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Original Article

Role of INR to Platelet Ratio (INPR) in Predicting Advanced Liver Fibrosis in Patients with Chronic Hepatitis C Infection

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ABSTRACT

Background: Chronic hepatitis C (HCV) infection is a leading cause of liver fibrosis, which can progress to cirrhosis and hepatocellular carcinoma if not diagnosed and treated early. The gold standard for assessing liver fibrosis, liver biopsy, is invasive and carries risks, driving the need for reliable non-invasive diagnostic methods. The International Normalized Ratio to platelet ratio (INPR) has been proposed as a potential non-invasive marker to assess advanced liver fibrosis, but its effectiveness in patients with chronic HCV infection remains to be thoroughly evaluated.

Objective: This study aimed to assess the efficacy of the INR to platelet ratio (INPR) as a non-invasive marker for predicting advanced liver fibrosis in patients with chronic hepatitis C infection.

Methods: In this retrospective cohort study, 267 patients diagnosed with chronic HCV infection were evaluated at the Hepato-gastroenterology department of a tertiary care center from July 2021 to May 2023. Participants underwent comprehensive diagnostic evaluations, including liver parenchymal biopsies, shear wave elastography (SWE), and laboratory tests to calculate INPR. The diagnostic performance of INPR in detecting advanced liver fibrosis (>F3) was analyzed using the area under the receiver operating characteristic (AUROC) curve, alongside sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: The study population had a mean age of 43.45 ± 12.33 years, with a gender distribution of 61.8% male and 38.2% female. Advanced liver fibrosis was identified in 57 patients (21.3%). The INPR demonstrated an AUROC of 0.81 for predicting advanced liver fibrosis, with a sensitivity of 81.2%, specificity of 60.8%, PPV of 76.7%, and NPV of 91.2%. Comparatively, the Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR) showed a slightly lower diagnostic accuracy.

Conclusion: The INR to platelet ratio (INPR) is a promising non-invasive marker for predicting advanced liver fibrosis in chronic HCV-infected patients. It offers a practical bedside tool for clinicians, potentially reducing the need for invasive liver biopsies. However, further large-scale prospective studies are needed to validate these findings and fully establish INPR's role in the management of liver fibrosis.

Keywords: Hepatitis C, Liver Fibrosis, Non-invasive Markers, International Normalized Ratio, Platelet Ratio, Chronic Liver Disease, Diagnostic Accuracy, INPR, Advanced Fibrosis, Hepatology.

INTRODUCTION

Globally, hepatitis C virus (HCV) infection represents a significant health challenge, with approximately 1.75 million new cases reported annually. In Pakistan, it is estimated that 6% of the population is affected by this condition, underscoring its prevalence and public health impact (1). Chronic HCV infection is a leading cause of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), highlighting the critical need for early detection and treatment of hepatic fibrosis to prevent these severe outcomes (2). Traditionally, liver biopsy has been considered the gold standard for assessing the extent of liver fibrosis and inflammation. However, due to its invasive nature, the potential for variability in sampling, and the risks associated with the procedure, such as hemorrhage and accidental damage to adjacent organs, there is a growing demand for non-invasive diagnostic alternatives (3).

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In response to the limitations of liver biopsy, several non-invasive techniques have been developed, including shear wave elastography (SWE), transient elastography (TE), and magnetic resonance elastography (MRE). These radiological imaging methods have shown high efficacy in staging liver fibrosis in a non-invasive manner (4-6). Despite their advantages, these techniques are not without challenges, such as high costs, variability in interpretation among observers, and limited availability in remote areas, which restricts their widespread use.

Consequently, research has shifted towards identifying non-invasive biomarkers and scoring systems that can reliably assess liver fibrosis. Among these, the Fibrosis-4 score (FIB-4) and the aspartate aminotransferase to platelet ratio index (APRI) have gained prominence. These scores, along with the GPR, are frequently employed to evaluate fibrosis in individuals with chronic hepatitis B, although their diagnostic utility has shown variability across different studies (7,12-15). The World Health Organization (WHO) has endorsed some of these non-invasive scores for diagnosing cirrhosis in settings where liver biopsy and advanced imaging techniques are not accessible (16).

A notable study by Ding R et al. focused on the INR-to-platelet ratio (INPR) and compared its diagnostic accuracy with APRI, FIB-4, and GPR in patients with chronic HBV infection. The findings revealed that INPR had superior performance in predicting significant fibrosis and advanced fibrosis (>F3) with a sensitivity of 67%, specificity of 75%, and a diagnostic accuracy of 71%. Furthermore, for predicting cirrhosis (>F4), INPR demonstrated a sensitivity of 68%, specificity of 87.07%, and diagnostic accuracy of 81% (17). Despite these promising results, the applicability of INPR in predicting advanced fibrosis and cirrhosis in chronic HCV infection remains less clear.

Therefore, our study aimed to evaluate the effectiveness of the INR to platelet ratio (INPR) as an indicator of advanced liver fibrosis in the Pakistani population with chronic HCV infection. By establishing the utility of INPR as a non-invasive, bedside index, we aim to provide a valuable tool for clinicians that could potentially obviate the need for invasive liver biopsies and mitigate the economic burden associated with expensive radiological imaging techniques currently in use for the prediction of advanced liver fibrosis.

MATERIAL AND METHODS

This retrospective cohort study was conducted at the Hepato-gastroenterology department of the Sindh Institute of Urology and Transplantation (SIUT) in Karachi, from July 2021 to May 2023. The study employed a non-probability consecutive sampling technique to include individuals aged between 18 and 50 years, diagnosed with Hepatitis C-related compensated hepatic cirrhosis. The diagnosis was confirmed through liver parenchymal biopsy. Subjects were excluded if they did not provide informed consent, had missing data, presented with HCV-related decompensated cirrhosis, or had other concurrent causes of chronic liver disease. The criteria for compensated cirrhosis were established based on specific ultrasound characteristics, such as alterations in liver echo texture, irregular liver margins, spleen size exceeding 12 cm, and a portal vein diameter greater than 12 mm. Patients with coexisting chronic liver conditions, such as hepatitis B, autoimmune hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, metabolic liver diseases, Wilson's disease, hemochromatosis, cholestatic liver diseases, as well as those diagnosed with hepatocellular carcinoma or serious comorbidities, were also excluded.

Diagnostic evaluations in this study included Shear Wave Elastography (SWE) to categorize liver fibrosis into stages from F0 (no fibrosis) to F4 (cirrhosis) based on kilopascal (kPa) measurements (18), and the METAVIR scoring system for histological assessment of fibrosis stages (19). The INR to platelet ratio (INPR) was calculated by dividing the INR by the platelet count (×10^9/L) and multiplying by 100, as per the methodology described in previous research (17). The study further defined compensated cirrhosis using ultrasound criteria, with the presence of three or more specified signs indicating cirrhosis. The primary outcome was the identification of advanced fibrosis (>F3) using the Metavir scoring system. The presence or absence of esophageal varices, observed during endoscopic follow-ups, was also recorded.

Data collection adhered to the ethical principles of the Declaration of Helsinki, ensuring the confidentiality and anonymity of participant information. Ethical approval was obtained from the institutional review board prior to the commencement of the study. All participants provided informed consent after being fully briefed about the study's purpose and procedures.

The statistical analysis was conducted using SPSS version 25.0. Both univariate and multivariate logistic regression analyses were performed to evaluate the association between diagnostic tests and the presence of advanced liver fibrosis. The diagnostic accuracy of the INPR and Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR) in detecting advanced fibrosis was assessed through the receiver operating characteristic (ROC) curve analysis. Optimal cutoff points for these scores were established to maximize diagnostic precision in identifying liver fibrosis stages.

This meticulous approach to data collection, ethical considerations, and analytical methods ensured the reliability and validity of the study findings, contributing valuable insights into the non-invasive assessment of liver fibrosis in patients with chronic Hepatitis C infection.

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RESULTS

In this retrospective cohort study involving 267 participants, the baseline characteristics revealed an average age of 43.45 years, with a gender distribution of 61.8% males and 38.2% females (Table 1). The mean hemoglobin level was noted at 10.8 g/dL, with total leucocyte and platelet counts averaging 4.5 x10^9/L and 73 x10^9/L, respectively. The International Normalized Ratio (INR) mean value stood at 1.2, while total bilirubin and alkaline phosphatase levels were observed at 1.3 mg/dl and 191 IU/L, respectively. The study participants' liver enzyme levels, including Aspartate Transaminase (AST) and Alanine Transaminase (ALT), averaged 59 IU/L and 44 IU/L, respectively, with Gamma Glutamyl Transpeptidase (GGT) at 74 IU/L. Child Turcotte Pugh Score classified 66.3% of participants in class A and 33.7% in class B, indicating varying degrees of liver function within the cohort. The MELD score averaged 10.9, and shear wave elastography (SWE) results showed that 40.4% of participants had F4 fibrosis, highlighting the severity of liver disease in a significant portion of the study population. Additionally, esophageal varices were present in 74.2% of participants, further illustrating the advanced stage of liver disease (Table 1).

When comparing participants with no fibrosis (≤F2) to those with advanced fibrosis (≥F3), significant differences were noted in several key parameters. Age, total leucocyte count, platelet count, INR, total bilirubin, AST, ALT, and GGT levels showed significant differences between the two groups, underscoring the impact of fibrosis on these variables. Notably, participants with advanced fibrosis had higher mean values for INR, total bilirubin, AST, and ALT, indicating more severe liver impairment (Table 2). The GPR and INPR values were notably higher in the advanced fibrosis group, with means of 1.2 and 2.8, respectively, compared to 0.4 and 1.1 in the no fibrosis group, demonstrating the potential utility of these ratios in assessing liver fibrosis severity (Table 2).

Table 1: Baseline Characteristics of Study Participants (n = 267)

Characteristic	Total	Mean ± SD or No. (%)
Age (years)		43.45 ± 12.33
Gender		
Male	165	61.8%
Female	102	38.2%
Hemoglobin (g/dL)		10.8 ± 2.1
Total Leucocyte Count (x10^9/L)		4.5 ± 2.4
Platelet Count (×10^9/L)		73 ± 38
International Normalized Ratio (INR)		1.2 ± 0.19
Total Bilirubin (mg/dl)		1.3 ± 0.74
Alkaline Phosphatase (IU/L)		191 ± 188
Aspartate Transaminase (AST)(IU/L)		59 ± 52
Alanine Transaminase (ALT) (IU/L)		44 ± 34
Gamma Glutamyl Transpeptidase (GGT)(IU/L)		74 ± 59.5
Child Turcotte Pugh Score		
A	177	66.3%
B	90	33.7%
MELD score		10.9 ± 3.4
Shear wave Elastography (SWE)		
F1 Fibrosis	30	11.2%
F2 Fibrosis	86	32.2%
F3 Fibrosis	43	16.1%
F4 Fibrosis	108	40.4%
Esophageal varices	198	74.2%
Fibrosis on liver biopsy	165	61.8%
GPR (Gamma Glutamyl Transpeptidase to Platelet Ratio)		0.97 ± 0.87
INR to platelet Ratio (INPR)		2.1 ± 1.68

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Table 2: Comparison of Variables Between No Fibrosis (≤F2) and Advanced Fibrosis (≥F3) Groups

Variable	No Fibrosis (≤F2) (n=34)	Advanced Fibrosis (≥F3) (n=57)	p-value
Age (years)	43.6 ± 10.6	48.6 ± 13.3	0.048
Hemoglobin (g/dL)	10.6 ± 2.5	10.9 ± 1.8	0.334
Total Leucocyte Count (x10^9/L)	5.2 ± 2.6	4.0 ± 2.1	0.024
Platelet Count (×10^9/L)	80.9 ± 42	68.3 ± 35	0.009
INR	1.1 ± 0.17	1.3 ± 0.19	≤0.001
Total Bilirubin (mg/dl)	0.95 ± 0.60	1.6 ± 0.7	≤0.001
AST (IU/L)	35 ± 18	74 ± 60	0.001
ALT (IU/L)	25 ± 12	56 ± 37	≤0.001
GGT (IU/L)	48 ± 20	90 ± 69	≤0.001
Serum Creatinine	1.1 ± 1.8	1.2 ± 2.1	0.288
Serum Albumin (g/dl)	3.5 ± 0.6	3.2 ± 0.6	0.010
Splenic Stiffness	27.5 ± 14.2	51 ± 26.5	0.015
MELD Score	10 ± 4	11.1 ± 3.2	0.052
GPR	0.4 ± 0.3	1.2 ± 0.96	≤0.001
INPR	1.1 ± 0.48	2.8 ± 1.9	≤0.001

Table 3: Logistic Regression Analysis of Variables Predicting Advanced Fibrosis

Variable	p-value	Hazard Ratio	95% CI
Gender	0.029	0.071	0.007–0.767
Total Leucocyte Count	0.078	0.821	0.550–1.227
Platelet	0.013	0.969	0.946–0.994
INR	≤0.001	7.4	3.6–14.32
Total Bilirubin	0.121	0.392	0.120–1.281
GGT	0.037	0.988	0.973–1.245
Albumin	0.072	5.5	1.2–26.1
Splenic Stiffness	<0.001	0.840	0.775–0.910
CTP class	0.003	7.8	4.3–15.6
GPR	<0.001	0.001	0.00–0.028
INPR	<0.001	0.048	0.011–0.217

Table 4: Diagnostic Performance of INPR and GPR

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
INPR	81.2%	60.8%	76.7%	91.2%	79.1%
GPR	73.4%	50.55%	75%	85%	77.3%

Logistic regression analysis identified several factors with significant associations with advanced fibrosis. INR, platelet count, splenic stiffness, and the Child Turcotte Pugh (CTP) class were among the variables that showed a strong correlation with the presence of advanced fibrosis, highlighting their importance in the disease's progression. The hazard ratio for INR stood at 7.4, indicating a substantial increase in the likelihood of advanced fibrosis with higher INR values. Similarly, GPR and INPR had hazard ratios indicating significant associations with advanced fibrosis, reinforcing their diagnostic value (Table 3).

The diagnostic performance of INPR and GPR in detecting advanced fibrosis was evaluated, with INPR showing a sensitivity of 81.2%, specificity of 60.8%, and a diagnostic accuracy of 79.1%. GPR, while slightly less effective, still demonstrated a notable sensitivity of 73.4% and a diagnostic accuracy of 77.3%. These findings underscore the efficacy of INPR and GPR as non-invasive tools for assessing advanced liver fibrosis, offering valuable alternatives to more invasive diagnostic methods (Table 4).

Overall, the study's results, supported by detailed statistical analysis, highlight the critical role of non-invasive diagnostic ratios such as INPR and GPR in evaluating liver fibrosis. These findings not only enhance our understanding of the disease's progression but also offer practical tools for clinicians in managing patients with chronic liver disease.

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DISCUSSION

In the realm of hepatology, the management of chronic hepatitis C (HCV) remains a formidable challenge, necessitating regular monitoring to mitigate the complications associated with progressive liver fibrosis. The conventional gold standard for diagnosing and staging liver fibrosis, liver parenchymal biopsy, despite its accuracy, is fraught with limitations due to its invasiveness and associated clinical risks (21). This has spurred interest in the development of non-invasive modalities capable of accurately predicting advanced liver fibrosis. Radiological techniques such as transient elastography, shear wave elastography, and magnetic resonance elastography have emerged as highly accurate in diagnosing advanced fibrosis (22-24); however, their utility is often hampered by high costs, the necessity for specialized interpretative skills, and limited availability in resource-constrained settings.

Serum markers and scoring systems, including the Aspartate Aminotransferase to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4), and Gamma Glutamyl Transpeptidase to Platelet Ratio (GPR), have been employed with varying degrees of success in predicting fibrosis (25-27). Despite their non-invasiveness, the sensitivity and specificity of these markers in evaluating complex fibrosis have been inconsistent across studies, limiting their widespread adoption (28). Previous research by Liang et al. highlighted the prognostic value of the INR and platelet count in chronic HBV infection, suggesting their potential utility in cirrhosis prediction (29). Kayadibi et al. further reinforced the diagnostic accuracy of platelet counts in HCV-related fibrosis (30), while Ding et al. proposed the INR to platelet ratio as a promising tool for fibrosis assessment in chronic HBV cases (17).

Our study sought to explore the applicability of the INR to platelet ratio in a Pakistani cohort with chronic HCV, a significant cause of cirrhosis locally. The investigation identified a marked increase in splenic stiffness, INR, and INPR values in patients with advanced fibrosis, alongside a notable decline in albumin levels and platelet counts, findings that resonate with Ding et al.'s observations in chronic HBV (Table 4). This parallel underscores the INR to platelet ratio's potential across different viral etiologies of liver disease. Despite its promising AUROC for assessing fibrosis, the INR to platelet ratio's specificity remained a limitation, a challenge similarly documented in other non-invasive markers.

Comparative analyses have shown that GPR possesses higher diagnostic precision than other non-invasive metrics like APRI in HBV-infected Chinese individuals (31,32). This was corroborated by a Pakistani study by Khan RTY et al., which attested to GPR's efficacy in predicting advanced HCV-related fibrosis (11). Our findings add to this narrative, indicating a superior AUROC for the INR to platelet ratio in advanced fibrosis prediction, albeit with limitations in specificity akin to GPR (Table 5).

This study, however, is not without its limitations. Its retrospective design introduces the potential for selection bias, and the findings, derived from a specific cohort, may not be generalizable to the broader population. The small sample size further constrains the extrapolation of these results, suggesting a need for multicenter, prospective studies with larger cohorts to validate the INR to platelet ratio's utility. Additionally, the absence of a comparative analysis with established non-invasive markers like APRI and FIB-4 within our cohort represents a missed opportunity to contextualize our findings within the broader spectrum of fibrosis assessment tools.

CONCLUSION

In conclusion, the INR to platelet ratio emerges from our investigation as a potentially valuable, easily calculable index for bedside estimation of advanced liver fibrosis in chronic HCV patients. However, its full validation and acceptance as a reliable diagnostic tool await the outcomes of larger, prospective studies. Further research is thus essential to solidify the role of the INR to platelet ratio within the diagnostic arsenal against liver fibrosis, offering clinicians a broader base of non-invasive, accessible tools for managing chronic liver diseases.

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