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COMPARISON OF GAMMA GLUTAMYL TRANSPEPTIDASE TO PLATELET RATIO (GPR), INR TO PLATELET RATIO (INPR), APRI, AND FIB-4 IN PREDICTING ADVANCED LIVER FIBROSIS IN HEPATITIS C POPULATION

Original Research

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is a major global health concern, leading to progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma. Early and accurate assessment of advanced liver fibrosis is essential for timely intervention and optimized patient management. While liver biopsy remains the gold standard, its invasiveness limits its routine use. Non-invasive fibrosis markers, including the Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR), INR to Platelet Ratio (INPR), Aspartate Aminotransferase to Platelet Ratio Index (APRI), and Fibrosis-4 (FIB-4) index, offer practical alternatives. This study aimed to compare the diagnostic accuracy of these four indices in predicting advanced liver fibrosis in HCV patients.

Objective: To evaluate and compare the diagnostic accuracy of INPR, GPR, APRI, and FIB-4 in predicting advanced liver fibrosis among HCV patients using shear wave elastography (SWE) as the reference standard.

Methods: This cross-sectional study was conducted at the Hepatogastroenterology Department, Sindh Institute of Urology and Transplantation, from April to September 2024. A total of 210 adult patients with chronic HCV infection underwent fibrosis assessment using SWE. Fibrosis severity was categorized into non-advanced (F1-F2) and advanced (F3-F4). Non-invasive fibrosis indices were calculated, and diagnostic performance was assessed using receiver operating characteristic (ROC) analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined for each index.

Results: Among 210 patients (mean age 43.7 ± 12.6 years; 62.9% male), advanced fibrosis was detected in 125 (59.5%). INPR exhibited the highest diagnostic accuracy (AUROC = 0.807, sensitivity = 83.4%, specificity = 60.8%, PPV = 73.4%, NPV = 62.2%). GPR showed an AUROC of 0.782, with the highest sensitivity (95.2%), specificity of 44.7%, PPV of 71.7%, and NPV of 86.3%. APRI demonstrated an AUROC of 0.744 (sensitivity = 90.4%, specificity = 51.8%, PPV = 73.4%, NPV = 78.6%), while FIB-4 had the lowest AUROC (0.669), with sensitivity and specificity of 81.2% and 35.3%, respectively.

Conclusion: INPR demonstrated the highest diagnostic accuracy, making it a preferred non-invasive marker for detecting advanced fibrosis. GPR, with its high sensitivity, emerged as a valuable rule-out test. APRI and FIB-4 exhibited moderate accuracy, warranting cautious interpretation. These findings reinforce the clinical utility of non-invasive fibrosis indices in optimizing liver fibrosis assessment and guiding HCV management strategies.

Keywords: Aspartate Aminotransferase to Platelet Ratio Index, Fibrosis-4, Gamma Glutamyl Transpeptidase to Platelet Ratio, Hepatitis C, INR to Platelet Ratio, Liver Cirrhosis, Shear Wave Elastography

INTRODUCTION

Hepatitis C virus (HCV) infection remains a major global health concern, affecting over 70 million individuals worldwide. Chronic HCV infection is a leading cause of liver-related morbidity and mortality, contributing to progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The early and accurate assessment of liver fibrosis is crucial for guiding therapeutic decisions, predicting disease progression, and determining eligibility for antiviral therapy. Traditionally, liver biopsy has been considered the gold standard for fibrosis assessment; however, its invasive nature, potential complications—including bleeding, infection, and sampling errors—and associated costs have limited its widespread use. These challenges have prompted the search for non-invasive, reliable, and cost-effective alternatives for assessing liver fibrosis (1,2). Over the past decades, numerous non-invasive biomarkers and scoring systems have been developed based on routine laboratory parameters, providing clinicians with valuable tools to estimate fibrosis severity without the need for invasive procedures. Among these, the Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR), INR to Platelet Ratio (INPR), Aspartate Aminotransferase to Platelet Ratio Index (APRI), and Fibrosis-4 (FIB-4) index have emerged as prominent indices for liver fibrosis assessment. GPR has gained attention for its potential utility in detecting liver fibrosis, particularly in patients with viral hepatitis, as Gamma Glutamyl Transpeptidase (GGT) levels are often elevated in liver disease due to oxidative stress and fibrosis progression, while platelet counts tend to decline in advanced liver disease due to portal hypertension and bone marrow suppression. Similarly, INPR integrates INR, a marker of hepatic synthetic capacity, with platelet count, making it a potentially valuable fibrosis assessment tool. APRI and FIB-4, both widely studied, have been incorporated into clinical guidelines for liver fibrosis evaluation in HCV patients (3,4).

Although these indices offer a non-invasive and accessible means of assessing liver fibrosis, variations in their diagnostic accuracy have been observed across different populations, influenced by factors such as patient demographics, disease severity, and concomitant conditions. Despite extensive research on these markers, there remains a lack of consensus on their comparative efficacy in predicting advanced fibrosis, particularly in populations such as those in Pakistan. Given the pressing need for reliable, non-invasive alternatives to liver biopsy, this study aims to compare the diagnostic accuracy of GPR, INPR, APRI, and FIB-4 in predicting advanced liver fibrosis in patients with chronic HCV infection. By evaluating these indices within a specific patient cohort, this research seeks to identify the most effective and clinically applicable non-invasive marker for fibrosis assessment, ultimately improving patient management and treatment outcomes (5,6).

METHODS

This study employed a cross-sectional design to evaluate the diagnostic performance of the Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR), INR to Platelet Ratio (INPR), Aspartate Aminotransferase to Platelet Ratio Index (APRI), and Fibrosis-4 (FIB-4) in predicting advanced liver fibrosis among patients with chronic hepatitis C virus (HCV) infection. The study was conducted at the Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, from April 1, 2024, to September 30, 2024. Ethical approval was obtained from the institutional review board (IRB) of the Sindh Institute of Urology and Transplantation, ensuring adherence to ethical principles. Written informed consent was obtained from all participants prior to enrollment (7,8). The study included adult patients (≥18 years) diagnosed with chronic HCV infection who had undergone liver fibrosis assessment using shear wave elastography (SWE) and had complete biochemical and hematological parameters available. Patients with coexisting liver diseases, including hepatitis B, autoimmune hepatitis, alcoholic liver disease, and hepatocellular carcinoma, were excluded. Additionally, pregnant and lactating women were not included in the study to eliminate potential confounding factors (9,10).

Baseline demographic data, biochemical parameters, and hematological indices were recorded for all participants. Liver fibrosis severity was determined using SWE and categorized into mild-to-moderate fibrosis (F1-F2) and advanced fibrosis or cirrhosis (F3-F4) based on elastography findings. The non-invasive fibrosis indices were calculated using standard formulas: GPR = (GGT / Platelet count) × 100, INPR = INR / Platelet count, APRI = [(AST / ULN AST) × 100] / Platelet count, and FIB-4 = (Age × AST) / (Platelet count × √ALT) (11). Statistical analysis was performed using SPSS software version 27.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent t-tests were used to compare continuous variables, whereas categorical variables were analyzed using chi-square tests. The diagnostic performance of each fibrosis index was assessed using the area under the receiver operating characteristic (AUROC) curve. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated to compare the predictive ability of GPR, INPR, APRI, and FIB-4 in identifying advanced liver fibrosis (12).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

To ensure the robustness of statistical analysis and the generalizability of findings, the sample size was determined using power analysis, considering an expected AUROC of ≥0.75 for at least one of the fibrosis indices, a 95% confidence interval, and a power of 80%. The final sample size was adjusted to account for potential dropouts and missing data. To minimize confounding factors, multivariate logistic regression was employed to adjust for variables such as age, gender, body mass index (BMI), diabetes mellitus, and baseline liver function tests, which could influence fibrosis progression. Sensitivity analyses were performed to evaluate the impact of missing data, with multiple imputation methods applied for handling missing biochemical and hematological parameters where necessary. The upper limit of normal (ULN) for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was defined based on institutional laboratory reference values, ensuring consistency in APRI and FIB-4 calculations.

RESULTS

A total of 210 patients were included in the study, with a mean age of 43.7 ± 12.6 years. Males accounted for 62.9% of the study population, while females comprised 37.1%. The mean hemoglobin level was 10.3 ± 2.2 g/dL, and the mean total leukocyte count was 4.8 ± 2.6 ×10⁹/L. The mean platelet count was significantly lower in patients with advanced fibrosis (76 ± 35 ×10⁹/L) compared to those without advanced fibrosis (105 ± 43 ×10⁹/L) (p=0.009), reinforcing the association between thrombocytopenia and fibrosis progression. Patients with advanced fibrosis (≥F3) exhibited significantly elevated levels of aspartate aminotransferase (AST) (76 ± 69 IU/L vs. 37 ± 20 IU/L, p≤0.001), alanine aminotransferase (ALT) (58 ± 41 IU/L vs. 27 ± 13 IU/L, p≤0.001), and gamma-glutamyl transpeptidase (GGT) (100 ± 75 IU/L vs. 47 ± 21 IU/L, p≤0.001) compared to those with non-advanced fibrosis (≤F2). Serum bilirubin levels were also significantly higher in patients with advanced fibrosis (1.5 ± 0.73 mg/dL vs. 1.02 ± 0.63 mg/dL, p≤0.001), whereas serum albumin was significantly lower (3.2 ± 0.7 g/dL vs. 3.4 ± 0.5 g/dL, p=0.024), indicating progressive hepatic dysfunction. The mean Model for End-Stage Liver Disease (MELD) score did not significantly differ between groups (10.8 ± 3.6 vs. 10.8 ± 4.3, p=0.993), suggesting limited utility of MELD in distinguishing fibrosis severity. Patients with advanced fibrosis were more likely to present with esophageal varices (71.2% vs. 62.4%, p=0.179), though the difference was not statistically significant. A significantly higher proportion of patients with advanced fibrosis fell into Child-Turcotte-Pugh (CTP) class B (44.8% vs. 21.2%, p<0.001), highlighting greater hepatic decompensation in this group.

Among the fibrosis indices assessed, INR to Platelet Ratio (INPR) demonstrated the highest diagnostic accuracy, with an area under the receiver operating characteristic (AUROC) curve of 0.807, sensitivity of 83.42%, and specificity of 60.80%. Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR) followed closely with an AUROC of 0.782, exhibiting the highest sensitivity (95.2%) but moderate specificity (44.71%), indicating its potential as a reliable marker for ruling out advanced fibrosis. The Aspartate Aminotransferase to Platelet Ratio Index (APRI) had an AUROC of 0.744, with sensitivity and specificity of 90.40% and 51.76%, respectively. The Fibrosis-4 (FIB-4) index had the lowest diagnostic performance, with an AUROC of 0.669, sensitivity of 81.2%, and specificity of 35.3%, suggesting its limited utility in detecting advanced fibrosis in this cohort. To enhance the clinical applicability of the findings, a comparative analysis of the fibrosis indices based on positive predictive value (PPV) and negative predictive value (NPV) was conducted. INPR, which demonstrated the highest AUROC (0.807), had a PPV of 73.4% and an NPV of 62.2%, indicating strong diagnostic accuracy in confirming advanced fibrosis while maintaining a moderate ability to rule it out. GPR, despite its high sensitivity (95.2%), exhibited a PPV of 71.69% and an NPV of 86.36%, making it particularly useful for ruling out advanced fibrosis in patients with chronic HCV. APRI showed comparable performance, with a PPV of 73.38% and an NPV of 78.57%, suggesting its reliability in fibrosis detection. FIB-4, with the lowest AUROC (0.669), demonstrated a PPV of 65.41% and an NPV of 58.82%, reflecting its limited utility in distinguishing advanced fibrosis from milder stages. Further subgroup analyses revealed that male patients had a higher prevalence of advanced fibrosis (70.4% vs. 51.8%, p=0.006), emphasizing the potential influence of gender on disease progression. Stratification based on hepatic function showed that patients classified under Child-Turcotte-Pugh (CTP) class B had significantly higher rates of advanced fibrosis, reinforcing the association between hepatic decompensation and fibrosis severity. Additionally, elevated liver enzymes (AST, ALT, and GGT) correlated strongly with fibrosis progression, while thrombocytopenia remained a consistent marker across all subgroups. These findings highlight the importance of integrating fibrosis indices with baseline liver function parameters to improve diagnostic precision and patient risk stratification.

Table: Baseline characteristics of the population included in the study (n-210)

Study population		n (%)
Mean age (Mean±S.D)		43.7 ± 12.6
Gender	Male	132(62.9)
	Female	78 (37.1)

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Hemoglobin(g/dL)		10.3 ± 2.2
Total Leucocyte Count(x109/L)		4.8 ± 2.6
Platelet Count(x109/L)		71 ± 48
International Normalized Ratio (INR)		1.24 ± 0.18
Total Bilirubin(mg/dl)		1.3 ± 0.76
Alkaline Phosphatase (IU/L)		197 ± 190
Aspartate Transaminase (AST)(IU/L)		60.5 ± 57.5
Alanine Transaminase (ALT)(IU/L)		45.7 ± 36.3
Gamma Glutamyl Transpeptidase (GGT)(IU/L)		79 ± 64
Child Turcotte Pugh Score	A	136 (64.8)
	B	74 (35.2)
MELD score		10.9±3.4
Shear wave Elastography (SWE)		
F1 Fibrosis		20 (9.5)
F2 Fibrosis		65 (31)
F3 Fibrosis		12 (5.7)
F4 Fibrosis		113 (53.8)
GPR (Gamma Glutamyl Transpeptidase to Platelet Ratio)		0.85 ± 0.67
INR to platelet Ratio (INPR)		1.8 ± 1.2
APRI		2.9 ± 3.8
FIB-4 index		7 ± 8.2

Table: Comparison of continuous variables in terms of advanced liver fibrosis

Variable	Advanced Fibrosis(≥F3) (N-125) Mean ± SD	No Fibrosis(≤F2) (N-85) Mean ± SD	p-value
Age	44.9 ± 13.5	42 ± 11.3	0.11
Hemoglobin(g/dL)	11.0 ± 1.8	10.5 ± 2.5	0.096
Total Leucocyte Count(x109/L)	4.6 ± 2.1	5.3 ± 2.7	0.041
Platelet Count(x109/L)	76 ± 35	105 ± 43	0.009
INR	1.2 ± 0.2	1.1 ± 0.2	0.097
Total Bilirubin(mg/dl)	1.5 ± 0.73	1.02 ± 0.63	≤0.001
Aspartate Transaminase (AST)(IU/L)	76 ± 69	37 ± 20	≤0.001
Alanine Transaminase (ALT)(IU/L)	58 ± 41	27 ± 13	≤0.001
Gamma Glutamyl Transpeptidase (GGT)(IU/L)	100 ± 75	47 ± 21	≤0.001
Serum Creatinine	1.3 ± 2.2	1.1 ± 2.1	0.288
Serum Albumin(g/dl)	3.2 ± 0.7	3.4 ± 0.5	0.024

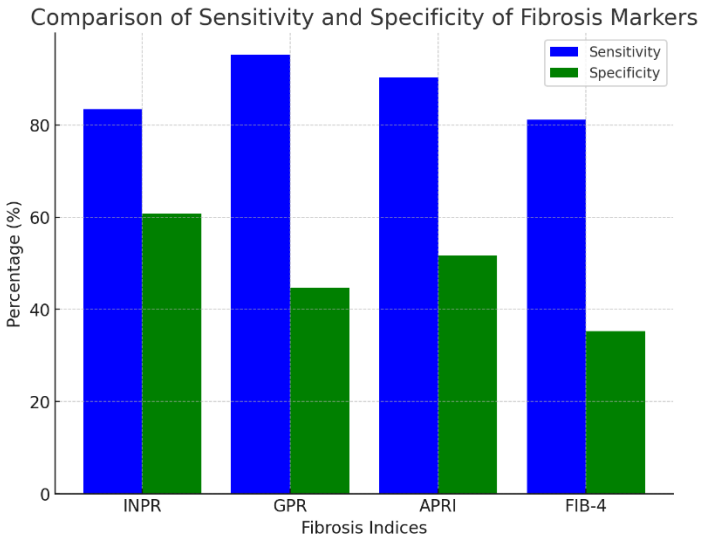
MELD Score	10.8 ± 3.6	10.8 ± 4.3	0.993
GPR	1.1 ± 0.7	0.5 ± 0.3	≤0.001
INPR	2.2 ± 1.3	1.1 ± 0.43	≤0.001
APRI	3.4 ± 3.9	2.1 ± 3.4	0.02
FIB-4	7.3 ± 6.2	6.8 ± 7.6	0.047

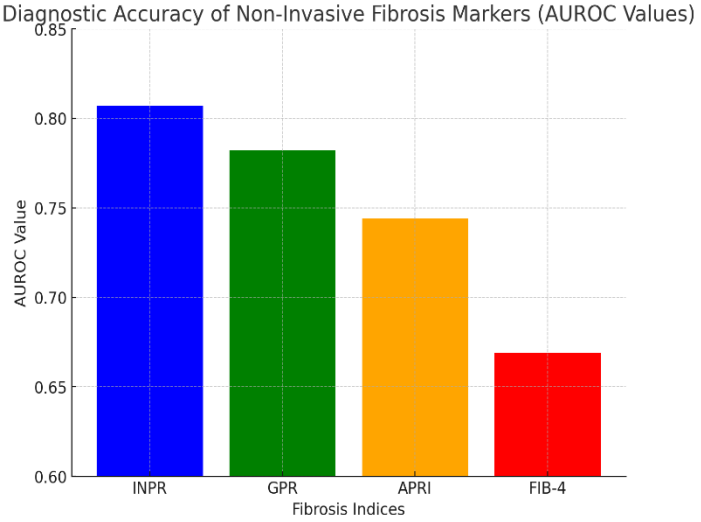
Table: Comparison of categorical variables in terms of advanced liver fibrosis (n-210)

Variable		Liver fibrosis (≥F3) (N-125) N (%)	No Fibrosis(≤F2) (N-85) N (%)	p-value
Gender	Male	88 (70.4)	44 (51.8)	0.006
	Female	37 (29.6)	41 (48.2)	
Esophageal varices	Yes	89 (71.2)	53 (62.4)	0.179
	No	36 (28.8)	32 (37.6)	
CTP score	A	69 (55.2)	67 (78.8)	<0.001
	B	56 (44.8)	18 (21.2)	

Table: Diagnostic accuracy of International Normalized Ratio (INPR), Gamma Glutamyl Transpeptidase (GPR), APRI and FIB-4 in predicting advanced liver fibrosis in patients with HCV infection

Variable	AUROC	p-value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
INPR	0.807	<0.001	83.42%	60.80%	73.4%	62.2%	79.1%
GPR	0.782	<0.001	95.20%	44.71%	71.69%	86.36%	74.76%
APRI	0.744	<0.001	90.40%	51.76%	73.38%	78.57%	72.31%
FIB-4	0.669	<0.001	81.2%	35.3%	65.41%	58.82%	63.81%





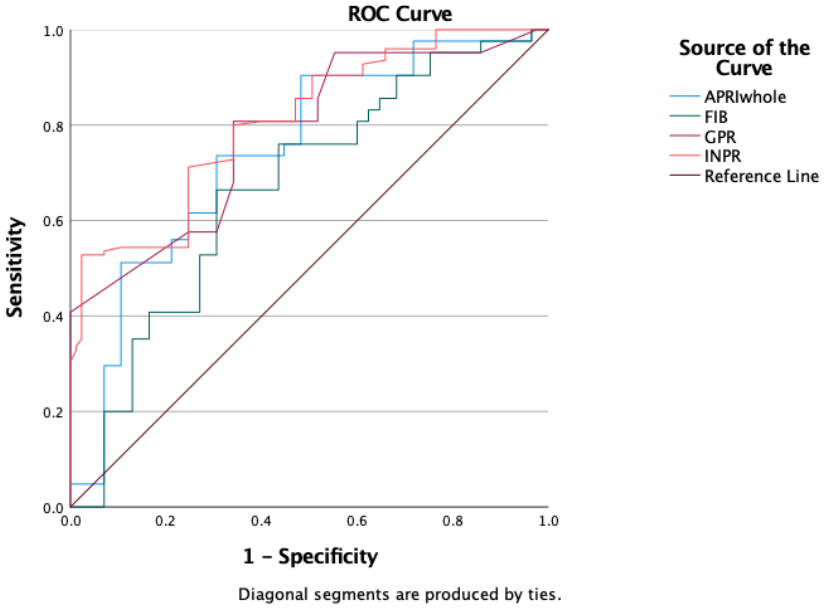


Figure: Area under ROC curve for INPR, GPR, APRI and FIB-4 is 0.807 (p≤0.001), 0.782 (p≤0.001), 0.744 (p≤0.001) and 0.699 (p≤0.001) respectively

DISCUSSION

The findings of this study provide a comprehensive evaluation of four widely used non-invasive fibrosis indices, highlighting the diagnostic superiority of INR to Platelet Ratio (INPR) followed closely by Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR) in predicting advanced liver fibrosis among patients with chronic hepatitis C virus (HCV) infection. The ability of these indices to accurately detect fibrosis progression has significant clinical implications, allowing for early intervention and optimized disease management (13). The observed high AUROC of INPR (0.807) underscores its diagnostic reliability, as it effectively integrates hepatic dysfunction indicators, including coagulation abnormalities and thrombocytopenia. Since INR reflects hepatic synthetic function and platelet count serves as a surrogate marker for portal hypertension, their combination provides a robust predictive value for advanced fibrosis. GPR, with an AUROC of 0.782 and an exceptional sensitivity of 95.2%, emerged as an effective rule-out tool, ensuring that patients with low GPR values are unlikely to have advanced fibrosis. The predictive value of GPR has been consistently supported by previous research, particularly in populations with viral hepatitis. The study findings reaffirm its clinical applicability, particularly in settings where invasive procedures are not feasible (14,15).

Aspartate Aminotransferase to Platelet Ratio Index (APRI) demonstrated moderate diagnostic accuracy, with an AUROC of 0.744, a high sensitivity (90.4%), but lower specificity, making it susceptible to false-positive results. While APRI has been widely endorsed in international guidelines, its moderate specificity raises concerns about its reliability in accurately differentiating between fibrosis stages in certain populations. The lower performance of APRI in this study aligns with findings from previous research, which reported variations in its diagnostic strength based on patient demographics and disease severity. Despite its limitations, APRI remains a useful tool due to its simplicity and accessibility, particularly in resource-limited settings (16). The Fibrosis-4 (FIB-4) index, although widely utilized, demonstrated the lowest AUROC (0.669), indicating weaker predictive accuracy in detecting advanced fibrosis. Its reliance on age as a parameter may introduce variability across different patient cohorts, which could explain the observed lower performance. Additionally, FIB-4 has shown greater reliability in distinguishing mild from moderate fibrosis rather than detecting more advanced stages. The findings suggest that while FIB-4 remains a valuable fibrosis assessment tool, its lower specificity and sensitivity in advanced fibrosis detection warrant cautious interpretation (17,18).

A major strength of this study lies in its direct comparison of multiple fibrosis indices within a single cohort, providing a standardized evaluation of their diagnostic accuracy. The non-invasive nature of these indices enhances their clinical utility, offering accessible and cost-effective alternatives to liver biopsy for fibrosis assessment. Additionally, the study utilized shear wave elastography (SWE) as the reference standard, a validated imaging modality known for its reliability in fibrosis staging. The findings contribute to the growing

body of evidence supporting the integration of non-invasive biomarkers in clinical practice, particularly in HCV management (19). However, several limitations should be acknowledged. The study was conducted at a single center, which may limit the generalizability of the findings to broader populations with varying demographic and clinical characteristics. Differences in genetic predisposition, comorbid conditions, and healthcare accessibility could influence the performance of these fibrosis indices in other settings. The reliance on SWE as the reference standard, while widely accepted, may not be as definitive as histopathological evaluation through liver biopsy. Although liver biopsy is invasive and associated with complications, it remains the gold standard for fibrosis assessment in certain clinical scenarios. Additionally, while the sample size was sufficient for statistical analysis, a larger multicenter study could provide a more comprehensive evaluation of these indices across diverse populations. Further research should also explore the impact of gender, comorbidities, and baseline liver function on the predictive accuracy of these indices to refine their clinical applicability (20). The findings reinforce the role of INPR and GPR as valuable diagnostic tools for predicting advanced fibrosis in HCV patients, with INPR demonstrating the highest accuracy and GPR serving as a highly sensitive rule-out test. APRI and FIB-4, while still useful, exhibited moderate diagnostic performance and should be interpreted cautiously in clinical decision-making. The non-invasive nature of these indices makes them particularly advantageous for large-scale screening and disease monitoring, especially in settings where liver biopsy is not readily available. Future studies with larger, multicenter cohorts and long-term follow-up data are needed to further validate these findings and establish standardized cutoff values tailored to specific populations.

CONCLUSION

This study highlighted the superior diagnostic performance of INR to Platelet Ratio (INPR) and Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR) in predicting advanced liver fibrosis among patients with chronic hepatitis C virus infection. INPR emerged as the most reliable non-invasive marker, offering a strong predictive value for fibrosis assessment, while GPR, with its high sensitivity, proved to be a valuable tool for ruling out advanced fibrosis. The findings underscore the clinical significance of these indices as accessible and cost-effective alternatives to invasive procedures, facilitating early detection and improved disease management. Integrating these markers into clinical practice could enhance the accuracy of fibrosis screening and risk stratification, ultimately optimizing patient care and treatment outcomes. Future research should focus on refining fibrosis prediction models and exploring their applicability in broader populations to further strengthen their role in routine hepatology practice.

AUTHOR CONTRIBUTIONS

Author	Contribution
Abdul Wahid Balouch	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Nida Rasool	Methodology, Investigation, Data Curation, Writing - Review & Editing
Ali Hyder	Investigation, Data Curation, Formal Analysis, Software
Vijesh Kumar	Software, Validation, Writing - Original Draft
Raja Taha Yaseen Khan	Formal Analysis, Writing - Review & Editing
Abbas Ali Tasneem	Writing - Review & Editing, Assistance with Data Curation
Nasir Hasan Luck	Investigation, Data Curation, Formal Analysis, Software
Huraira Ali	Software, Validation, Writing - Original Draft
Syeda Maryam Mehdi	Formal Analysis, Writing - Review & Editing
Abdullah Nasir	Writing - Review & Editing, Assistance with Data Curation

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