Reassessment of gamma-glutamyl transpeptidase to platelet ratio (GPR): a large-sample, dynamic study based on liver biopsy in a Chinese population with chronic hepatitis B virus (HBV) infection

Recently, Lemoine and colleagues[1] presented a novel marker of liver fibrosis, the gamma-glutamyl transpeptidase to platelet ratio (GPR), as a more accurate non-invasive marker than either the aspartate aminotransferase to platelet ratio index (APRI) or the fibrosis index based on four factors (FIB-4) for diagnosing liver fibrosis in patients with chronic hepatitis B virus (HBV) infection in West Africa, and a simple and inexpensive alternative to transient elastography and liver biopsy. Boyd and colleagues[2] demonstrated good results for GPR in the diagnosis of liver fibrosis in patients with HBV/HIV co-infection in France. However, Stockdale and colleagues[3] reported that in patients with HBV / human immunodeficiency virus (HIV) co-infection in West Africa, GPR showed poor correlation with transient elastography. Lemoine and colleagues[4] subsequently responded that the diagnostic accuracy of GPR differed when using liver biopsy or transient elastography as the reference. These inconsistent opinions indicated that the value of GPR for diagnosing liver fibrosis was still uncertain and needed further validation, not to mention its value for dynamic assessment of treatment response in patients with chronic HBV infection.

To further evaluate the accuracy of GPR for diagnosing liver fibrosis, we undertook a retrospective study in China of 1168 patients, with chronic HBV infection and without alcoholic liver disease, non-alcoholic fatty liver disease, primary liver cancer, obstructive jaundice, thrombocytopenia or thrombocytosis, endowed with METAVIR liver fibrosis scores via liver biopsy (a scoring system presented by the French METAVIR Cooperative Study Group for histological grading and staging of chronic hepatitis) at our department between 2005 and 2016. The patients were mostly male (75.3%), the median age was 36 years (P25–P75: 27–45), the median body mass index was 21.2 kg/m^2 (18.7–23.8), and the median platelet count was 175×10^9/L (136–215). The median alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase concentrations were 52.0 IU/L (28.0–141.0), 41.0 IU/L (27.0–92.0) and 32.0 IU/L (19.0–68.0), respectively. The METAVIR liver fibrosis scores were distributed as follows: F0–1=286 (24.5%), F2=245 (21.0%), F3=323 (27.7%) and F4=314 (26.9%).

To analyse the responsiveness[5] of GPR during treatment (ie, the ability to detect the actual change in liver fibrosis during treatment or the suitability for dynamic assessment of treatment response, which is different from the concepts of reliability and agreement[6]), we selected, from the cohort above, 92 patients who (A) had undergone two liver biopsies, (B) at baseline, had never been treated with nucleoside/nucleotide analogues (NAs), and (C) after the first biopsy, were treated with NAs but not with thrombopoietic drugs, platelet transfusion or splenic artery embolisation. The median interval between the two biopsies was 1.6 years (1.1–2.3).

The diagnostic accuracy of GPR in comparison to APRI and FIB-4 was evaluated using receiver operating characteristic (ROC) curves and area under the ROC curves (AUROCs), as shown in table 1. For diagnosing significant fibrosis (F2–4), the AUROC of GPR (0.67, 95% CI 0.64 to 0.70) was comparable to that of APRI

Table 1 Diagnostic performance of the gamma-glutamyl transpeptidase to platelet ratio (GPR), aspartate aminotransferase to platelet ratio index (APRI), and fibrosis index based on four factors (FIB-4) in a Chinese population with chronic hepatitis B virus (HBV) infection

GPR	F0–1 versus F2–4		F0–2 versus F3–4		F0–3 versus F4	
AUROC (95% CI)	**0.67 (0.64 to 0.70)**		**0.70 (0.67 to 0.72)**		**0.71 (0.68 to 0.73)**	
Cut-off values*	0.32		0.32		0.56	
Sensitivity/specificity (%)	40/78		47/79		36/85	
Correctly classified (%)	49		61		72	
PPV/NPV (%)	85/30		72/55		46/78	
Positive/negative LR	1.8/0.8		2.2/0.7		2.3/0.8	
APRI						
AUROC (95% CI)	**0.68 (0.65 to 0.71)**		**0.70 (0.67 to 0.73)**		**0.66 (0.63 to 0.69)**	
Cut-off values†	0.5	1.5			1.0	2.0
Sensitivity/specificity (%)	69/59	30/87			51/70	28/82
Correctly classified (%)	67	44			65	68
PPV/NPV (%)	84/38	88/29			38/79	37/76
Positive/negative LR	1.7/0.5	2.4/0.8			1.7/0.7	1.6/0.9
Indeterminate results (%)	37				15	
FIB-4						
AUROC (95% CI)	**0.73 (0.70 to 0.76)**		**0.76 (0.74 to 0.79)**		**0.77 (0.75 to 0.80)**	
Cut-off values‡			1.45	3.25		
Sensitivity/specificity (%)			64/74	26/93		
Correctly classified (%)			69	56		
PPV/NPV (%)			75/63	82/51		
Positive/negative LR			2.5/0.5	3.9/0.8		
Indeterminate results (%)			30			
Comparison of AUROCs						
GPR versus APRI	p=0.473		p=0.768		p<0.001	
GPR versus FIB-4	p<0.001		p<0.001		p<0.001	

*Predetermined cut-off values of GPR were used (0.32 to distinguish significant fibrosis, 0.32 to distinguish extensive fibrosis and 0.56 to distinguish cirrhosis).
†Predetermined cut-off values of APRI were used (0.5 and 1.5 to distinguish significant fibrosis, and 1.0 and 2.0 to distinguish cirrhosis).
‡Predetermined cut-off values of FIB-4 were used (1.45 and 3.25 to distinguish extensive fibrosis).
APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis index based on four factors; GPR, gamma-glutamyl transpeptidase to platelet ratio; HBV, hepatitis B virus; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

(0.68, 95%CI 0.65 to 0.71, p=0.473), but lower than FIB-4 (0.73, 95%CI 0.70 to 0.76, p<0.001). For diagnosing extensive fibrosis (F3–4), the AUROC of GPR (0.70, 95%CI 0.67 to 0.72) was also comparable to that of APRI (0.70, 95%CI 0.67 to 0.73, p=0.473), but lower than FIB-4 (0.76, 95%CI 0.74 to 0.79, p<0.001). For diagnosing cirrhosis (F4), the AUROC of GPR (0.71, 95%CI 0.68 to 0.73) was greater than that of APRI (0.66, 95%CI 0.63 to 0.69, p<0.001), but lower than FIB-4 (0.77, 95%CI 0.75 to 0.80, p<0.001).

The responsiveness of GPR, APRI and FIB-4 during treatment of NAs was evaluated using Spearman's correlation coefficient, as shown in table 2. As liver biopsy is the gold standard and the change in the METAVIR liver fibrosis score (Δscore) reflects the actual change in liver fibrosis during treatment, the correlation between the change in GPR, APRI or FIB-4 (ΔGPR, ΔAPRI or ΔFIB-4) and the Δscore reflects the ability of each index to detect the actual change in liver fibrosis during treatment. The responsiveness of GPR (r=0.58, p<0.001) was greater than that of APRI (r=0.45, p<0.001) and FIB-4 (r=0.39, p<0.001).

In conclusion, the accuracy of GPR to diagnose significant fibrosis (F2–4) and extensive fibrosis (F3–4) was comparable to that of APRI, while its accuracy to diagnose cirrhosis (F4) was better. However, its accuracy to diagnose all stages of liver fibrosis was worse compared with FIB-4. In addition, the responsiveness of GPR was greater than that of APRI and FIB-4 during treatment of NAs. Thus, we believe that GPR should be considered as a suitable, simple, non-invasive marker for the diagnosis of liver fibrosis and the dynamic assessment of treatment response in Chinese patients with chronic HBV infection.

Table 2 Responsiveness of the gamma-glutamyl transpeptidase to platelet ratio (GPR), aspartate aminotransferase to platelet ratio Index (APRI) and fibrosis index based on four factors (FIB-4) during treatment of nucleoside/nucleotide analogues (NAs)

	Spearman's r	p Value
ΔGPR* and Δscore †	0.58	p<0.001
ΔAPRI‡ and Δscore	0.45	p<0.001
ΔFIB-4§and Δscore	0.39	p<0.001

*Change in GPR between two liver biopsies during treatment of NAs.
†Change in METAVIR liver fibrosis score between two liver biopsies during treatment of NAs.
‡Change in APRI between two liver biopsies during treatment of NAs.
§Change in FIB-4 between two liver biopsies during treatment of NAs.
APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis index based on four factors; GPR, gamma-glutamyl transpeptidase to platelet ratio; NA, nucleoside/nucleotide analogue.

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