Original Article

The Role of Neutrophil-Lymphocyte Ratio (NLR), Red Blood Cell Distribution Width (RDW) and Red Blood Cell Distribution Width-Platelet Ratio (RPR) in Assessment of Severity of Liver Damage in Cirrhotic Patients

R Akhter[1], SH Mollick2, A Wadud[3], NC Roy[4], A Rahut[5], MM Saleheen[6]

Abstract

Background: Liver cirrhosis is a major worldwide health issue, marked by ongoing liver damage that leads to the development of fibrosis and regenerative nodules. The conversion of compensated to decompensated cirrhosis indicates an unwanted outcome. This necessitates tools to assess severity and guide clinical management. This study evaluates the utility of hematological indices Neutrophil-Lymphocyte Ratio (NLR), Red Cell Distribution Width (RDW), and RDW-to-Platelet Ratio (RPR) as non-invasive markers of cirrhosis severity, compared to established scoring systems like Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver disease (MELD).

Materials and Methods: A cross-sectional type of observational study was conducted on 100 cirrhotic patients at Khulna Medical College, Khulna (KMCH), Khulna. Data was collected on selected age group, their clinical history, and laboratory values. Hematological indices (NLR, RDW, RPR) were compared against CTP scores to evaluate diagnostic accuracy. Statistical analyses were done using SPSS-26, and a p-value < 0.05 is considered significant.

Results: Among the patients, RPR demonstrated the highest diagnostic accuracy (AUC=0.805, sensitivity=76.5%, specificity=53.3%) for cirrhosis severity, followed by RDW (AUC=0.780). NLR showed limited diagnostic value (AUC=0.541). Elevated RDW and RPR correlated significantly with advanced cirrhosis ($p<0.001$). Patients predominantly presented with ascites (57%), and hepatitis B was the leading etiology (55%).

Conclusion: RPR and RDW are promising non-invasive markers for assessing liver cirrhosis severity, with RPR being the most reliable. Incorporating these indices into traditional scoring systems could enhance diagnostic accuracy and risk stratification.

Keywords: Neutrophil to lymphocyte ratio, Red blood cell distribution width, Red blood cell distribution width platelet ratio, Cirrhosis of liver, Predictor.

Authors:

Rehena Akhter, MBBS, MCPS(Medicine), MD(Gastroenterology), Medical Officer, Department of Gastroenterology, Khulna Medical College Hospital, Khulna, Email: rehenalovely@gmail.com

Shahidul Hassan Mollick, MBBS, MD (Gastroenterology), Professor and Head of Department of Gastroenterology, Khulna Medical College Hospital, Khulna, mollick.sh@gmail.com.

Abdul Wadud, MBBS, MD (Gastroenterology), Registrar, Department of Gastroenterology, Khulna Medical College Hospital, Khulna, Email: drwadud40@gmail.com.

Nikhil Chandra Roy, MBBS, MD (Gastroenterology), Assistant Professor, Bangladesh Medical College and Hospital, Dhaka, Email: nroy47015@gmail.com.

Antora Rahut, MBBS, MD (Gastroenterology), Medical Officer, Department of Gastroenterology, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Email: antora37@yahoo.com.

Muhammad Misqatus Saleheen, MBBS, DDV (Dermatology and venerology), Junior Consultant, Department of Skin and VD, Khulna Medical College Hospital, Khulna,
Email: muhammadsaleheen129644@gmail.com.

Corresponding Author:
Rehena Akhter, Medical officer, Department of Gastroenterology, Khulna Medical College Hospital, Khulna, Bangladesh,
Email: rehenalovely@gmail.com, Phone:+8801671407954.

Introduction:

Liver cirrhosis is a major public concern responsible for significant morbidity and mortality. It is associated with 2.4% of global deaths in 2019. The 2017 Global Burden of Disease (GBD) Study found 112 million people globally were living with compensated cirrhosis, reflecting an age-standardized worldwide prevalence of 1,395 cases per 100,000 individuals.[1]

The primary reasons for liver cirrhosis include chronic hepatitis B, alcoholism, chronic hepatitis C, and metabolic dysfunction-associated steatotic liver disease.2,3 In Bangladesh, the prevalence of hepatitis B virus (HBV) averages 4%-7% in the communities and is the predominant aetiology of chronic liver disease in Bangladesh. 4-6

All chronic liver diseases have the potential to develop into cirrhosis. During this progression, the fibrotic process occurs in several stages, involving abnormal collagen build-up that alters both the composition and amount of the intercellular matrix. Cirrhosis represents a structural alteration of the liver, defined by the formation of regenerative nodules, and indicates a late stage of liver disease. Once cirrhosis reaches an advanced stage, treatment options become very limited.2 Each year, about 5–12% of patients transition from a compensated stage to a decompensated stage of liver disease, which may involve complications such as ascites, hepatic encephalopathy, or variceal bleeding.1 Decompensated cirrhosis is generally associated with a limited survival time of 3 to 5 years. In this scenario, a liver transplant is recommended in the absence of contraindications and needs to be evaluated. It is recommended that a different scoring system should be used to identify and predict the stage of liver failure. As an instance, Child-Turcotte Pugh is generally scored based on different variables, which include bilirubin level, albumin, INR, ascites, and hepatic encephalopathy. In addition to that, the Model for End-stage Liver Disease (MELD) can help us determine stages of liver failure. This can also help to prioritize the patient eligible for liver transplantation, and influence their health-related quality of life and the outcome.[7]

Recently, there has been a growing field to find simple, noninvasive, and cost-effective biomarkers that can reflect the extent of liver injury. Among the emerging biomarkers, hematological indices derived from complete blood counts have gained potential. Necroinflammation is frequently observed in individuals with advanced liver cirrhosis. The neutrophil-to-lymphocyte ratio (NLR) serves as a marker of systemic inflammation, illustrating the interaction between two key immune mechanisms.[8-10] On the other hand, in advanced cirrhotic patients, elevated RDW levels and decreased platelet counts reflect impaired erythropoiesis due to chronic disease and thrombocytopenia from splenic sequestration, respectively.[11] Thus, the neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW), and RDW-to-platelet ratio (RPR) are increasingly being studied for their association with systemic inflammation, disease severity, and clinical outcomes in various inflammatory diseases, malignancies, and hepatic conditions.[10, 12-16]

This study proposed to explore the significance of NLR, RDW, and RPR in the assessment of liver damage in patients with cirrhosis. By analyzing their correlation with established markers of liver injury, we aimed to evaluate their utility as adjuncts in the diagnostic workup and monitoring of cirrhotic patients.

Materials and Methods:

This cross-sectional type of observational study was conducted at Inpatient Department of Gastroenterology and the Department of Medicine, Khulna Medical College Hospital (KMCH), Khulna, Bangladesh, over twelve months, extending from November 2023 to October 2024.

The study included all adult patients (over 18 years old) diagnosed with liver cirrhosis who were admitted to the Department of Gastroenterology at KMCH. A purposive nonprobability sampling technique was performed. Patients with space-occupying lesions in the liver, liver transplant before admission, hematological disorders such as iron deficiency anemia, myeloproliferative disorders, myelodysplastic syndrome, and recent blood transfusion (within 3 months) were excluded. Informed written consent was taken from the patients before they participated in the study. A total of 100 patients were finally enrolled in this study.

Detailed clinical information was taken from each patient and documented on a pre-structured questionnaire. Liver cirrhosis was diagnosed based on clinical, laboratory, radiological, and endoscopic methods. Laboratory parameters were obtained, including complete blood count (CBC), S. albumin, S. bilirubin, prothrombin time (PT), international normalized ratio (INR), S. creatinine, and viral markers (Hepatitis B surface antigen and Anti Hepatitis C virus). The CBC was performed using an automated hematology analyzer. Hematological indices, such as NLR (Neutrophil count / Lymphocyte count), RDW (References range: 11.5-14.5%), and RPR [RDW% / platelet count (×109/ L)] were calculated from the CBC. The severity of cirrhosis was assessed using both the Child-Turcotte-Pugh (CTP) score and the MELD score. After collection, the overall data was carefully reviewed, coded, and revised to ensure accuracy and completeness.

Data analysis was carried out using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables, including age and laboratory results, were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were summarized as frequencies and percentages. Patients were grouped into Child-Turcotte-Pugh (CTP) classes A, B, and C to assess disease severity. Group comparisons were conducted using independent t-tests or Mann-Whitney U tests for continuous data, and Chi-square or Fisher's exact tests for categorical variables. The relationship between hematological markers (NLR, RDW, RPR) and the severity of cirrhosis was analyzed using Pearson or Spearman correlation coefficients. Receiver Operating Characteristic (ROC) curve analysis was employed to assess the diagnostic performance of these indices, calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the Area Under the Curve (AUC). A p-value less than 0.05 was considered statistically significant, reinforcing the validity of the results.

An ethical review committee of Khulna Medical College, Khulna, cleared the ethical issue, References no. KMC/ERC/106 dated: 16 April 2023 and conducted following the Declaration of Helsinki for human study.

Results:

Of the 100 patients enrolled in this cross-sectional study, 68% were male and 32% were female. The mean age was 50.2 ± 13.6 years, with the majority (44%) falling within the 40 to 60-year age group. Chronic hepatitis B was the most common cause of cirrhosis (55%), followed by Non-B Non-C causes (44%) and alcoholism (1%). About 85% of patients were in a decompensated state (CTP B and C). Ascites (57%) was the most common clinical presentation, followed by variceal bleeding (27%), jaundice (15%), and hepatic encephalopathy (6%) (Table 1).

Table 1: Distribution of study population according to demographic profile (N=100)

Characteristics	Number(%)
Age	
<40 years	29 (29%)
40-60 years	44 (44%)
> 60 years	27(27%)
Mean±SD	50.2±13.6
Gender	
Male	68 (68%)
Female	32 (32%)
Aetiology	
HBV	55 (55%)
Alcohol	1 (1%)
Non B, Non C	44 (44%)
Clinical Symptoms	
Ascites	57 (57%)
Variceal bleeding	27 (27%)
Jaundice	15 (15%)
Hepatic encephalopathy	6 (6%)
Child Turcotte Pugh (CTP) scores	
CTP A	15 (15%)
CTP B	53 (53%)
CTP C	32 (32%)

Table 2 demonstrates S. Bilirubin, ESR, RDW, RPR, and MELD score were significantly higher and S. Albumin and platelet count were significantly lower in class B and C in comparison to class A.

Table 2: Laboratory parameters of the studied population with compensated and decompensated cirrhosis (N=100)

	Class A (n=15) mean±SD	Class B and C (n=85) mean±SD	p-value
S. Bilirubin (mg/dL)	0.92 ± 0.11	4.66 ± 6.98	<0.001**
S. Albumin (g/dL)	20.04 ± 16.34	7.56 ± 8.85	<0.001**
Hemoglobin (g/dL)	10.93 ± 1.20	9.80 ± 2.24	0.061*
TC (cells/mm³)	7863.33 ± 2847.10	9453.18 ± 6291.29	0.340*
Neutrophil (%)	61.39 ± 8.21	63.85 ± 14.20	0.517*
Lymphocyte (%)	29.65 ± 5.98	24.93 ± 10.36	0.090*
NLR	3.13 ± 1.61	3.59 ± 3.39	0.610*
Platelet (cells × 10³/µL)	180.33 ± 43.79	141.35 ± 55.61	0.012*
S. Creatinine (mg/dL)	1.10 ±0.14	1.20 ± 0.43	0.391*
ESR (mm in 1st hour)	28.47 ± 21.52	50.08 ± 26.82	0.004*
PT (seconds)	13.93 ± 1.67	16.32 ± 7.44	0.221*
INR	5.23 ± 5.87	5.91 ± 6.36	0.695*
RDW (%)	14.87 ± 2.69	17.41 ± 3.29	0.006*
RPR	0.09 ± 0.02	0.15 ± 0.09	0.007*
MELDscore	7.79 ± 0.9	14.90 ± 4.81	<0.001*

p-value was determined by *Independent sample t test and **Mann-Whitney test.

[ESR, erythrocyte sedimentation rate; PT, prothrombin time; INR, international normalized ratio; NLR, neutrophil to lymphocyte ratio; RDW, red blood distribution width; RPR, red blood cell distribution width to platelet ratio; MELD, model for end-stage liver disease.]

RDW (%) and RPR level significantly increased with the increased severity of the disease. In Class C, RDW (%) was significantly higher in comparison to Class A and Class B.A significant difference was found between Class A and Class C CTP categories regarding RPR (Table 3).

Table 3: Comparison of NLR, RDW (%), and RPR among different severity of disease using CTP category (N=100)

	Class A	Class B	Class C	p-value*
	Mean±SD	Mean±SD	Mean±SD	
NLR	3.1±1.6	3.3±2.6	4.1±4.4	0.452
RDW (%)	14.9±2.7	16.6±3.2	$18.7\pm3.1^{\alpha\beta}$	<0.001
RPR	0.09±0.02	0.15±0.07	$0.16\pm0.11^{\alpha}$	0.018

*p-value was determined by Post Hoc analysis by Bonferroni test of One Way ANOVA test.

NLR, RDW (%), and RPR were all positively correlated with MELD score. But RDW (%) and MELD score showed significant correlation (Table 4, Figure 1).

Table 4: Correlation of NLR, RDW (%), and RPR with MELD score of the patients (N=100)

	MELD score	
	Correlation coefficient (r)	p-value*
NLR	0.103	0.153
RDW (%)	0.323	0.001
RPR	0.089	0.190

*p-value was determined by the Pearson correlation test.

[NLR, neutrophil to lymphocyte ratio; RDW, red blood distribution width; RPR, red blood cell distribution width to platelet ratio; MELD, model for end-stage liver disease.]

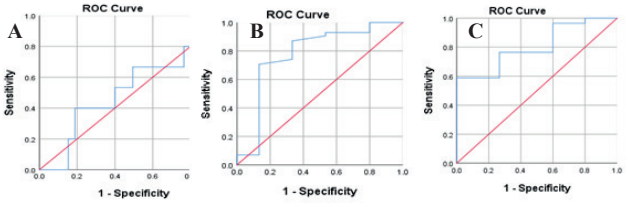

Figure 1: ROC curve analysis of NLR (A), RDW (%) (B), and RPR (C) in the prediction of cirrhosis severity based on CTP score.

In this study, RPR at a cut-off value of 0.10 showed a better marker, with the highest AUC (0.805), better sensitivity (76.5%), and strong PPV (90.3%). Although RDW at a cut-off value of 14.9 % also performs well and has slightly better specificity (74.1%), but a lower AUC (0.780) compared to RPR. NLR at a cut-off value of 2.5 with AUC (0.541) has the poorest performance as diagnostic accuracy (Table 5).

Table 5: Area under the curve, Diagnostic accuracy of NLR, RDW (%), and RPR in the prediction of severity of liver cirrhosis according to CTP score.

	Cut off value	AUC	95% CI	SN (%)	SP (%)	PPV (%)	NPV (%)	Accuracy	p-value
NLR	2.5	0.541	0.386-0.697	49.4	46.7	84	14	49	0.612
RDW (%)	14.9	0.780	0.625-0.934	74.1	66.7	92.6	31.3	73	0.001
RPR	0.10	0.805	0.705-9.04	76.5	53.3	90.3	28.6	73	<0.001

[AUC, area under curve; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval]

Discussion:

Liver cirrhosis develops gradually over time from chronic liver injury and is often characterized by irreversible fibrosis of liver tissue. As the disease progresses, it disrupts liver function and increases systemic inflammation, making the assessment of disease severity crucial for management and prognosis. This study was tailored to assess the diagnostic accuracy of RDW, RPR, and NLR in evaluating the severity of liver cirrhosis based on Child-Turcotte-Pugh (CTP) scoring.

In this study, most of the patients (71%) were aged 40 years or older, with a mean age of 50.2 ± 13.6 years. This finding is consistent with the study by Hossain et al., which involved patients aged between 22 and 106 years and reported a mean age of 52.33 years.[17] In the previous study by Sungkar et al., the mean age of the patients was 52.76±12.57 years, which was similar to the current study [9]. Another study conducted in Bangladesh, where the mean age was 59.05 ± 12.05 years among cirrhosis patients, which was slightly higher than the current study.[18] A study conducted in China, where the mean age of the cirrhosis patients was 47.23 ± 12.78 years, which was lower than the current study.[19] These differences may reflect regional demographic differences or healthcare accessibility variations.

A male predominance was observed among the patients, with 68% being male, as reported in a previous study. Similarly, out of 78 cirrhosis patients, 62 were male.18 Hossain et al. also found that the majority of cases were male (69.7%), with a male-to-female ratio of 1:0.44, which aligns with the findings of the current study.[17] Another study was conducted by Hong Zhao et al. among the liver cirrhosis patients of China also found a male predominance of 72%.20 This gender disparity likely reflects higher exposure to risk factors like HBV infection and alcohol consumption among males. But a study by Rahut et al. found slightly higher female patients with 52.7%, which may reflect differences in healthcare-seeking behavior or underlying etiological factors like autoimmune or metabolic causes more common in females.[18]

Among all the patients, 55% had HBV, 1% had liver cirrhosis due to alcohol, and 44% showed a Non-B Non-C cause. A previous study reported hepatitis B virus (HBV) as the most common cause of infection, responsible for 53.7% of cases, while 46.3% had no identifiable cause. These results are consistent with findings from other studies in Bangladesh that also recognize HBV as the leading cause of liver disease.[6,17] The low prevalence of alcohol-related cirrhosis (3%) is notable, reflecting cultural or policy-driven low alcohol consumption in the region.

In the present study, ascites was the most frequent clinical manifestation, observed in 57% of patients, followed by variceal bleeding (27%), jaundice (15%), and hepatic encephalopathy (6%). Similarly, a study conducted in Faridpur, Bangladesh, reported ascites in 49.4% of cases, gastrointestinal bleeding in 27%, peripheral edema in 24.7%, and encephalopathy in 21.3% of patients.[17] Previous studies also revealed that ascites as the leading symptom in cirrhosis-related hospitalizations.[5,6]

Among all the patients, 15% had a Class A CTP score, 53% had a Class B, and 32% had a Class C CTP score. Besides, a significant association of S. Bilirubin, S. Albumin, and platelet count with CTP classes repeats their role as critical indicators of cirrhosis severity, and these findings were consistent with other studies.[21,22]

CBC is a simple, inexpensive, readily accessible, and reproducible tool in all resource settings, usually done during the initial evaluation of all patients. The NLR, calculated from CBC, is a marker of systemic inflammation. In liver cirrhosis, the NLR reflects the heightened inflammatory milieu and immune dysregulation characteristic of advanced liver disease. Elevated neutrophil counts indicate a pro-inflammatory state, while lymphopenia reflects immune suppression, both of which are hallmarks of cirrhosis.[23] RDW is the measuring tool to estimate the variation in red blood cell size or anisocytosis, and is a routine parameter in the complete blood count. In cirrhotic patients, elevated RDW levels reflect the interplay of several pathological processes, including systemic inflammation, malnutrition, and impaired erythropoiesis due to chronic disease. The pro-inflammatory cytokines associated with cirrhosis, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), disrupt erythropoiesis and iron metabolism, contributing to increased RDW.24 RPR is a novel composite index combining RDW and platelet count,[25] two parameters frequently altered in cirrhosis. Thrombocytopenia, a hallmark of cirrhosis, results from splenic sequestration, reduced thrombopoietin production, and bone marrow suppression.[26]

In the current study, RPR and RDW are the best markers for severity assesment, with RPR having the highest AUC of 0.805 at a cutoff value of 0.10, demonstrating 76.5% sensitivity, 53.3% specificity, 90.3% positive predictive value (PPV), and 28.6% negative predictive value, along with 73% accuracy and a significant p-value (<0.001). RDW also performs well, with an AUC of 0.780 at a cutoff value of 14.9%, 74.1% sensitivity, 66.7% specificity, 92.6% PPV, and 31.3% NPV, achieving 73% accuracy and a p-value of 0.001. In contrast, NLR shows a lower severity assesment value with an AUC of 0.541 at a cutoff value of 2.5, 49.4% sensitivity, 46.7% specificity, 84% PPV, 14% NPV, and 49% accuracy, making it less effective compared to RPR and RDW. Hashemi et al. demonstrated that the NLR, with an optimal cut-off value of > 1.95, showed a sensitivity of 84.75% and specificity of 93.91% in predicting complications during a 1-year follow-up (AUC = 0.905, P < 0.0001).8 A previous study found that RDW and RPR levels were significantly higher in decompensated cirrhosis patients compared to those with compensated cirrhosis (all P < 0.001). The area under the curve (AUC) for NLR was 0.801, with a cut-off value of 2.06, demonstrating 71.7% sensitivity and 78.1% specificity. The AUC values for RDW and RPR were 0.815 (cut-off value: 15.5%; sensitivity: 76.1%; specificity: 75.0%) and 0.876 (cut-off value: 0.166; sensitivity: 93.5%; specificity: 75.0%), respectively. Both NLR, RDW, and RPR were significantly elevated and correlated with disease severity in HBV-related cirrhosis patients, with RPR emerging as the most reliable marker for assessing disease severity, followed by RDW(%).[24] Another study by Li et al. also revealed that liver cirrhosis was significantly associated with an increased RPR and area under the curve (0.821) of RPR levels, indicating that it has high diagnostic performance for predicting disease severity.19 Another study suggested that RPR and RDW are strong biomarkers for assessing disease severity in liver cirrhosis. Among these, RPR is highlighted as the most effective, with a higher sensitivity and AUC value compared to other biomarkers. RPR showed a high sensitivity of 93.5% and specificity of 75%, making it the best non-invasive biomarker for predicting complications in cirrhosis patients.[11]

In this study, a comparison of NLR, RDW (%) and RPR among different classes of CTP scores showed that RDW (%) and RPR levels significantly increased with the increased severity of disease. Besides, correlation analysis of NLR, RDW (%), and RPR with the MELD score was found positive in this study. However, only RDW (%) and MELD score showed a correlation with a p-value equal to 0.001 (r = 0.323).

A positive correlation with a significant p value was also observed between NLR, RDW and RPR with MELD scores, respectively ($r = 0.340$, $r = 0.425$, and $r = 0.464$).[24] In a similar study by HeQ et al. Correlation between NLR and CTP score was also obtained significantly ($r = 0.326$, $p = 0.008$ and $p < 0.001$ respectively) by other studies.[9,23]

In this current study, NLR showed the least diagnostic accuracy. The value of NLR could be influenced by certain factors like timing of blood sampling, ongoing treatment of subjects, renal dysfunction, hematological alterations due to hypersplenism in an advanced cirrhotic stage, and point time of approach of the cross-sectional study might limit the findings of the study. Therefore, future studies of larger sample sizes that consider confounding variables are needed.

Conclusion:

This study emphasizes the value of hematological indices-Red Blood Cell Distribution Width (RDW), RDW-to-Platelet Ratio (RPR), and Neutrophil-to-Lymphocyte Ratio (NLR)-as non-invasive tools for evaluating liver damage severity in patients with cirrhosis. Among these, RPR exhibited the highest diagnostic accuracy, demonstrating notable sensitivity and specificity in identifying advanced cirrhosis (Child-Turcotte-Pugh Classes B and C). RDW also showed strong predictive capability, while NLR was comparatively less accurate. As these markers are cost-effective and readily available through routine blood tests, they can serve as useful adjuncts to conventional scoring systems like CTP and MELD. The findings support the integration of RPR and RDW into standard evaluation protocols to enhance early detection and management of liver cirrhosis.

Conflicts of Interest: There is no conflict of interest.

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