

Predictive Value of Gamma Glutamyl Transferase Platelet Ratio in The Development of Liver Fibrosis and Steatohepatitis in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Karaciğer Fibrozisi ve Steatohepatit Gelişiminde Gamma Glutamil Transferaz Trombosit Oranının Öngörü Değeri

¹Mine Büşra BOZKÜRK, ²Yusuf COŞKUN, ³Gülnur KUL, ¹Funda GÜÇEL, ¹Ramazan Berk US, ³Merve Tura ÇELİK, ¹Alpaslan OZTURK, ³Ediz TÜTÜNCÜ

¹ Department of Clinical Biochemistry, Ankara Etlik City Hospital, Ankara, Türkiye

² Department of Gastroenterology, Ankara Etlik City Hospital, Ankara, Türkiye

³ Department of Infectious Diseases and Clinical Microbiology, Ankara Etlik City Hospital, Ankara, Türkiye

Mine Büşra Bozkürk: <https://orcid.org/0000-0002-9329-3513>

Yusuf Coşkun: <https://orcid.org/0000-0001-6016-6297>

Gülnur Kul: <https://orcid.org/0000-0001-7317-3461>

Funda Güçel: <https://orcid.org/0000-0001-5929-9199>

Ramazan Berk Us: <https://orcid.org/0009-0000-0575-8804>

Merve Tura Çelik: <https://orcid.org/0009-0005-4403-7723>

Alpaslan Ozturk: <https://orcid.org/0000-0003-4525-3477>

Ediz Tütüncü: <https://orcid.org/0000-0002-7583-8081>

ABSTRACT

Objective: Chronic hepatitis B (CHB) represents a major contributor to fibrosis and cirrhosis worldwide. In this study, we aimed to investigate the relationship and predictive value of the gamma-glutamyl transferase (GGT)-to-platelet ratio (GPR) with liver fibrosis and steatohepatitis.

Materials and Methods: This retrospective cohort study included 100 patients with CHB and 100 healthy controls. Fibrosis indices were calculated and compared with ultrasound results for fibrosis status and steatohepatitis identified on liver biopsy. The diagnostic performance of these parameters was assessed using receiver operating characteristic (ROC) curve analysis.

Results: The body mass index, liver enzyme levels, and fibrosis indices were higher in patients with chronic hepatitis B than in healthy individuals, while platelet counts were lower in these patients (all $p < 0.05$). ROC analysis showed that GPR had the highest discriminative performance in distinguishing CHB patients from healthy controls, with an AUC of 0.960, sensitivity of 96%, and specificity of 80%, and it outperformed both APRI and FIB-4. GGT and FIB-4 exhibited the strongest discriminatory performance. Although GPR showed a strong correlation with APRI and FIB-4, only FIB-4 was independently associated with Ishak fibrosis stages ($OR \approx 1.8$, $p = 0.037$). None of the indices significantly predicted hepatic steatosis severity.

Conclusion: GPR demonstrates high accuracy in distinguishing CHB patients from healthy individuals. FIB-4 was found to be more valuable than GPR for staging fibrosis progression, indicating that GPR should be interpreted primarily as a disease discrimination index, rather than as a fibrosis staging tool. The combined use of these indices could provide a cost-effective, noninvasive diagnostic tool for the diagnosis and follow-up of patients with CHB and serve as a useful biomarker for clinicians.

Keywords: Chronic Hepatitis B, FIB-4 index, gamma-glutamyl transferase to platelet ratio, liver fibrosis, steatohepatitis

ÖZ

Amaç: Kronik hepatit B (KHB), dünya çapında karaciğer fibrozisinin ve sirozun önemli bir nedenidir. Bu çalışmada, gama-glutamil transferaz (GGT)/trombosit oranının (GPR) karaciğer fibrozisi ve steatohepatit ile ilişkisini ve öngörü değerini araştırmayı amaçladık.

Materyal ve Metot: Bu retrospektif kohort çalışmaya 100 KHB'li hasta ve 100 sağlıklı kontrol dahil edildi. Fibrozis indeksleri hesaplandı ve karaciğer biyopsisinde tespit edilen fibrozis durumu ve steatohepatit için ultrason sonuçlarıyla karşılaştırıldı. Bu parametrelerin tanısal performansı, alıcı işletim karakteristiği (ROC) eğrisi analizi kullanılarak değerlendirildi.

Bulgular: Kronik hepatit B hastalarında vücut kitle indeksi, karaciğer enzim düzeyleri ve fibrozis indeksleri sağlıklı bireylere kıyasla daha yüksekti; trombosit sayıları ise bu hastalarda daha düşüktü (tümü $p < 0.05$). ROC analizi, GPR'nin CHB hastalarını sağlıklı kontrollerden ayırt etmede en yüksek ayırt edici performansa sahip olduğunu, AUC değerinin 0.96, duyarlılığının %96 ve özgüllüğünün %80 olduğunu ve hem APRI hem de FIB-4'ten daha iyi performans gösterdiğini ortaya koymuştur. GGT ve FIB-4 en güçlü ayırt edici performansı sergiledi. GPR, APRI ve FIB-4 ile güçlü bir korelasyon göstermesine rağmen, yalnızca FIB-4, Ishak fibrozis evreleriyle bağımsız olarak ilişkiliydi ($OR \approx 1.8$, $p = 0.037$). Endekslerin hiçbirisi hepatik steatozun şiddetini anlamlı şekilde tahmin etmedi.

Sonuç: GPR, KHB hastalarını sağlıklı bireylerden ayırmada yüksek doğruluk göstermektedir. FIB-4'ün fibrozis ilerlemesinin evrelendirilmesinde GPR'den daha değerli olduğu bulunmuştur; bu da GPR'nin öncelikle bir fibrozis evreleme aracı olarak değil, bir hastalık ayırt etme indeksi olarak yorumlanması gerektiğini göstermektedir. Bu indekslerin birlikte kullanımı, KHB'li hastaların tanı ve takibi için uygun maliyetli ve invaziv olmayan bir tanı aracı sağlayabilir ve klinisyenler için faydalı bir biyobelirteç görevi görebilir.

Anahtar Kelimeler: Kronik hepatit B, FIB-4 indeksi, gama-glutamil transferaz/trombosit oranı, karaciğer fibrozu, Steatohepatit

Corresponding Author / Sorumlu Yazar:

Merve Mine Büşra Bozkürk

Address: Varlık Neighborhood, Halil Sezai Erkut Street, Yenimahalle, Ankara, 06170, Etlik City Hospital Ankara, Türkiye

E-Mail: drminebusra@gmail.com

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INTRODUCTION

Chronic hepatitis B (CHB), caused by persistent infection with the hepatitis B virus (HBV), affects approximately 316 million individuals worldwide.¹ In CHB, ongoing hepatic inflammation and scarring lead to fibrosis.² Despite widespread HBV vaccination, about 20% of patients progress to cirrhosis or hepatocellular carcinoma (HCC).^{3,4} Globally, CHB affects roughly 3.9% of the population, while non-alcoholic fatty liver disease (NAFLD) affects about 24%.^{5,6} Both disorders cause significant liver-related morbidity, and the prevalence of NAFLD among CHB patients ranges between 13.6% and 59.3%.⁷ Although hepatic steatosis contributes to cirrhosis, HCC, and increased mortality, its exact impact on CHB progression remains unclear.^{8,9} Unlike chronic HCV infection, which is clearly associated with metabolic syndrome, evidence linking HBV to hepatic fat accumulation is inconsistent.^{10,11}

Advanced fibrosis, identified by noninvasive serum biomarkers, is a validated predictor of complications and mortality.^{12,13} Although liver biopsy remains the diagnostic gold standard for assessing hepatitis and fibrosis, its invasiveness, potential risks, and need for repeated sampling limit clinical applicability.^{14,15} Methods for assessing fibrosis that are non-invasive, accurate, cost-effective, and reproducible have become increasingly important. Serum-based indices using biochemical and hematologic parameters offer promising alternatives, yet reliance on a single marker often lacks sufficient diagnostic precision.

Gamma-glutamyl transferase (GGT) and platelet count (PLT) represent two complementary indicators of hepatic injury and fibrotic progression. GGT, a microsomal enzyme involved in glutathione metabolism, is a marker of oxidative stress and cholestasis. Elevated GGT levels indicate hepatocellular injury and oxidative stress, both of which promote the activation of hepatic stellate cells and collagen deposition. Conversely, platelet counts decline with advancing fibrosis due to splenic sequestration, reduced thrombopoietin synthesis, and bone marrow suppression, thereby reflecting portal hypertension and fibrotic severity.^{16,17}

The gamma-glutamyl transferase-to-platelet ratio (GPR) combines these parameters, potentially offering a more comprehensive evaluation of hepatic injury and fibrosis-related hemodynamic changes than either marker alone.¹⁸ Therefore, this study aimed to evaluate the diagnostic performance of GPR as a noninvasive biochemical index for distinguishing patients with chronic hepatitis B from healthy individuals and to compare its performance with established fibrosis indices in relation to liver fibrosis and steatohepatitis.

MATERIALS AND METHODS

Ethics Committee Approval: The study protocol was approved by the Ankara Etlik City Hospital Scientific Research, Evaluation and Ethics Committee (Date: 15.04.2025, decision no: 2025-011). The study was carried out following the principles of the Declaration of Helsinki.

Study Setting: As the study had a retrospective design, patient consent forms were not collected. This study included a cohort of 100 individuals diagnosed with CHB who were followed up at the Infectious Diseases Clinic of Etlik City Hospital between January 1, 2023, and December 31, 2024. The exclusion criteria comprised patients under 18 years of age, those with hepatic disorders other than chronic hepatitis B, incomplete medical documentation, chronic kidney disease, acute or chronic infections, or a history of prolonged medication use. The control group consisted of 100 subjects without chronic hepatitis B, all of whom exhibited normal clinical and laboratory parameters at diagnosis and throughout follow-up. All controls had normal liver enzyme levels and negative serological test results for HBV, HCV, and HIV. Individuals with obesity, diabetes mellitus, alcohol consumption, or other metabolic comorbidities such as dyslipidemia, hypertension, or thyroid dysfunction were excluded to minimize potential confounding factors that might influence liver enzyme activity or platelet counts.

Retrospective Data Analysis: A comprehensive analysis was conducted on a variety of biological indicators in both the patient and control groups, encompassing body mass index (BMI), GGT, GPR, haemoglobin, white blood cell (WBC) count, red blood cell (RBC) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, blood urea nitrogen (BUN), creatinine, liver biopsy-based fibrosis score, and ultrasonography-based steatohepatitis stage. An extensive comparison of all parameters was conducted to identify statistically significant differences between the study groups.

Statistical Analysis: Data analyses were performed using SPSS 23.0 (IBM Corp., USA), Analyze-it add-in for Microsoft Excel (Analyze-it Software Ltd., Leeds, UK), MedCalc version 22.016, and the MetaboAnalyst 5.0 platform (www.metaboanalyst.com). For two-group comparisons, either the independent samples t-test or the Mann–Whitney U test was employed, depending on the data distribution. In analyses involving more than two

groups, the Kruskal–Wallis test was used, followed by post hoc pairwise testing with Bonferroni or Dunn–Bonferroni adjustments. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of the studied parameters, and the area under the curve (AUC) with 95% confidence intervals (CI) was calculated. In addition, principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) were applied using the MetaboAnalyst platform to assess clustering behavior and pinpoint variables with the greatest influence on group separation. Statistical significance was set at $p < 0.05$. The sample size for the primary comparison of the study (patients vs. healthy individuals) was calculated a priori using G*Power 3.1.9.7 software. The effect size was estimated based on the study by Ekin et al. using the laboratory means and standard deviations reported in the CHB population.¹⁹ In this study, the effect size (Cohen's d) was calculated to be approximately 0.576 by determining the means and standard deviations for the selected biochemical markers in the patient and healthy groups. Under the assumptions of a two-tailed hypothesis, $\alpha=0.05$, power=0.95 ($1-\beta$), and a 1:1 sampling distribution, and using power equivalent to the Wilcoxon–Mann–Whitney test if the parametric test assumption is not met, the minimum sample size required was found to be $n=84$ for each group, and the total $N=168$. In our study, a total sample size of $n=200$ was achieved by including 100 individuals from each group, which exceeded the minimum requirement.

RESULTS

There were no significant differences in age or sex distribution between the patient and control groups. However, patients with chronic hepatitis B had a significantly higher body mass index compared than healthy individuals. Serum biochemical assessments showed markedly elevated AST, ALT, and GGT levels in the patient group, whereas the platelet counts were significantly lower. Similarly, the noninvasive fibrosis indices FIB-4, APRI, and GPR were significantly higher in patients than in controls. All demographic, clinical, and laboratory findings are presented in Table 1. All numerical findings presented in Table 1 are described exactly as they appear in the table, and p-values are reported solely to indicate statistically significant differences between groups without additional interpretation.

Table 1. Comparison of demographic, clinical, and biochemical parameters between healthy controls and patients with chronic hepatitis B.

Parameters		Healthy Control Group (N= 100)	Chronic Hepatitis B Patient Group (N=100)	Effect size	p-value
Gender, n (%)	Female	50 (50)	39 (39)	ND	0.118
	Male	50 (50)	61 (61)		
HT, n (%)	Absent	100 (100)	48 (48)	ND	ND
	Present	0 (0)	52 (52)		
Hepatic Steatosis Grade, n (%)	Absent	100 (100)	0 (0)	ND	ND
	Grade 1	0 (0)	33 (33)		
	Grade 2	0 (0)	30 (30)		
	Grade 3	0 (0)	37 (37)		
Liver Fibrosis Score (Ishak score), n (%)	Ishak-0	100 (100)	12 (12)	ND	ND
	Ishak-1	0 (0)	16 (16)		
	Ishak-2	0 (0)	15 (15)		
	Ishak-3	0 (0)	17 (17)		
	Ishak-4	0 (0)	13 (13)		
	Ishak-5	0 (0)	14 (14)		
	Ishak-6	0 (0)	13 (13)		

Continuation of **Table 1**.

Parameters	Healthy Control Group (N= 100) Median (%25-75)	Chronic Hepatitis B Patient Group (N=100) Median (%25-75)	Effect size	p-value
Age (Year)	46 (41-52)	47 (37-55)	r= 0.03	0.625
BMI (kg/m ²)	22.05 (20.2-23.65)	23.3 (19.9-25.95)	r= 0.156	0.026
Albumin (g/dL)	45 (42.5-48)	45.05 (43.05-48.4)	r=0.099	0.160
Creatinine (mg/dL)	0.9 (0.8-1)	0.795 (0.6-0.8)	r= 0.417	0.001
GFR (mL/min/1.73 m ²)	80 (74-84)	102 (92-112.5)	r= 0.683	0.001
BUN (mg/dL)	29 (20.5-34.5)	27.35 (22.1-35.45)	r= 0.051	0.476
AST (U/L)	23 (13-32.5)	28 (21.5-51)	r= 0.33	0.001
ALT (U/L)	22.5 (10-30.5)	33 (21.5-66.5)	r= 0.424	0.001
HBV DNA (IU/mL)	0 (0-0)	56905 (7525-1928134)	N.D.	N.D.
PLT (x10 ⁹ /L)	294 (218-381)	231.5 (186-274)	r= 0.348	0.001
GGT (U/L)	24 (10.5-37)	68.5 (52-76.5)	r= 0.791	0.001
FIB-4	0.782 (0.458-1.229)	0.999 (0.657-1.735)	r= 0.462	0.001
APRI	0.18 (0.105-0.285)	0.328 (0.217-0.601)	r= 0.211	0.001
GPR	0.078 (0.037-0.117)	0.271 (0.196-0.373)	r= 0.795	0.001

ND: Not determined. ALT: Alanine Aminotransferase; APRI: Aspartate Aminotransferase to Platelet Ratio Index; AST: Aspartate Aminotransferase; BMI: Body Mass Index; BUN: Blood Urea Nitrogen; FIB-4: Fibrosis-4 Index; GFR: Glomerular Filtration Rate; GGT: Gamma-Glutamyl Transferase; GPR: Gamma-Glutamyl Transferase to Platelet Ratio; HBV DNA: Hepatitis B Virus Deoxyribonucleic Acid; HT: Hypertension; ND: Not Determined; PLT: Platelet Count.

Group-based comparisons showed that patients with chronic hepatitis B had significantly higher GGT levels and GPR values, whereas platelet counts were significantly lower than those in healthy individuals (all $p < 0.05$). These differences clearly illustrate the elevation of cholestatic and fibrosis-related biochemical markers, alongside reduced platelet levels, in the patient group. The distributions of PLT, GGT, and GPR in both groups are shown in Figure 1.

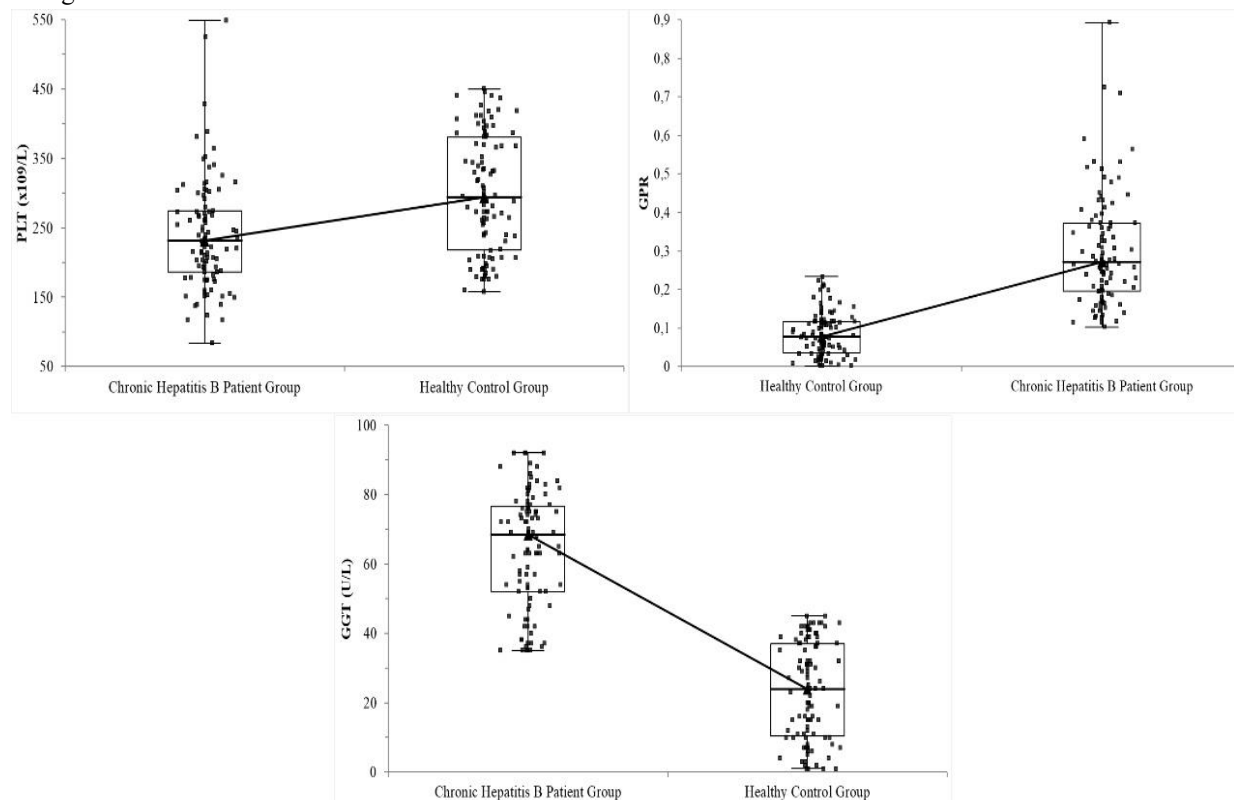


Figure 1. Group-wise comparison of PLT, GGT, and GPR in healthy controls and chronic hepatitis B patients.

The receiver operating characteristic analysis demonstrated that all three noninvasive fibrosis indices—APRI, FIB-4, and GPR— distinguished patients with chronic hepatitis B from healthy controls. Among these parameters, GPR showed the largest separation between groups, with the highest curve elevation, followed by APRI and FIB-4. A graphical comparison of the diagnostic performances of these indices is presented in Figure 2.

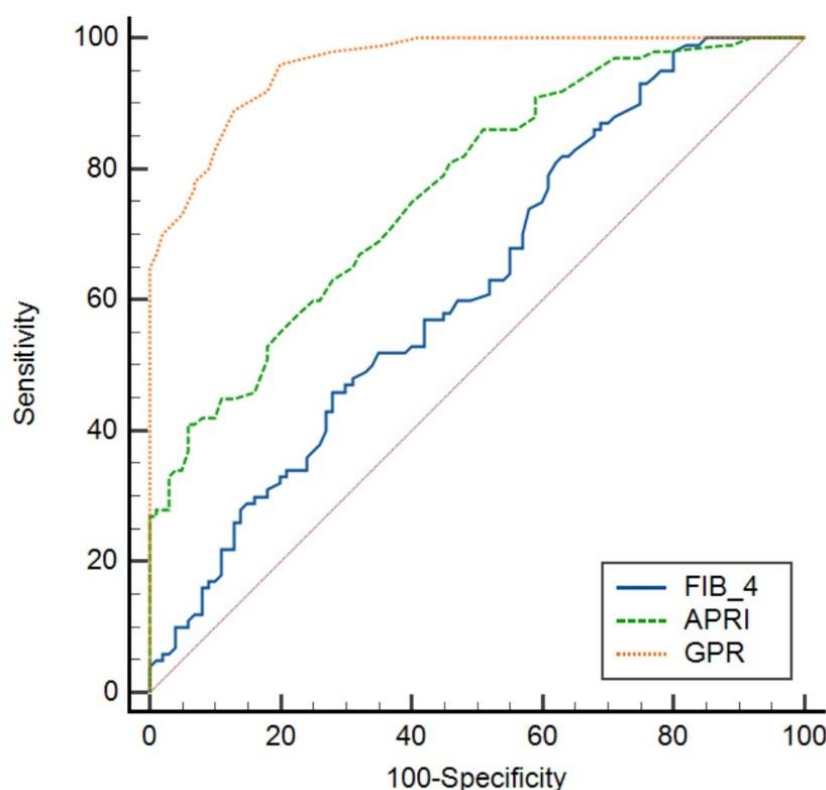


Figure 2. ROC curves for APRI, FIB-4, and GPR in differentiating patients from controls.

Table 2 summarizes the numerical diagnostic performance metrics obtained from ROC analyses. GPR demonstrated the highest discriminative performance, with the largest AUC value, accompanied by high sensitivity and specificity at the optimal cutoff. APRI showed moderate diagnostic performance, whereas FIB-4 exhibited the lowest discriminative ability among the three indices. All cutoff values, AUCs, and confidence intervals are listed in Table 2. This high performance should be interpreted with caution, as it reflects the discrimination between patients with CHB and healthy individuals rather than the differentiation among fibrosis stages within the CHB population.

Table 2. Diagnostic performance metrics of APRI, FIB-4, and GPR based on ROC curve analysis.

Variable	Cutoff	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
APRI	0.17	0.767 (0.703-0.824)	86 (77-92)	49 (38-59)
FIB-4	0.61	0.623 (0.552-0.691)	82 (73-89)	37 (27-49)
GPR	0.12	0.960 (0.923-0.982)	96 (90-98)	80 (71-87)

AUC: Area Under the ROC Curve; APRI: Aspartate Aminotransferase to Platelet Ratio Index; CI: Confidence Interval; FIB-4: Fibrosis-4 Index; GPR: Gamma-Glutamyl Transferase to Platelet Ratio.

Finally, ordinal logistic regression analysis based on Ishak score (Table 3) yielded a significant overall model fit ($\chi^2=10.190$, $p=0.017$), though the explanatory power was limited (Cox & Snell $R^2=0.097$; Nagelkerke $R^2=0.099$). Although FIB-4 was the only variable significantly associated with fibrosis stage, the overall explanatory power of the model was limited (Nagelkerke $R^2 \approx 0.10$), suggesting that these findings should be interpreted as exploratory rather than definitive. Overall, these results suggest that while FIB-4 retains modest predictive value for fibrosis progression, GPR and APRI demonstrate limited discriminatory performance in this cohort.

Table 3. Results of ordinal logistic regression analysis of the relationship between Ishak fibrosis score and serum fibrosis indices in chronic hepatitis B patients.

		Estimate	Std. Error	Wald	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Threshold	[LiverFibrosisScore = 0]	-1.669	0.490	11.580	0.001	-2.630	-0.708
	[LiverFibrosisScore = 1]	-0.573	0.444	1.671	0.196	-1.443	0.296
	[LiverFibrosisScore = 2]	0.129	0.437	0.087	0.768	-0.727	0.985
	[LiverFibrosisScore = 3]	0.852	0.444	3.691	0.055	-0.017	1.722
	[LiverFibrosisScore = 4]	1.481	0.461	10.311	0.001	0.577	2.385
	[LiverFibrosisScore = 5]	2.457	0.516	22.692	0.001	1.446	3.467
Location	GPR	-1.717	1.611	1.136	0.286	-4.874	1.440
	APRI	0.347	0.484	0.516	0.473	-0.600	1.295
	FIB-4	0.585	0.281	4.344	0.037	0.035	1.135

APRI: Aspartate Aminotransferase to Platelet Ratio Index; FIB-4: Fibrosis-4 Index; GPR: Gamma-Glutamyl Transferase to Platelet Ratio.

DISCUSSION AND CONCLUSION

This study evaluated the diagnostic performance of the GPR in patients with CHB and compared it with two established noninvasive fibrosis indices, FIB-4 and APRI. The findings showed that all three indices were significantly higher in CHB patients than in healthy controls, confirming their association with liver injury and fibrotic progression. Among these, GPR demonstrated the highest discriminative performance, supporting previous evidence that this index may be a sensitive indicator of liver damage in HBV infection. However, despite its strong discriminatory ability in the ROC analysis, GPR did not correlate independently with histological fibrosis stages. This suggests that its primary utility in our cohort lies in identifying CHB-related biochemical alterations rather than fibrosis staging alone.

Despite its high diagnostic value in distinguishing patients from healthy individuals, GPR failed to independently predict the severity of hepatic steatosis or histological fibrosis in this cohort, suggesting that GPR functions primarily as a biochemical discriminator rather than as a fibrosis staging tool. Ordinal regression analyses revealed that GPR, APRI, and FIB-4 were not significantly associated with steatosis grade, whereas FIB-4 showed a modest correlation with fibrosis stage. Given the low explanatory power of the regression model and the limited sample size, the generalizability of these findings should be approached cautiously. These findings suggest that biochemical indices can differentiate patients with CHB from healthy individuals. However, their utility in precisely staging fibrosis or steatosis remains limited, possibly because of the narrow range of fibrosis severity in this population. However, this finding should be interpreted with caution. In our study, steatohepatitis severity was assessed using ultrasonography, a semi-quantitative and operator-dependent modality with limited histological accuracy compared to liver biopsy and advanced imaging techniques.

Multivariate analyses identified GGT and FIB-4 as the most informative markers for distinguishing patients with CHB from controls, indicating that oxidative stress-related enzymes and composite fibrosis indices play a central role in the biochemical differentiation of CHB in routine clinical evaluation. From a clinical perspective, this finding suggests that simple and routinely available laboratory parameters, such as GGT and FIB-4, may be particularly useful in the initial identification of CHB-related liver injury, even when histological staging is not feasible.

Recent data have supported the role of GPR as a noninvasive marker of liver fibrosis in CHB. Purkayastha et al. reported that GPR performed better than APRI and FIB-4 and showed an accuracy comparable to that of transient elastography for detecting significant fibrosis.¹⁴ Similarly, Luo et al. demonstrated that GPR correlated well with liver stiffness and had good diagnostic accuracy in patients with CHB and NAFLD.²⁰ Consistent with these findings, our study also showed that GPR had the highest AUC for distinguishing patients with CHB from healthy individuals. This finding should not be interpreted as evidence of fibrosis staging accuracy but rather as an indicator of biochemical discrimination between diseased and healthy populations. However, unlike these reports, GPR was not independently associated with histological fibrosis stages in the present cohort. In contrast, FIB-4 was significantly associated with HCC.

Beyond fibrosis staging, the GPR has been linked to hepatic inflammation and clinical outcomes. Wang et al. showed that GPR outperformed ALT, AST, and GGT in predicting significant hepatic inflammation in treatment-

naïve patients with.²¹ Furthermore, studies have demonstrated that an elevated GPR predicts poorer survival and higher recurrence rates after surgery in HBV-related HCC and is associated with an increased HCC risk in CHB populations.^{22,23} Although our study did not assess prognosis, the marked differences in GPR between patients and controls support the concept that GPR reflects necroinflammatory activity and more advanced disease biology.

Recent literature has also underscored the utility of the FIB-4 as a simple indicator of advanced fibrosis and long-term outcomes. Blanco-Grau et al. reported that FIB-4 effectively identifies individuals at risk of advanced fibrosis who require specialist evaluation.²⁴ In patients with CHB, Kim et al. showed that FIB-4 predicted HCC development more accurately than APRI or GPR and correlated strongly with histological fibrosis⁵. Consistently, in our study, only FIB-4 was independently associated with Ishak fibrosis stages, whereas GPR mainly contributed to distinguishing patients from controls rather than fibrosis stage.

Nevertheless, this study has certain limitations, including its retrospective design, relatively small sample size, and uneven distribution of fibrosis stages, which may restrict the generalizability of the results. Larger prospective studies incorporating detailed metabolic profiling and histological validation are needed to better define the clinical utility of these indices in chronic hepatitis B. In addition, the use of a control group consisting exclusively of healthy individuals may have led to an overestimation of the diagnostic performance of the GPR, particularly its AUC value. This is because the ROC analysis compared two biologically distinct populations rather than different fibrosis stages within the CHB cohort. Therefore, the clinical utility of the GPR in this study appears to be largely confined to distinguishing patients with CHB from healthy controls, rather than accurately stratifying fibrosis severity among patients with CHB. Future studies comparing GPR across fibrosis stages within homogeneous CHB populations are warranted to better define its role in staging fibrosis. Another important limitation of our study is the assessment of steatohepatitis based on ultrasonographic findings rather than histological evaluations. Ultrasonography is a semi-quantitative and operator-dependent technique with limited sensitivity for grading steatohepatitis severity, particularly in mild and moderate diseases. Therefore, the lack of association between the evaluated indices and steatohepatitis severity may reflect methodological constraints rather than the true absence of a biological relationship.

In conclusion, GPR, APRI, and FIB-4 demonstrated significant diagnostic value in distinguishing patients with chronic hepatitis B from healthy individuals, with GPR showing the highest discriminative performance. This discriminative performance reflects its ability to differentiate patients with CHB from healthy individuals rather than staging fibrosis severity. However, only FIB-4 exhibited an independent association with fibrosis severity, while none of the noninvasive indices reliably predicted hepatic steatosis severity as assessed by ultrasonography. These findings suggest that GPR may be useful primarily for initial disease identification and differentiation from healthy individuals, whereas FIB-4 appears to provide modest but relatively superior value in estimating fibrosis progression compared to GPR in this cohort study.

Ethics Committee Approval: The study protocol was approved by the Ankara Etlik City Hospital Scientific Research, Evaluation and Ethics Committee (Date: 15.04.2025, decision no: 2025-011). The study was carried out following the principles of the Declaration of Helsinki.

Informed Consent: As the study had a retrospective design, patient consent forms were not collected.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declare no conflicts of interest in this study.

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REFERENCES

1. GBD 2019 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol*. 2022;7(9):796-829. doi:10.1016/S2468-1253(22)00124-8
2. Bera C, Hamdan-Perez N, Patel K. Non-Invasive Assessment of Liver Fibrosis in Hepatitis B Patients. *J Clin Med*. 2024;13(4):1046. Published 2024 Feb 12. doi:10.3390/jcm13041046
3. Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med*. 2004;350(11):1118-1129. doi:10.1056/NEJMra031087

4. Broquetas T, Carrión JA. Past, present, and future of long-term treatment for hepatitis B virus. *World J Gastroenterol.* 2023;29(25):3964-3983. doi:10.3748/wjg.v29.i25.3964
5. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64(1):73-84. doi:10.1002/hep.28431
6. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol.* 2018;3(6):383-403. doi:10.1016/S2468-1253(18)30056-6
7. Lin CW, Huang XL, Liu HL, Wang Y. Interactions of Hepatitis B Virus Infection with Nonalcoholic Fatty Liver Disease: Possible Mechanisms and Clinical Impact. *Dig Dis Sci.* 2015;60(12):3513-3524. doi:10.1007/s10620-015-3772-z
8. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 2015;148(3):547-555. doi:10.1053/j.gastro.2014.11.039
9. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology.* 2017;65(5):1557-1565. doi:10.1002/hep.29085
10. Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology.* 2004;126(2):586-597. doi:10.1053/j.gastro.2003.11.020
11. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology.* 2015;61(5):1547-1554. doi:10.1002/hep.27368
12. Angulo P, Bugianesi E, Björnsson ES, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology.* 2013;145(4):782-9.e4. doi:10.1053/j.gastro.2013.06.057
13. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. *Hepatology.* 2013;57(4):1357-1365. doi:10.1002/hep.26156
14. Purkayastha S, Jha AK, Kumar R, Dayal VM, Jha SK. Serum Gamma-Glutamyl Transpeptidase-to-Platelet Ratio as a Noninvasive Marker of Liver Fibrosis in Chronic Hepatitis B. *Cureus.* 2023;15(1):e33744. Published 2023 Jan 13. doi:10.7759/cureus.33744
15. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Hígado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol.* 2015;63(1):237-264. doi:10.1016/j.jhep.2015.04.006
16. Zhong LK, Zhang G, Luo SY, Yin W, Song HY. The value of platelet count in evaluating the degree of liver fibrosis in patients with chronic hepatitis B. *J Clin Lab Anal.* 2020 Jul;34(7):e23270. doi: 10.1002/jcla.23270
17. Gandhi CR. Oxidative Stress and Hepatic Stellate Cells: A PARADOXICAL RELATIONSHIP. *Trends Cell Mol Biol.* 2012;7:1-10
18. Sayar S, Atalay R, Çakmak Ş et al. Diagnostic Performance of Non-invasive Fibrosis Indexes in Hepatitis B Related Fibrosis. *Viral Hepat J.* 2020;26(2):78-84. doi:10.4274/vhd.galenos.2020.2019.0038
19. Ekin N, Ucmak F, Ebik B, et al. GPR, King's Score and S-Index are superior to other non-invasive fibrosis markers in predicting the liver fibrosis in chronic Hepatitis B patients. *Acta Gastroenterol Belg.* 2022;85(1):62-68. doi:10.51821/85.1.9156
20. Luo Y, Li X, He L, et al. Gamma-Glutamyl Transpeptidase-to-Platelet Ratio (GPR) as a noninvasive biomarker for liver fibrosis in patients with chronic hepatitis B and concurrent NAFLD. *Diagnostics (Basel).* 2021;11(12):2236. doi:10.3390/diagnostics11122236
21. Wang H, Wu R, Chen J, et al. Diagnostic value of gamma-glutamyl transpeptidase-to-platelet ratio for predicting significant liver inflammation in chronic hepatitis B patients with normal or mildly elevated ALT. *BMC Gastroenterol.* 2020;20:18. doi:10.1186/s12876-020-1168-y
22. Zhang Y, Chen L, Wu H, et al. Gamma-glutamyl transpeptidase-to-platelet ratio predicts recurrence and survival after curative resection in HBV-related hepatocellular carcinoma. *World J Gastrointest Oncol.* 2024;16(12):4579-4590. doi:10.4251/wjgo.v16.i12.4579

23. Kim JH, Kim MN, Han KH, et al. Noninvasive fibrosis indices as predictors of hepatocellular carcinoma in chronic hepatitis B: Comparison of APRI, FIB-4, and GPR. *Hepatol Int.* 2019;13(4):444-452. doi:10.1007/s12072-019-09965-8
24. Blanco-Grau A, Fajardo A, López-Martínez R, et al. FIB-4 index as a simple tool for identifying individuals at risk of advanced fibrosis in primary care settings. *Cureus.* 2023;15(7):e33744. doi:10.7759/cureus.33744