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Comparison of the Diagnostic Accuracy of the Gamma-Glutamyl-Transpeptidase/Platelet Ratio with Aspartate Aminotransferase-Platelet Ratio Index and Fibrosis-4 Index in Liver Fibrosis in Chronic Hepatitis B

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Abstract

Objective: The gamma-glutamyl transpeptidase/platelet ratio (GPR) is a newly developed non-invasive serum marker of significant fibrosis and cirrhosis in patients with chronic hepatitis B (CHB) in West Africa. This study aimed to compare the diagnostic accuracy of the GPR with the aspartate aminotransferase-platelet ratio index (APRI) and with the fibrosis-4 (FIB-4) index for detecting liver fibrosis in Turkish patients with CHB.

Methods: Seventy-nine patients with CHB who had undergone liver biopsy were included, and GPR, APRI, and FIB-4 data were obtained. The receiver operating characteristic (ROC) curves and area under the ROC curves (AUROCs) were compared.

Results: As regards the fibrosis stages of 79 patients, 5 were F0 (6.3%), 17 were F1 (21.5%), 23 were F2 (29.1%), 23 were F3 (29.1%), and 11 were F4 (13.9%). The AUROCs of the GPR and APRI were similar in the diagnosis of significant fibrosis (0.70 vs. 0.69; p=0.928), advanced fibrosis (0.80 vs. 0.72; p=0.174), and cirrhosis (0.73 vs. 0.75; p=0.771) groups. The AUROCs of the GPR and FIB-4 index were similar for diagnosing significant fibrosis (0.70 vs. 0.79; p=0.090) and advanced fibrosis (0.80 vs. 0.77; p=0.569). However, the AUROCs of the FIB-4 index for diagnosing cirrhosis was significantly higher than those for the GPR (0.73 vs. 0.90; p=0.024) and APRI (0.75 vs. 0.90; p=0.024).

Conclusion: The GPR can be used to detect significant fibrosis, advanced fibrosis, and cirrhosis, but was not superior to the APRI or FIB-4 index. FIB-4 index performed better than the GPR and APRI for diagnosing cirrhosis.

Keywords: Gamma-glutamyl transpeptidase to platelet ratio, APRI, FIB-4, hepatic fibrosis, chronic hepatitis B

INTRODUCTION

Infection with hepatitis B virus (HBV) is an important health problem worldwide. According to the data of the World Health Organization (WHO), approximately 257 million people have chronic hepatitis B (CHB) infection (1). CHB is associated with an increased risk of cirrhosis and hepatocellular carcinoma (2). Early diagnosis and treatment are important in controlling disease progression and in reducing morbidity and mortality (3). The gold standard for the diagnosis of liver fibrosis is liver biopsy. However, its invasiveness, risk of complications, and contraindications, as well as patient discomfort, have limited its widespread use. It also has poor repeatability and sampling variability (4). Transient elastography (FibroScan) is a good alternative tool for diagnosing hepatic fibrosis because of its non-invasiveness, repeatability, and effectiveness. However, the FibroScan device (and annual maintenance thereof) is expensive

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and unavailable in many hospitals in Turkey. Additionally, the performance of FibroScan is compromised by many factors, such as ascites and obesity (5). Early detection of hepatic fibrosis with a simple, inexpensive, and non-invasive index in patients is important for timely treatment. Therefore, several serum marker panels, such as the aspartate aminotransferase (AST)-platelet ratio index (APRI) and fibrosis-4 (FIB-4) score, have been extensively investigated to detect liver fibrosis (6,7). The WHO has recommended an APRI score >2 to determine the presence of cirrhosis in adult patients with CHB, when resources are limited (8). However, the sensitivity and accuracy of the APRI and FIB-4 index in detecting HBV-associated fibrosis are only moderate (6). Lemoine et al. (9) developed the gamma-glutamyl transpeptidase (GGT)/platelet ratio (GPR) to predict liver fibrosis in West African patients with CHB and showed that GPR is superior to APRI and FIB-4 in detecting hepatic fibrosis. GPR performed better than APRI and FIB-4 index in a Chinese cohort (5), but such was not observed in patients with CHB in France nor in two other Chinese cohorts (9-11). Thus, further evaluation of the GPR in other cohorts is needed.

In this study, we investigated the diagnostic value of the GPR for liver fibrosis and cirrhosis in Turkish patients with CHB. This study thus aimed to compare the performance of the GPR, APRI, and FIB-4 index for diagnosing significant fibrosis and cirrhosis in patients with CHB.

METHODS

Data of 91 patients with CHB who underwent liver biopsy between January 2017 and March 2020 in the gastroenterology department of the University of Health Sciences Gaziosmanpasa Hospital were retrospectively analyzed. However, patients with insufficient clinical data, with high GGT values due to excess alcohol consumption or obesity, and with hepatitis D were excluded; thus, the remaining 79 patients were included in the study. Liver biopsies of patients with CHB were taken prior to the start of the antiviral therapy. The diagnosis of CHB infection was determined by positive hepatitis B surface antigen for at least 6 months (12). Medical records of the patients and laboratory measurements such as AST, alanine transaminase, GGT, platelet count, HBV deoxyribonucleic acid (DNA) levels, and HBV serological markers were recorded retrospectively.

The degree of hepatic fibrosis was noted in all patients. Histologically, liver fibrosis was classified according to the METAVIR scoring system (13): F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with several septa; F3, multiple septa without cirrhosis; and F4, cirrhosis. In addition, significant fibrosis was identified as ≥F2, advanced fibrosis as ≥F3, and cirrhosis as F4.

This study protocol was approved by the Ethics Committee of Gaziosmanpaşa Training and Research Hospital (no: 189, date: 18.11.2020) and conformed with the Declaration of Helsinki. All patients were enrolled after they provided informed consent.

The formulas for the GPR, APRI, and FIB-4 index are shown below:

1- GPR=[GGT (IU/L)/upper limit of normal (ULN) of GGT]/platelet count (10^9/L) x100

2) APRI=[AST (IU/L)/ULN of AST)]/platelet count (10^9/L) x100

3) FIB-4 index=[age (years) x AST (IU/L)]/(platelet count (10^9/L) x [ALT (IU/L)$^{1/2}$]

Note: ULN of AST=35 IU/L; ULN of GGT=38 IU/L.

Statistical Analysis

SPSS 22.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for the analyses. The normality of the distributions of the numerical variables was tested with the Shapiro-Wilk test. The Mann-Whitney U test was used to compare variables that were not normally distributed between two independent groups, and Kruskal-Wallis and Dunn tests were used to compare more than two groups. The relationship between the numerical variables was tested with Spearman's rank correlation coefficient analysis. A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off points of the variables in the fibrosis groups. The area under the ROC curves (AUROCs) for significant fibrosis (≥ F2), advanced fibrosis (≥ F3), and cirrhosis (F4), were obtained by comparing F2-F4 patients with F0-F1 patients, F3-F4 patients with F0-F2 patients, and F4 patients with F0-F3 patients, respectively. A p value <0.05 was considered significant.

RESULTS

Baseline Patient Characteristics

The baseline characteristics of the patients are presented in Table 1. A total of 79 patients [male, 48 (60.8%); female, 31 (39.2%)] participated in this study. The average age of the patients was 44.11±13.65 years. There were 60 (75.9%) patients negative for hepatitis B e-antigen (HBeAg) and 19 (24.1%) patients positive for HBeAg. The distribution of patients according to their fibrosis stages is as follows: F0, n=5 (6.3%); F1, n=17 (21.5%); F2, n=23 (29.1%); F3, n=23 (29.1%); and F4, n=11 (13.9%). The median (interquartile range) HBV DNA level was 67,000 (20,900-

14,384,997) IU/L, the AST level was 36.6 (25.0, 52.0) IU/L, the ALT level was 50.0 (26.0, 84.0) IU/L, the GGT level was 25.0 (16.0, 44.0) IU/L, and the platelet count was 207 (170, 242) x10^9/L. The median GPR, APRI, and FIB-4 index values were 0.32 (0.19, 0.64), 0.39 (0.23, 0.55), and 0.96 (0.66, 1.70), respectively.

Correlations of the GPR, APRI, and FIB-4 Index with Liver Fibrosis Stage

Relationships between serum models and liver fibrosis stages were evaluated using Spearman's correlation analysis. A positive correlation was detected between the liver fibrosis score and the GPR (r=0.470, p<0.01), APRI (r=0.354, p<0.01), and FIB-4 index (r=0.565, p<0.01). The highest correlation coefficient was seen between the fibrosis and FIB-4 index.

The GPR (p=0.001), APRI (p=0.003), FIB-4 index (p=0.001), and GGT (p=0.001) value were significantly higher in patients with significant fibrosis (F ≥2) than in those without fibrosis. GPR, APRI, and FIB-4 index values increased with fibrosis stages in patients with CHB (Table 2).

Table 1. Baseline patient characteristics

	Patients (n=79)
Age (y), mean (SD)	44.11 (13.65)
Male sex, n (%)	48 (60.8)
HBV DNA (IU/mL), median (IQR)	67000 (20,900-14,384,997)
AST (IU/L), median (IQR)	36.6 (25.0-52.0)
ALT (IU/L), median (IQR)	50.0 (26.0-84.0)
GGT (IU/L), median (IQR)	25.0 (16.0-44.0)
Platelet (10^9/L), median (IQR)	207 (170-242)
Fibrosis stages n (%)	
F0	5 (6.3%)
F1	17 (21.5%)
F2	23 (29.1%)
F3	23 (29.1%)
F4	11 (13.9%)
GPR, median (IQR)	0.32 (0.19-0.64)
APRI, median (IQR)	0.39 (0.23-0.55)
FIB-4, median (IQR)	0.96 (0.66-1.70)

IQR: Interquartile range, HBV: Hepatitis B virus, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl-transpeptidase, GPR: Gamma-glutamyl-transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4, SD: Standard deviation

Diagnostic Performance of the GPR, APRI, and FIB-4 for Liver Fibrosis and Cirrhosis

The AUROCs of the serum models for cirrhosis and liver fibrosis are shown in Table 3. The AUROCs of the GPR and APRI were comparable for significant fibrosis (0.70 vs. 0.69; p=0.928), advanced fibrosis (0.80 vs. 0.72; p=0.174), and cirrhosis (0.73 vs. 0.75; p=0.771). The AUROCs of the GPR and FIB-4 index were comparable for diagnosing significant fibrosis (0.70 vs. 0.79; p=0.090) and advanced fibrosis (0.80 vs. 0.77; p=0.569); however, the AUROC of the FIB-4 index for diagnosing cirrhosis was significantly higher than that of the GPR (0.73 vs. 0.90; p=0.024). Similarly, the AUROC of the FIB-4 index was higher than that of the APRI in predicting cirrhosis (0.75 vs. 0.90; p=0.024). The ROC curves of the GPR, APRI, and FIB-4 index for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis are shown in Figure 1.

DISCUSSION

In this study, we measured the accuracy of the GPR to non-invasively diagnose hepatic fibrosis, using the gold standard (liver biopsy) as a reference. The AUROC values of the GPR for significant fibrosis, advanced fibrosis, and cirrhosis in patients

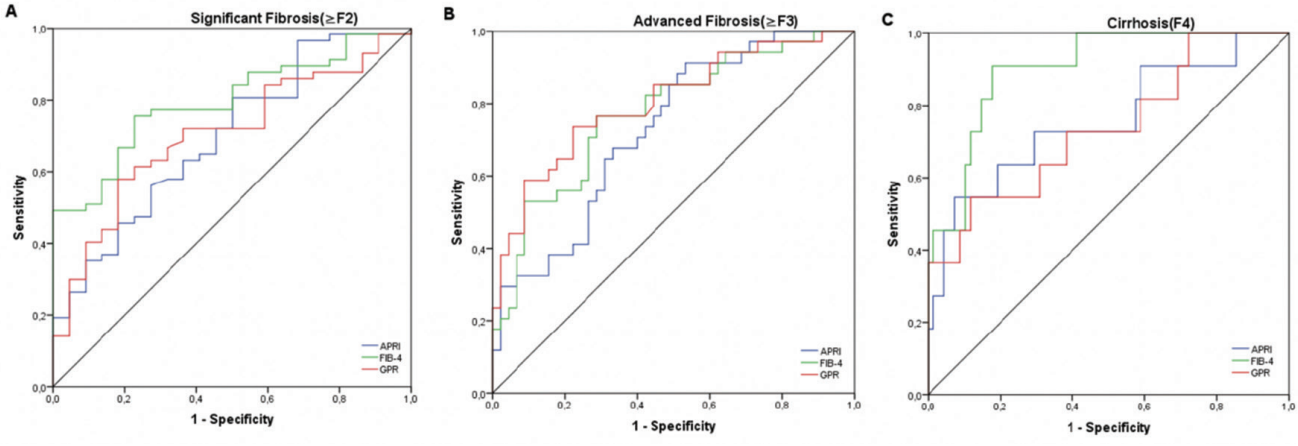

Figure 1. ROC curves of the GPR, APRI, and FIB-4 index for diagnosing significant fibrosis (A), advanced fibrosis (B), and cirrhosis (C).
ROC: Receiver operating characteristic, GPR: Gamma-glutamyl transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4

with CHB were 0.70, 0.80, and 0.73, respectively. In addition, a positive correlation was found between the GPR and fibrosis stage. However, the GPR was not superior to the APRI or FIB-4 index in determining significant fibrosis, advanced fibrosis, or cirrhosis in our Turkish patients with CHB.

Continuous monitoring of fibrosis, which causes mortality and morbidity in patients with CHB, is important for prognosis and informing treatment decisions (14). Serum models have been developed as an alternative to liver biopsy in determining the severity of a liver disease (10). Increased GGT activity has recently been reported as an important marker of liver damage and fibrosis progression (15). In addition, a negative correlation has been observed between significant fibrosis and platelet count (16). Lemoine et al. (9) developed the GPR as a new marker of the degree of hepatic fibrosis based on the GGT and platelet count. Studies have compared the performance of the GPR with the APRI and FIB-4 index for diagnosing hepatic fibrosis, but the results have been inconsistent. A study has suggested that GPR is superior to APRI and FIB-4 index for diagnosing significant fibrosis and cirrhosis in Gambia and Senegal cohorts, while GPR is not superior to APRI or FIB-4 index for evaluating hepatic fibrosis in a French cohort (9). Li et al. (11) evaluated the diagnostic value of the GPR in a retrospective study in China that included 372 patients with CHB and demonstrated that the GPR was not superior to the APRI or FIB-4 index for determining hepatic fibrosis. The performance of the GPR, APRI, and FIB-4 index was comparable for diagnosing hepatic fibrosis in another Chinese cohort (10). However, Hu et al. (5) showed that the AUROC values of GPRs were more accurate than those of APRI and FIB-4 index with respect to the degree of liver fibrosis.

In our study, the AUROC values of GPR for significant fibrosis and cirrhosis (0.70 and 0.73, respectively) were lower than those obtained by Lemoine et al. (9) (0.80 and 0.83, respectively), while the AUROC values for advanced fibrosis were similar between the two studies (0.80 and 0.81, respectively). Moreover, the GPR values correlated with the degree of hepatic fibrosis. According to these results, the GPR had acceptable performance for detecting liver fibrosis in our study population (p=0.001). However, the performance of the GPR in diagnosing liver fibrosis was not better than that of APRI or FIB-4 index. The AUROC values of APRI were 0.69, 0.72, and 0.75, and those of FIB-4 index were 0.79, 0.77, and 0.90, for significant fibrosis, advanced fibrosis, and cirrhosis, respectively. FIB-4 could be a better serum marker of cirrhosis than the GPR (AUROC: 0.90 and 0.73, respectively; p=0.024) and APRI (AUROC: 0.90 and 0.75,

Table 2. Serum markers by liver fibrosis stage

	Fibrosis stages				
Serum markers	**F0-F1**	**F2**	**F3**	**F4**	**p values**
GPR	0.23 (0.16-0.34)	0.30 (0.18-0.43)	0.54 (0.29-0.76)	0.80 (0.35-1.74)	0.001*
APRI	0.28 (0.17-0.45)	0.37 (0.19-0.59)	0.40 (0.26-0.49)	0.85 (0.38-1.09)	0.003*
FIB-4	0.71 (0.55-0.81)	0.94 (0.70-1.78)	1.21 (0.71-1.77)	2.39 (1.73-3.55)	0.001*
GGT	21.00 (15.00-29.50)	19.50 (14.00-28.00)	42.00 (23.00-65.00)	37.50 (19.50-87.50)	0.001*

Median (IQR) *p<0.05, IQR: Interquartile range, GGT: Gamma-glutamyl-transpeptidase, GPR: Gamma-glutamyl-transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4

Table 3. Diagnostic performance of serum markers for liver fibrosis and cirrhosis

	Significant fibrosis			Advanced fibrosis			Cirrhosis		
	≥ F2 (F0-F1 vs. F2-F4)			≥ F3 (F0-F2 vs. F3-F4)			F4 (F0-F3 vs. F4)		
	GPR	**APRI**	**FIB-4**	**GPR**	**APRI**	**FIB-4**	**GPR**	**APRI**	**FIB-4**
AUROC	0.703	0.697	0.794	0.802	0.727	0.771	0.737	0.757	0.902
95% CI	0.59-0.80	0.58-0.79	0.69-0.88	0.70-0.88	0.61-0.82	0.66-0.86	0.62-0.83	0.65-0.85	0.81-0.96
Cut-off value	0.35	0.24	0.81	0.36	0.26	0.96	0.72	0.74	1.41
Sensitivity	57.89	80.70	75.44	73.53	91.18	76.47	54.55	54.55	90.91
Specificity	81.82	50.00	77.27	77.78	46.67	71.11	88.24	92.65	82.35
PPV, %	42.85	50.00	53.33	79.07	87.50	80.00	92.30	92.64	98.24
NPV, %	89.19	80.70	87.75	69.44	56.36	66.66	42.85	54.54	45.45

AUROC: Area under the receiver operating characteristic curve, PPV: Positive predictive value, NPV: Negative predictive value, GPR: Gamma-glutamyl-transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4, CI: Confidence interval

respectively; p=0.024). The cut-off value of the FIB-4 index for diagnosing cirrhosis was 1.41, with 90% sensitivity and 82.5% specificity. Teshale et al. (17) reported high AUROC values for APRI and FIB-4 index in the diagnosis of liver fibrosis in patients with CHB, and high specificity and sensitivity for APRI and FIB-4 in distinguishing F2-F4 from F0-F1. However, some Chinese studies have reported that GPR has a higher AUROC value for the diagnosis of significant fibrosis and cirrhosis in patients with CHB (5,18). Lemoine et al. (9) observed poor performance of the APRI and FIB-4 index for detecting significant fibrosis and cirrhosis.

One possible reason for the inconsistent results is related to the differences in interregional HBV genotypes. According to epidemiological evidence, genotype A is common in Africa and Europe and genotypes B and C in Asia (19). As genotype D is the most common HBV genotype in the Mediterranean region, we assumed that this HBV genotype is also common in Turkey (20).

Study Limitations

Patient selection bias cannot be ruled out, primarily because this was a single-center study conducted in a tertiary referral center, in which patients with significant and advanced fibrosis are more prevalent than the general patient population. Moreover, the sample size of our study (especially the number of patients with cirrhosis) was relatively small. In addition, data were obtained retrospectively, and no dynamic GPR measurements were taken.

CONCLUSION

The GPR showed acceptable diagnostic performance for significant fibrosis, advanced fibrosis, and cirrhosis, but was not superior to the APRI or FIB-4 index. The correlations with fibrosis stage were similar among the GPR, APRI, and FIB-4 index. The FIB-4 index showed better diagnostic performance for cirrhosis than the GPR and APRI. Further large-scale studies are needed to confirm these results.

Ethics

Ethics Committee Approval: This study protocol was approved by the Ethics Committee of Gaziosmanpasa Training and Research Hospital (no: 189, date: 18.11.2020) and conformed with the Declaration of Helsinki.

Informed Consent: All patients were enrolled after they provided informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Ö.K., Y.G., Design: D.Ö.K., Y.G., Data Collection or Processing: D.Ö.K., Y.G., Analysis or Interpretation: D.Ö.K., Y.G., Literature Search: D.Ö.K., Y.G., Writing: D.Ö.K., Y.G.

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