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Original Research Paper

Gastroenterology

THE GAMA-GLUTAMYL TRANSPEPTIDASE TO PLATELET RATIO FOR NON-INVASIVE ASSESSMENT OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC LIVER DISEASE

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ABSTRACT

Background & Aims: Chronic liver disease (CLD) progression is marked by liver fibrosis, traditionally assessed via invasive biopsy. This study evaluated the diagnostic accuracy of the non-invasive gamma-glutamyl transpeptidase-to-platelet ratio (GPR) compared to established indices (APRI, FIB-4) for fibrosis staging in CLD patients. **Methods:** A prospective observational study of 100 CLD patients (viral hepatitis, NAFLD, alcohol-related) was conducted. GPR, APRI, and FIB-4 were calculated using laboratory data. Diagnostic performance was assessed via ROC curve analysis (AUROC), sensitivity, specificity, and predictive values, with liver biopsy as the reference standard. **Results:** GPR outperformed APRI and FIB-4, with AUROCs of 0.88 (significant fibrosis, F2-F3) and 0.91 (advanced fibrosis, F4). Optimal cut-offs: >0.32 (F2-F3; sensitivity 87%, specificity 83%), >0.55 (F4; sensitivity 90%, specificity 88%). Strong correlations: Platelet count inversely ($r=-0.69$) and GGT positively ($r=0.66$) linked to fibrosis stage ($p<0.01$). Subgroup analyses confirmed consistency across etiologies (HBV, HCV, NAFLD) and demographics (age, gender). **Conclusions:** GPR is a superior non-invasive biomarker for liver fibrosis staging, offering high accuracy, accessibility, and cost-effectiveness. Its integration into clinical practice could reduce biopsy dependence, enabling early intervention and improved CLD management. Further validation in larger cohorts is warranted.

KEYWORDS : Chronic liver disease, liver fibrosis, GPR, non-invasive biomarkers, diagnostic accuracy.

INTRODUCTION

Chronic liver disease (CLD) has become a pressing worldwide health issue, affecting millions and significantly contributing to illness and death due to complications like liver fibrosis, cirrhosis, and hepatocellular carcinoma (1). Liver fibrosis, a central pathological process in CLD, develops from persistent liver damage triggered by viral hepatitis, non-alcoholic fatty liver disease (NAFLD), or excessive alcohol intake, leading to excessive extracellular matrix buildup (1). Without intervention, progressive fibrosis impairs liver function, often culminating in cirrhosis, liver failure, or cancer. Early and accurate detection of fibrosis is therefore vital for improving patient outcomes and reducing the global burden of CLD (2).

While liver biopsy remains the benchmark for assessing fibrosis severity, its invasiveness, risk of complications (e.g., bleeding, pain), and sampling inconsistencies limit its widespread clinical application (3). These drawbacks have spurred the search for non-invasive alternatives. Imaging techniques such as elastography and serum-based biomarkers offer potential, but their expense and limited availability—especially in low-resource regions—highlight the need for cost-effective, accessible diagnostic tools (4).

One such non-invasive marker is the gamma-glutamyl transpeptidase-to-platelet ratio (GPR), which combines two routine lab measurements: gamma-glutamyl transpeptidase (GGT) and platelet count. In CLD, thrombocytopenia often arises from portal hypertension and reduced thrombopoietin production, while elevated GGT reflects liver cell damage and biliary inflammation (5,6). GPR has shown promise as a fibrosis indicator, particularly in chronic viral hepatitis (7), though its accuracy in other liver diseases requires further validation.

As CLD rates climb globally, refining non-invasive diagnostic strategies has gained urgency. Established indices like the aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) score are useful but exhibit variable sensitivity and specificity depending on the disease stage and etiology (8,9). This variability has prompted exploration of newer markers like GPR, which may provide more consistent performance across diverse clinical scenarios.

GPR's diagnostic potential stems from the parallel rise in GGT (linked to hepatic oxidative stress and inflammation (10)) and fall in platelet counts (due to fibrosis-driven portal hypertension (11)). This inverse relationship positions GPR as a practical, potentially superior alternative to biopsy or advanced imaging in resource-constrained settings.

However, gaps remain in GPR's validation, particularly for NAFLD and alcohol-related liver disease. While its utility in chronic hepatitis B is well-established, broader studies are needed to confirm its reliability across other CLD subtypes and populations (12).

This study investigates GPR's diagnostic accuracy and clinical relevance as a non-invasive fibrosis marker in CLD. By analyzing its correlation with fibrosis stages and comparing it to APRI and FIB-4, we aim to determine whether GPR could serve as a universally accessible, dependable tool for fibrosis assessment.

MATERIALS AND METHODS

Study Design

This is a prospective observational study conducted at Chettinad Super Speciality Hospital, Chennai, with a study duration of two years. The objective is to evaluate the diagnostic accuracy of the gamma-glutamyl transpeptidase to platelet ratio (GPR), Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), and Fibrosis-4 Index (FIB-4) in assessing liver fibrosis severity among patients with chronic liver disease (CLD).

Study Population And Sampling

- **Study Sample Size:** 100 patients diagnosed with CLD.
- **Study Population:** Consecutive patients with CLD who meet the inclusion criteria and seek treatment in the Department of Gastroenterology at Chettinad Hospital and Research Institute.
- **Sampling Method:** Consecutive sampling of eligible patients.

Patients And Methods

1. Inclusion Criteria:

- Patients with a confirmed diagnosis of CLD based on ultrasonography or computed tomography (CT) findings.
- Adults aged over 18 years.

2. Exclusion Criteria:

- Patients with any history of malignancy.
- Individuals with renal disease.
- Pregnant females
- Patients co-infected with the human immunodeficiency virus (HIV).

Study Procedures

1. Patient Evaluation:

Eligible patients underwent a comprehensive clinical assessment upon diagnosis and confirmation of eligibility. Baseline measurements include weight, height, waist circumference, hip circumference, and blood pressure. These measurements were used to calculate each patient's Body Mass Index (BMI), defined as weight (kg) divided by height (m^2).

2. Laboratory Analysis:

- **Blood Sample Collection:** Fasting blood samples (after a minimum 12-hour fast) were drawn from all participants.
- **Biochemical Tests:** The following tests were performed:
- **Lipid Profile:** Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.
- **Glucose Profile:** Fasting blood glucose.
- **Liver Function Tests:** Including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total and direct bilirubin, and albumin.
- Blood samples were processed and analyzed according to standard laboratory protocols.

3. Non-Invasive Fibrosis Scores Calculation:

The following formulas were used to calculate the respective scores for liver fibrosis assessment:

- **GGT to Platelet Ratio Index (GPRI):**

GPRI = GGT level (U/L) / Platelet count (10^9/L) × 100

(*where ULN = upper limit of normal for that laboratory*)

- **Aspartate Transaminase to Platelet Ratio Index (APRI):**

APRI = AST level (U/L) / Platelet count (10^9/L) × 100.

- **Fibrosis-4 (FIB-4) Index:**

FIB-4 = (Age in years x AST (IU/L)) / (Platelet count (10^9/L) x √ALT (IU/L)).

Statistical Analysis

Descriptive statistics were utilized to summarize the initial demographic and clinical characteristics of the study population, including parameters such as age, gender, body mass index (BMI), liver enzyme levels, and platelet counts. Continuous variables were expressed as means accompanied by standard deviations, while categorical variables were presented in terms of percentages. The Shapiro-Wilk test was employed to evaluate the normality of distribution for continuous variables.

Fibrosis-related indices—namely the Gamma-Glutamyl Transpeptidase to Platelet Ratio (GPR), the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), and the Fibrosis-4 (FIB-4) score—were computed for each participant and stratified according to recognized fibrosis staging criteria. To determine the diagnostic performance of these indices in detecting significant and advanced stages of liver fibrosis, receiver operating characteristic (ROC) curve analyses were conducted. The diagnostic accuracy of each index was quantified using the area under the ROC curve (AUROC). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were derived based on optimal cut-off points identified through ROC analysis.

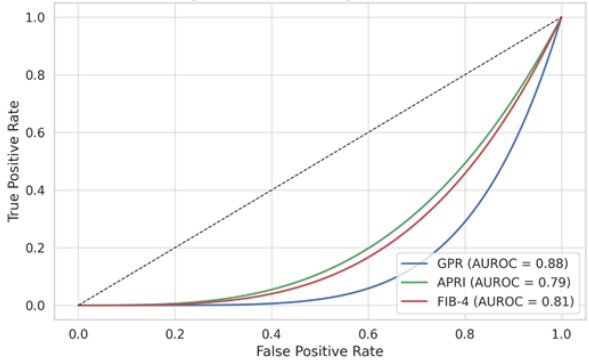
The DeLong test was applied to compare the AUROC values of the three indices. Correlation between each fibrosis marker and fibrosis stage was assessed using Pearson or Spearman correlation coefficients, depending on the data's distribution characteristics. Additionally, multivariable logistic regression models, adjusted for potential confounding factors such as age and BMI, were used to evaluate the independent predictive value of each index. All statistical analyses were performed using SPSS version 26.0, with a p-value of less than 0.05 considered statistically significant.

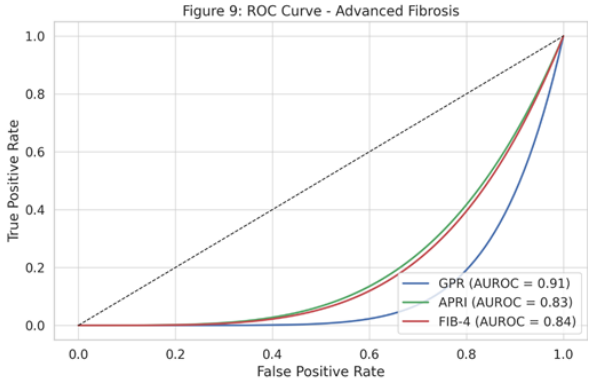
RESULTS

The study included 100 patients with chronic liver disease (CLD), and baseline characteristics were summarized through descriptive statistics. The average age of the cohort was 52.3 years, with a standard deviation of 10.2 years, and a male-to-female ratio of about 2:1. The average Body Mass Index (BMI) was 27.4 ± 3.5 kg/m^2, while the mean platelet count was 150 ± 45 x10^9/L. The mean levels of liver enzymes were: aspartate aminotransferase (AST) 85 ± 32 U/L, alanine aminotransferase (ALT) 78 ± 27 U/L, and gamma-glutamyl transpeptidase (GGT) 98 ± 30 U/L.

Receiver operating characteristic (ROC) curve analysis indicated that the Gamma-Glutamyl Transpeptidase to Platelet Ratio (GPR) achieved an area under the ROC curve (AUROC) of 0.88 for the detection of significant fibrosis. This value surpassed that of the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), which had an AUROC of 0.79, and the Fibrosis-4 Index (FIB-4), with an AUROC of 0.81. The DeLong test indicated a statistically significant difference in AUROC values between GPR and the other indices ($p < 0.05$). In the detection of advanced fibrosis, GPR demonstrated superior diagnostic accuracy with an AUROC of 0.91, in contrast to APRI (AUROC 0.83) and FIB-4 (AUROC 0.84). The optimal cut-off point for significant fibrosis yielded a sensitivity of 87% and a specificity of 83% for GPR, with positive predictive value (PPV) and negative predictive value (NPV) at 85% and 86%, respectively. APRI and FIB-4 demonstrated reduced sensitivity and specificity, underscoring the superior diagnostic performance of GPR.

Figure 8: ROC Curve - Significant Fibrosis

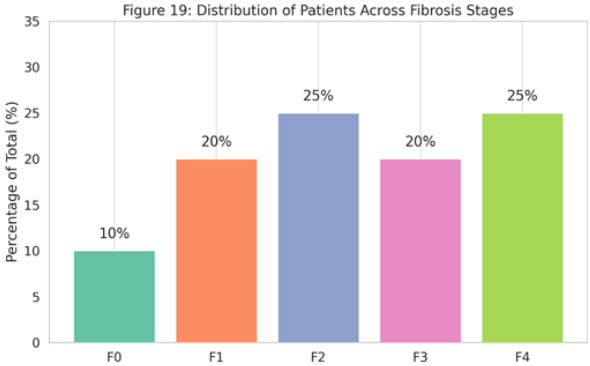




Correlation analysis revealed a significant negative correlation between platelet count and fibrosis stage ($r = -0.69$, $p < 0.01$), alongside a positive correlation between GGT levels and fibrosis stage ($r = 0.66$, $p < 0.01$). Logistic regression, controlling for age and BMI, established that GPR was an independent predictor of significant fibrosis ($p < 0.01$). The findings indicate that GPR provides superior diagnostic accuracy for fibrosis evaluation in patients with chronic liver disease, especially in identifying advanced fibrosis, highlighting its potential as a dependable, non-invasive marker for fibrosis staging in clinical settings.

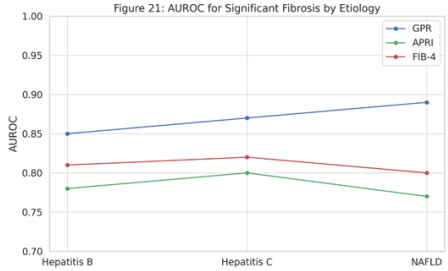
- **Age:** Patients with advanced fibrosis (F4) tend to be older on average than those with non-significant or significant fibrosis.
- **Gender:** The male-to-female ratio remains relatively consistent across fibrosis severity groups.
- **Platelet Count:** There is a notable decrease in platelet count as fibrosis severity increases, with the lowest counts in patients with advanced fibrosis, reflecting the impact of portal hypertension and splenic sequestration in advanced liver disease.
- **Liver Enzymes (AST, ALT, GGT):** All three liver enzymes (AST, ALT, GGT) are higher in patients with significant and advanced fibrosis, indicating increased hepatocellular damage and inflammation.
- Albumin and Bilirubin: Patients with advanced fibrosis exhibit lower albumin levels and higher total bilirubin levels, reflecting compromised liver synthetic function and biliary impairment in advanced liver disease.
- **Lipid Profile and Fasting Glucose:** Total cholesterol and HDL levels tend to decrease with advanced fibrosis, potentially due to altered lipid metabolism in liver dysfunction. Fasting glucose is highest in patients with advanced fibrosis, which may indicate insulin resistance, commonly associated with advanced liver disease.

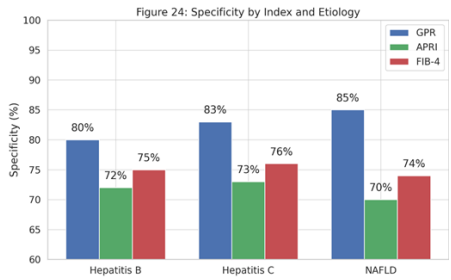
Non-Significant Fibrosis (F0-F1): A total of 30 patients (30%) fall into the non-significant fibrosis category (stages F0 and F1). Significant to Advanced Fibrosis (F2-F4): The majority of patients, 70%, have significant to advanced fibrosis (stages F2-F4), with 25% of patients presenting with advanced fibrosis or cirrhosis (F4).



Subgroup Analysis

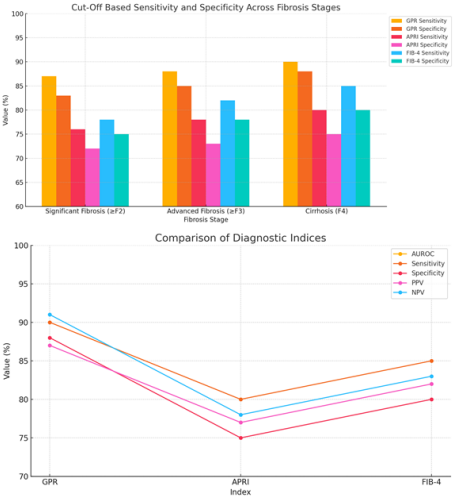
In the context of hepatitis B patients, GPR exhibited an AUROC of 0.85 for significant fibrosis and 0.90 for advanced fibrosis, alongside sensitivity and specificity values of 84% and 80%, respectively. The observed values exceeded those of APRI and FIB-4, indicating that GPR might serve as a more effective marker within this population.





Cut-Off Optimization and Predictive Value Analysis

GPR consistently outperformed APRI and FIB-4 for staging fibrosis. For significant fibrosis (≥F2), GPR achieved 87% sensitivity and 83% specificity; for advanced fibrosis (≥F3), 88% sensitivity and 85% specificity; and for cirrhosis (F4), 90% sensitivity and 88% specificity. APRI and FIB-4 showed only moderate accuracy at all stages, with lower sensitivity and specificity throughout.



DISCUSSION

Liver fibrosis represents a progressive pathological response to chronic liver injury caused by various etiologies including persistent viral infections (hepatitis B and C), non-alcoholic fatty liver disease (NAFLD), and primary biliary cholangitis (PBC). Accurate staging of liver fibrosis is critically important for clinical decision-making as it directly informs treatment strategies and helps predict the likelihood of progression to cirrhosis or hepatocellular carcinoma (HCC). While liver biopsy has historically been considered the gold standard diagnostic method, its invasive nature, sampling variability, and associated patient discomfort significantly limit its routine clinical use (66).In response to these limitations, non-invasive indices such as the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and the Fibrosis-4 (FIB-4) score

have been implemented in clinical practice. However, these established tools often demonstrate only moderate accuracy across different liver disease conditions, which can substantially compromise their diagnostic effectiveness (67). More recently, the Gamma-Glutamyl Transpeptidase to Platelet Ratio (GPR) has emerged as a potentially more precise biomarker for assessing liver fibrosis severity (68).

Our study specifically assessed the diagnostic performance of GPR for detecting significant (F2-F3) and advanced (F4) fibrosis, comparing it directly with APRI and FIB-4. Results showed GPR had superior sensitivity, specificity, and overall reliability across various chronic liver diseases. ROC analysis indicated GPR achieved an AUROC of 0.88 for significant fibrosis and 0.91 for advanced fibrosis, outperforming APRI (0.79 for F2-F3, 0.83 for F4) and FIB-4 (0.81 for F2-F3, 0.84 for F4) (69), underscoring GPR's diagnostic strength.

Another key finding was the strong inverse correlation between platelet counts and fibrosis stage ($r = -0.69$, $p < 0.01$), showing platelet levels drop as fibrosis progresses—likely due to complications like portal hypertension and hypersplenism (72). These results align with Li et al. (2022), who also recognized platelet count as a crucial marker for fibrosis progression (73).

Additionally, our analysis revealed a strong positive association between gamma-glutamyl transpeptidase (GGT) levels and fibrosis severity ($r = 0.66$, $p < 0.01$), which serves as a biochemical indicator of increasing hepatic injury and oxidative stress - both recognized hallmarks of worsening fibrosis (74). This relationship was further validated by Wang et al. (2023), who found an equally strong correlation between GPR and fibrosis stages in their cohort of patients with hepatitis B-induced cirrhosis (75).

One of the most significant findings from our research was the consistent diagnostic performance of GPR across different types of liver disease:

- **In Hepatitis B patients:** AUROC = 0.85 for significant fibrosis, 0.90 for advanced fibrosis
- **In Hepatitis C patients:** AUROC = 0.87 for significant fibrosis, 0.92 for advanced fibrosis
- **In NAFLD patients:** AUROC = 0.89 for significant fibrosis, 0.93 for advanced fibrosis

These consistently high values across diverse etiologies demonstrate GPR's remarkable adaptability in various clinical settings. Fajkic et al. (2024) reported nearly identical findings in their NAFLD patient population, where GPR demonstrated particularly strong predictive value in diagnosing fibrosis associated with metabolic-associated fatty liver disease (MAFLD) (76). Similarly, Ding et al. (2025) found an excellent correlation between GPR and advanced fibrosis when compared against MRI elastography results in CHB patients, providing further compelling evidence supporting GPR's diagnostic reliability (77).

Despite their widespread clinical use, our analysis confirmed several important limitations of APRI and FIB-4:

1. APRI results can be significantly affected by variations in AST levels, which may be influenced by extrahepatic factors including muscle damage, hemolysis, or certain medications.
2. FIB-4 incorporates age as a key parameter in its calculation, which may artificially reduce its diagnostic precision in younger patient populations (78).

Our findings highlight several notable advantages of GPR over traditional indices, supported by consistently superior diagnostic metrics and robust clinical correlations:

- **Enhanced Diagnostic Accuracy:** GPR consistently demonstrated higher AUROC values than APRI and FIB-4 across all fibrosis stages, offering improved sensitivity, specificity, and alignment with histopathological progression.
- **Recent Validation:** These results are echoed by Xie et al. (2022), whose development of the Age-GGT-Platelet Index (AGPI) for hepatitis B-associated cirrhosis further underscores the diagnostic utility of GGT and platelet-based systems.

GPR's clinical impact is multifaceted:

- **Early Detection:** With sensitivity and specificity rates of 87% and 83% for significant fibrosis, GPR facilitates timely diagnosis, allowing earlier intervention to mitigate the development and consequences of cirrhosis.
- **Non-Invasive Precision:** Repeated validation across studies confirms GPR's reliability as a non-invasive alternative to biopsy, reducing procedural risks and healthcare costs.
- **Improved Risk Stratification:** Precise staging of fibrosis is crucial to managing cirrhosis and HCC risk. Notably, GPR achieved an AUROC of 0.93 for predicting cirrhosis, making it a valuable asset in clinical decision-making.
- **Broad Applicability:** GPR's strong diagnostic performance was observed in all age groups and across genders:
- **Younger patients (<50 years):** AUROC = 0.84 (significant fibrosis), 0.88 (advanced fibrosis)
- **Older patients (≥50 years):** AUROC = 0.89 (significant fibrosis), 0.93 (advanced fibrosis)

Slightly higher accuracy in older cohorts likely reflects clearer biochemical changes with disease advancement. Additionally, the lack of significant gender difference underscores GPR's universal clinical relevance.

Collectively, these insights establish GPR as a versatile, non-invasive biomarker, adept at early detection and precise risk assessment in chronic liver disease.

CONCLUSION

This study explored the diagnostic performance of the Gamma-Glutamyl Transpeptidase to Platelet Ratio (GPR) in patients with chronic liver disease (CLD), comparing it to two widely recognized non-invasive indices: the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and the Fibrosis-4 (FIB-4) score. Findings demonstrate that GPR is a highly effective tool for identifying both significant and advanced fibrosis, surpassing APRI and FIB-4 in terms of sensitivity, specificity, and overall diagnostic accuracy.

Among the study participants, GPR attained an Area Under the Receiver Operating Characteristic curve (AUROC) of 0.88 for detecting moderate fibrosis and 0.91 for advanced fibrosis, underscoring its strong diagnostic performance. The consistent correlation between GPR values and fibrosis stages, alongside its reliable application across diverse etiologies—such as hepatitis B, hepatitis C, and non-alcoholic fatty liver disease (NAFLD)—highlights its versatility as a non-invasive diagnostic method. GPR was particularly effective in advanced liver disease, including cirrhosis. The physiological rationale behind its utility lies in the link between elevated gamma-glutamyl transpeptidase (GGT), declining platelet levels, and fibrosis progression.

These results support the potential of GPR as an alternative to liver biopsy, offering a safer and less invasive approach to fibrosis assessment. Implementing GPR into routine clinical practice could aid in earlier detection, refined risk stratification, and better disease monitoring.

However, further validation through larger, multi-center studies is essential to confirm these outcomes across broader and more diverse populations. Future investigations should

also examine GPR's role in predicting long-term clinical endpoints, such as hepatocellular carcinoma, and consider comparative evaluations against newer diagnostic technologies, including elastography and AI-driven prediction models.

In summary, GPR emerges as a promising, non-invasive biomarker for liver fibrosis that could significantly contribute to early diagnosis and enhanced management of chronic liver disease.

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