U/L) if female) / platelet count (10^9/L)], neutrophil to lymphocyte ratio (NLR), NLR to platelet ratio and the FIB-4 score [5–10]. The latter was calculated as age x AST/platelet count x $ALT^{½}$ [6]. Chronic HBV patients were tested for the presence of HBeAg. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of our institute.

Analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL). Distribution was verified by the Kolmogorov–Smirnov test. Statistical significance was accepted for $p < 0.05$. To determine the significant indices discriminating liver fibrosis and non-liver fibrosis groups, we performed a multivariate logistic regression analysis with those indices significant in univariate analysis. Receiver operating characteristic curve (ROC) analysis was performed to compare the abilities of variables to differentiate between liver fibrosis and non-liver fibrosis.

Results

Table 1 shows laboratory and LSM data of the 278 patients (median [interquartile range] 47 [40–54] years, 176 men) of whom 116 (41.7%) were positive for HBeAg. The strongest correlations ($r > \pm 0.4$) between LSM and directly measured indices were with GGT, AST, ALT, the platelet count and the INR. Of the derived indices, there were significant correlations ($r > 0.67$) between LSM and APRI, GPR and FIB-4.

Table 2 shows data sorted by category of increased liver stiffness. Platelet count decreased as LSM increased,

Table 1. Baseline characteristics of the 278 hepatitis B virus patients.

Parameters	Data	Correlation with LSM[a]
Direct indices		
LSM (kPa)	8.5 (5.4–15.7)	NA
Platelet count (×10^9/L)	177 (130–223)	−0.62, $p < 0.001$
GGT (U/L)	43 (22–83)	0.59, $p < 0.001$
Cholesterol (mmol/L)	4.5 (3.8–5.1)	−0.25, $p < 0.001$
AST (U/L)	37 (26–60)	0.61, $p < 0.001$
ALT (U/L)	40 (24–70)	0.44, $p < 0.001$
INR (sec)	1.04 (1.01–1.11)	0.52, $p < 0.001$
Bilirubin (µmol/L)	14 (9–19)	0.28, $p < 0.001$
HBV DNA (IU/mL)	1.9×10^4 (800–1.3×10^6)	0.35, $p < 0.001$
Triglyceride (mmol/L)	0.97 (0.71–1.27)	−0.04, $p = 0.517$
MPV (fL)	8.2 (7.7–8.8)	0.38, $p < 0.001$
Derived indices		
AST/ALT	0.94 (0.72–1.18)	−0.11, $p = 0.078$
APRI	0.55 (0.35–1.19)	0.74, $p < 0.001$
GPR	0.48 (0.21–1.21)	0.72, $p < 0.001$
NLR	1.52 (1.12–2.04)	−0.05, $p = 0.384$
NLR/platelet count	0.009 (0.006–0.014)	0.37, $p < 0.001$
FIB-4	1.67 (1.02–3.0)	0.68, $p < 0.001$

Notes: Data median (inter-quartile range). LSM, liver stiffness measurement. GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalised ratio of prothrombin time; MPV, mean platelet volume; APRI, AST to platelet ratio index; FIB-4, fibrosis index based on four factors; GPR, GGT to platelet ratio; NLR, neutrophil to lymphocyte ratio.
[a]Spearman rho and *p* value.

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

Scale of liver stiffness measurement (kPa)	<5.3 kPa	5.3–<7.2 kPa	7.2–<9.4 kPa	9.4–<12.2 kPa	≥12.2 kPa
Number	60	54	38	34	92
Age [year]	44 ± 13	47 ± 11	47 ± 12	47 ± 10	49.5 ± 10
Male (n, %)	34, 56.7	34, 63.0	20, 52.6	19, 55.9	69, 75.0
Liver stiffness measurement (kPa)	4.0 ± 0.7	6.0 ± 0.5[a]	8.1 ± 0.7[d]	10.7 ± 0.9	24.9 ± 12.8
Platelet count (×10^9/L)	231 ± 51	198 ± 59[b]	194 ± 82[d]	189 ± 63	129 ± 55
AST (U/L)	30 ± 33	34 ± 19	58 ± 50[d]	57 ± 41	147 ± 284
ALT (U/L)	40 ± 93	41 ± 37	81 ± 96[d]	69 ± 72	198 ± 474
FIB-4	1.06 ± 0.57	1.54 ± 1.02[c]	2.02 ± 1.81[d]	2.02 ± 1.13	4.66 ± 3.96

Notes: Data mean with standard deviation or absolute numbers with percentage. See Table 1 for abbreviations.
[a]$p < 0.001$ between LSM <5.3 and 5.3–<7.2 kPa; [b]$p = 0.002$ between LSM <5.3 and 5.3–<7.2 kPa; [c]$p = 0.003$ between LSM < 5.3 and 5.3–<7.2 kPa; [d]$p < 0.001$ between LSM 5.3–<7.2 and ≥7.2 kPa.

whereas AST, ALT and FIB-4 were generally increased with LSM. FIB-4 and GPR (0.25 ± 0.27 v 0.43 ± 0.48, p = 0.018) were higher in the mild liver fibrosis group than in the non-liver fibrosis group, whereas platelet count was lower in mild liver fibrosis group than in non-liver fibrosis group. In comparing mild liver disease (LSM 5.3–<7.2 kPa) with severe disease (LSM ≥ 7.2 kPa), there were increases in GGT (0.43 ± 0.48 v 1.38 ± 1.83 U/L), AST (34 ± 19.0 v 108 ± 219 U/L), ALT (41 ± 37 v 144 ± 363 U/L), INR (1.02 ± 0.06 v 1.12 ± 0.16), MPV (8.0 ± 0.7 v 8.5 ± 0.9 fL), APRI (0.50 ± 0.39 v 2.27 ± 5.47), FIB-4 (1.6 ± 1.0 v 3.5 ± 3.4), GPR (0.43 ± 0.48 v 1.38 ± 1.8) and NLR to platelet count (0.009 ± 0006 v 0.013 ± 0.01) were higher (all p < 0.001), whereas platelet count (198 ± 59 v 156 ± 71 x 10^9/L, p < 0.001) and cholesterol (177 ± 35 v 166 ± 33, p = 0.033) were lower.

In multivariate logistic regression analysis, FIB-4 (OR = 2.3, 95% CI: 1.2–4.2, p = 0.01) and GPR (OR = 9.1, 95% CI: 1.7–50.0, p = 0.011) were significant independent predictors of liver fibrosis (TE, ≥5.3 kPa) and non-liver fibrosis (TE, <5.3 kPa). In ROC analysis, areas under the curve were 0.82 for FIB-4 and 0.84 for GPR (Figure 1). The cut-off values and diagnostic sensitivities and specificities, with positive and negative predictive value of the markers, alone and in combination, are shown in Table 3. The combination of FIB-4 and GPR had the lowest sensitivity, but the highest specificity, and positive and negative predictive value.

Discussion

As chronic HBV infection inevitably leads to fibrosis and subsequent hepatic failure [1,11], we compared the several blood markers with the LSM index to determine which could have potential in noninvasively assessing the severity of liver fibrosis. The proportion of patients with clinically diagnosed liver cirrhosis and hepatocellular carcinoma development has been shown to be significantly greater among those with a higher LSM [14] and thus, these measurements may provide a useful means of noninvasively screening for liver fibrosis during regular health check-up. TE is widely used for this purpose and has been shown to be a powerful tool for determining the level of fibrosis in chronic liver diseases [15,16].

We focused on noninvasive blood markers likely to reflect liver fibrosis status in chronic HBV patients [5–10]. It is an important issue to determine TE cut-off level for assessing liver fibrosis severity in chronic liver disease patients. The TE cut-off range for the upper normal TE level has been established to be 7–8 kPa [17,18]. One meta-analysis reported a significant liver fibrosis (F2) at a TE level of >13 kPa [19] and in a study on the assessment of liver fibrosis using LSM in chronic HBV patients a cut-off level of 7.2 kPa was reported [20]. In the present study, we used 7.2 kPa as a cut-off to determine the presence of severe liver fibrosis based on the previous study [20], a recent systematic meta-analysis [12] and a Korean study conducted in the general population [13]. Trend analysis showed that GGT, INR, MPV, APRI, FIB-4 and GPR

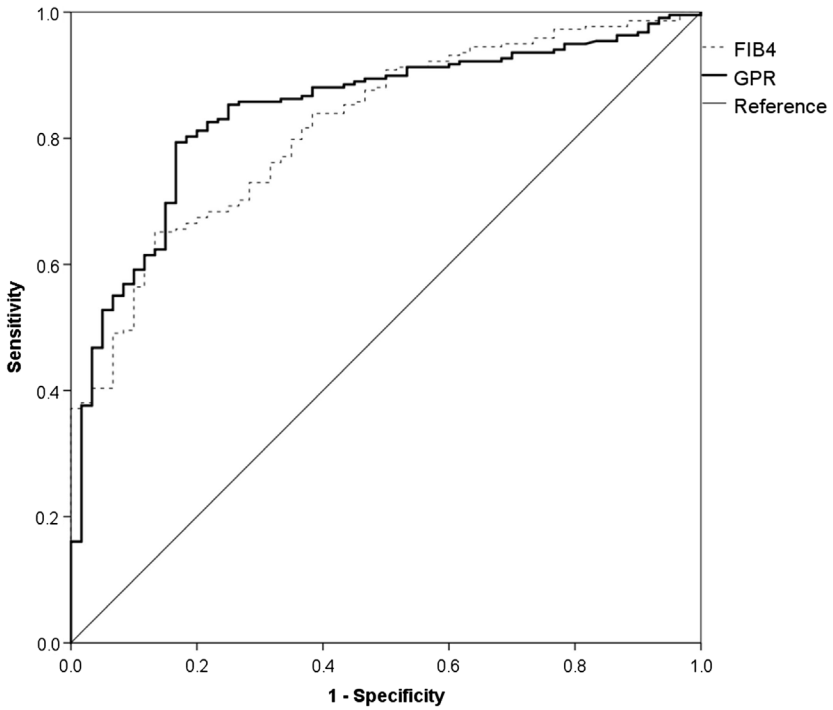

Figure 1. Receiver operating characteristic (ROC) curve analysis of GPR and FIB-4 for the evaluation of liver fibrosis based on transient elastography (fibroscan) results. GPR, gamma-glutamyl transferase to platelet ratio; FIB-4, fibrosis index based on four factors.

Table 3. Comparison of the sensitivity, specificity and positive and negative predictive values of FIB-4 and GPR singly, in dual combinations, for liver fibrosis.

Markers	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
FIB-4 (cut-off: 1.571)	65.1	86.7	86.7	86.7
GPR (cut-off: 0.299)	79.4	83.3	83.3	83.3
FIB-4 and GPR	59.2	93.3	93.3	93.3
FIB-4 or GPR	85.3	73.3	73.3	73.3

Notes: FIB-4, fibrosis index based on four factors; PPV, positive predictive value; NPV, negative predictive value; GPR, GGT to platelet ratio.

increased with LSM level, whereas platelet count significantly decreased as LSM increases. Only FIB-4, GPR and platelet count showed differences between normal LSM and mild LSM group, whilst several potential markers were altered in the severe liver fibrosis group than those of mild liver fibrosis group. However, multivariate risk assessment showed that FIB-4 and GPR blood markers were independently and significantly increased with the LSM scale, and ROC curve analysis showed that GPR was the most sensitive marker.

We recognise several limitations. As a retrospective, case-controlled study we did not exclude obese subjects or patients with a high ALT level. The latter may be related to causes of false results of TE-predicted liver fibrosis [21–23]. All candidate markers were compared with TE results as the reference method – liver biopsies were not performed. Nevertheless, Foucher et al. reported that the mass of the liver assessed by TE volume is around 100 times greater than that of biopsy specimens, and thus, TE values are more representative of entire hepatic parenchyma.[24] We therefore accept the point that liver damage was not assessed histologically.

However, this study may be helpful in clarifying which blood markers can help to screen for liver fibrosis and discriminate liver fibrosis from non-liver fibrosis with cost-effectiveness and repeatable access. Most of all, this present study indicates GPR is a promising marker of liver fibrosis and that it provides a potential means of screening for mild liver fibrosis. GPR was developed for the assessment of liver fibrosis in HBV mono-infected individuals in a West African setting [8], where it was more accurate than APRI or FIB-4, although not superior to APRI or Fib-4 in France [25], and that GPR could be used as a noninvasive marker to assess the risk of hepatocellular carcinoma development in chronic HBV infection [26]. When we examined GPR or FIB-4 in combination, we found this increased the relative diagnostic sensitivity to 85.3% for the screening of liver fibrosis. Further prospective study is needed to elucidate whether these markers in combinated with Fibroscan or liver ultrasonography provide better diagnostic performances.

Other blood markers include the enhanced liver fibrosis (ELF) test. Trembling et al.[27] reported that although ELF performs well in the detection of liver fibrosis in patients with chronic HBV, TE performs better in identifying severe fibrosis/cirrhosis. Therefore, we should consider that a combination diagnostic modality can increase diagnostic sensitivity for assessing liver fibrosis. For example, with the use of ELF and LSM algorithm, a significant proportion of patients can avoid liver biopsy [28]. These extended noninvasive liver fibrosis markers can easily be monitored and used to be helpful for medical practitioners.

More prospective and large-scale studies need to be conducted to validate the diagnostic values of these noninvasive blood markers in clinical practice. This work represents an advance in biomedical science because it shows that GPR and FIB-4 can significantly screen liver fibrosis statuses in chronic HBV patients, and that GPR showed best diagnostic performance.

Summary table

What is known about this subject?
- Development of noninvasive liver fibrosis assessment markers is an important issue in chronic hepatitis B and C virus infections
- Blood markers such as liver enzymes and certain blood cell counts, and the Fibroscan, have been assessed in screening for liver fibrosis
- The FIB-4 score has been assessed in dual hepatitis C/HIV infections, the gamma-glutamyl transpeptidase to platelet ratio (GPR) in chronic hepatitis B virus infection

What this paper adds:
- GPR and FIB-4 elevations are superior to AST, ALT, the AST/ALT ratio and the NLR in assessing HBV induced liver fibrosis
- ROC areas under the curve for GPR was 0.84, and for FIB-4 was 0.82 for detecting liver fibrosis related with hepatitis B virus infection
- GPR is a promising marker of liver fibrosis, and that it provides a potential means of screening for mild liver fibrosis

Disclosure statement

No potential conflict of interest was reported by the authors.

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