



Original Article

Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Markers of Disease Activity in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory disease that adversely affects quality of life by impairing joint function. **Objectives:** To examine the use of NLR and PLR as activity indicators in RA. To ascertain their independent prediction by examining the relationships between these DAS28-ESR fractions of disease activity and other conventional inflammatory indicators like ESR and CRP. **Methods:** This study involved 230 rheumatoid arthritis patients assessed in the Department of Rheumatology, Khyber Teaching Hospital, Peshawar. Disease Activity Score 28 (DAS28) was used to assess disease activity together with clinical parameters, erythrocyte sedimentation rate, C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and others. Multivariate regression and rank correlation (Spearman) were done to determine the relationship between these biomarkers and DAS28. **Results:** Significant positive correlations were identified between inflammatory markers and activity of the disease (DAS28), with NLR ($\rho = 0.772$, $p < 0.001$) and PLR ($\rho = 0.768$, $p < 0.001$) demonstrating notable connections. ESR ($\rho = 0.912$, $p < 0.001$) and CRP ($\rho = 0.917$, $p < 0.001$) exhibited more robust relationships. In multivariable regression analysis, CRP ($\beta = 0.454$, $p < 0.001$) and ESR ($\beta = 0.423$, $p < 0.001$) were the strongest independent predictors of disease activity, while NLR remained a significant contributor ($\beta = 0.116$, $p = 0.001$). ROC analysis showed good diagnostic performance for both NLR (AUC = 0.892) and PLR (AUC = 0.898), with PLR demonstrating slightly higher accuracy in identifying high disease activity. **Conclusions:** NLR and PLR are useful and cost-effective markers of disease activity in rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a common and chronic inflammatory disorder that affects the synovial joints and causes inflammation, pain, and changes in them. It is defined by inflammation caused by immune cells such as neutrophils and lymphocytes in the synovial tissues. Over time, movement may be decreased and quality of life impaired due to joint damage caused by chronic inflammation, which may be permanent. Infections and smoking are believed to have a role in RA's pathogenesis,

which is a mix of environmental and genetic variables. Moreover, as reported by Zhao *et al.* the extra-articular symptoms, including cardiovascular disease, osteoporosis, and psychiatric disorders, are frequently connected with RA, making it difficult to treat patients [1]. It is critical to identify RA early and monitor disease activity effectively to optimize patient outcomes. Clinicians often use the Disease Activity Score 28 (DAS28) to assess the severity of RA illness. The patient's wellbeing, the number



of inflamed and sensitive joints, and the ESR (erythrocyte sedimentation rate) can easily be found through this tool. Nonetheless, they are time-intensive and not necessarily able to give a complete picture of the activity of the disease, and more convenient, less expensive biomarkers should be identified, as reported by Pisaniello et al. [2]. Because they are simple, inexpensive, and can be quickly acquired by a standard complete blood count (CBC) test, NLR and PLR are useful tools for clinical practice. The two ratios indicate a correlation between the various categories of blood cells that are engaged in inflammation [3]. Neutrophils, being the early responders to inflammation, are generally increased in active RA, whereas lymphocytes, which play an immunomodulatory role, are usually decreased in the same scenario. Platelets, which are highly relevant in the process of clotting and inflammation, may also be higher in RA, which adds to the hyperactivity of the disease. Computing the ratios of such cells, NLR and PLR, may potentially become tools for systemic inflammation and disease progression [4, 5]. There is a set of studies that indicated that high NLR and PLR correlate with increased disease activity in RA patients. Indicatively, other studies have observed that the correlations between these ratios and DAS28-ESR score are positive, and thus it is possible that an increase in NLR and PLR is a sign of inflammation and poor control of the disease [6, 7]. Further inflammatory indicators that are often used to monitor RA development, including ESR and C-reactive protein (CRP), have also been associated with increased levels in these ratios. While these results are promising, more research is needed to determine exactly how NLR, PLR, and RA are related to the severity of the disease [8, 9]. This research may serve as an important source of information on the possible use of NLR and PLR as diagnostic and prognostic indicators of RA management.

In contrast to well-known markers like ESR and C-reactive protein, the precise role of haematological indices like the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) and indicators of systemic inflammation remains unclear. Moreover, variability in reported cut-off values and limited data from local populations restrict their clinical applicability. This study aimed to look at how NLR and PLR are linked to RA disease activity, how well they may predict disease activity on their own, and how well they work as diagnostic tools with the Disease Activities Score 28 (DAS28-ESR).

METHODS

This cross-sectional study was done at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, from December 2025 to March 2026. The study had the ethical approval of the institutional review board of the Khyber

Teaching Hospital with IREB number 1083/DME/KTH, dated 27 November 2025, and assured the participant of the study about the confidentiality of their information and privacy of their information given and secured in the study. The intended methodology was developed with the purpose of shedding light on the criteria of whether NLR and PLR could be simple and cheap biomarkers that could be used by patients with RA to measure disease activity and inflammation. In case of success, it would result in better clinical control of diseases and patient care. All patients who met the inclusion criteria and presented throughout the research period were recruited using a successive sampling procedure. Information was gathered from patient discussions and medical records, in addition to clinical evaluation and laboratory testing, using a sequential sampling method. The current research aimed to determine if the Neutrophil-to-lymphocyte Ratio (NLR) and the Platelet-to-lymphocyte Ratio (PLR) might be useful in RA disease activity prediction. People enrolled in the study had to be 18 years old or older; 230 people from a university hospital made up the sample. The sample size was calculated for correlation analysis using the formula: $n = [(Z\alpha + Z\beta)/C]^2 + 3$, where $C = 0.5 \times \ln[(1+r)/(1-r)]$. Based on the reported moderate correlation coefficient of ($r = 0.30$) between NLR, PLR, and RA disease activity in previous studies by Erre et al. and Li et al. there was an assumption that this moderate correlation would be observed in the present study [10, 11]. A larger sample ($n = 230$) was added to provide greater power and reliability of analysis. All individuals signed written informed consent forms before they were involved in the research, and participation was completely voluntary. The confidentiality of the patients' information was always ensured. Patients were excluded who had a previous malignancy, persistent infection, or other autoimmune disorder. The aim of defining parameters of inclusion and exclusion was to have a homogeneous research population and to eliminate confounding variables. Those who had an appointment at a more advanced medical facility, excluding patients with other inflammatory markers (NLR and PLR) or with cancer, infection, or other autoimmune diseases. The information obtained included demographic factors (age, sex, BMI), history of illness, and drug use history. A methodological approach was used in gathering the data. To begin, we used the inclusion criteria to find and enrol patients who met our eligibility requirements. Next, we made sure that all subjects gave their informed consent. Thirdly, clinical and demographic information was recorded, such as the patient's age, sex, length of illness, and drug history. A patient's global evaluation for the DAS28 score and a count of painful and swollen joints were part of the clinical assessment that came in at number four. Fifthly, Blood

samples were tested in the laboratory, including ESR, CRP, Neutrophil, Lymphocyte, and platelet count. The final step was to calculate NLR and PLR, and then input the information into a structured database and statistical analysis. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) were used as definitions, respectively. Through the use of DAS28-ESR, disease activity was categorised as remission (<2.6), low (2.6-3.2), moderate (3.2-5.1), and high (>5.1). The Disease Activity Score 28 (DAS28-ESR) was designed to measure disease activity and consists of elements including swelling of the joints, the erythrocyte sedimentation rate (ESR), the health appraisal by the patient, and the soreness of the joints. In addition, blood samples were collected for testing PLR and NLR. Blood samples were also collected in order to test PLR and NLR. Interleukin (IL)-6 and C-reactive protein (CRP) were also used as indicators of systemic inflammation. Evidence suggests that the DAS28-ESR is a valid marker of RA disease activity. The NLR and PLR were calculated using standardised laboratory procedures using regular full blood count data. Tertiles were used to classify NLR and PLR into low, moderate, and high categories. In order to find the best cut-off values (NLR = 2.0 and PLR ≈ 120-130) for predicting severe disease activity, ROC curve analysis was also used. The researchers relied on univariate and multivariate linear regression to allow covering the possible confounding factors (age, sex, body mass index (BMI), illness duration, and medication use). Moreover, the study also employed binary logistic regression to determine the relationship between NLR and PLR and the probability of high levels of disease activity (DAS28 > 5.1).

To determine whether the data were normally distributed, the Shapiro-Wilk test was applied. Since the data did not follow a normal distribution ($p < 0.001$), the Kruskal-Wallis test and Spearman's correlation were used. The results of the logistic regression and multivariable analyses of linear regression were considered statistically significant when the p -value was less than 0.005. Disease activity, as determined by the continuous variable DAS28-ESR, was the main outcome variable. Logistic regression and ROC analyses used disease activity categorisation (DAS28 > 5.1) as a secondary outcome. A p -value lower than 0.005 was taken as significant, and all analyses were done by use of SPSS version 26.0.

RESULTS

In all, 230 RA patients were considered for the study to conclude. On average, the participants' illness had been present for 6.13 ± 4.44 years, and their average age was 51.39 ± 11.25 years. At 2.06 ± 0.93 , the mean neutrophil-to-lymphocyte ratio (NLR) and 130.01 ± 55.62 , respectively, were recorded. A mean C-reactive protein (CRP) level of

19.96 ± 12.71 mg/L and an average erythrocyte sedimentation rate (ESR) of 42.99 ± 24.92 mm/hr were both shown by the inflammatory markers. The average Disease Activity Score (DAS28) was 4.40 ± 1.53 , indicating a modest amount of disease activity (Table 1).

Table 1: The Patient's Demographic and Clinical Baseline

Variables	Mean $\pm$ SD	Min-Max
Age (years)	51.39 ± 11.25	20-80
Disease Duration (years)	6.13 ± 4.44	0.9-20.0
NLR	2.06 ± 0.93	0.63-6.60
PLR	130.01 ± 55.62	44.1-446.1
ESR (mm/hr)	42.99 ± 24.92	5-98
CRP (mg/L)	19.96 ± 12.71	0.1-50.0
DAS28	4.40 ± 1.53	2.00-7.47

The allocation of disease activity showed that 30.4% of patients had high activity, 44.8% had moderate activity, 10% were in remission, and 14.8% had moderate to severe activity. With 71.3% females and 28.7% men, the cohort showed a clear female preponderance. 59.6% of patients had comorbidities, with the most common diseases being diabetes (21.3%) and hypertension (25.2%). Figure 1 illustrates that 40.4% of respondents had no comorbid medical conditions. The distribution of gender, activity of the disease categories, comorbidities, and other demographic and clinical features is shown (Table 2).

Table 2: Distribution of Demographic and Clinical Characteristics of Study Participants (n=230)

Variables	Category	n (%)
Gender	Male	66 (28.7%)
	Female	164 (71.3%)
Disease Activity (DAS28)	Remission	23 (10.0%)
	Low	34 (14.8%)
	Moderate	103 (44.8%)
	High	70 (30.4%)
Comorbidities	Present	137 (59.6%)
	Absent	93 (40.4%)
	Hypertension	58 (25.2%)
	Diabetes mellitus	49 (21.3%)

All variables included in the analysis had complete data with no missing values ($n = 230$, 100%). The mean NLR was 2.06 ± 0.93 with a median of 1.92, while PLR had a mean of 130.01 ± 55.62 and a median of 114.65. ESR and CRP demonstrated mean values of 42.99 ± 24.92 mm/hr and 19.96 ± 12.71 mg/L, respectively. The mean DAS28 score was 4.40 ± 1.53 . Notably, NLR and PLR exhibited positive skewness (1.34 and 1.49, respectively) with elevated kurtosis, indicating a right-skewed distribution, whereas ESR, CRP, and DAS28 showed mild skewness with near-normal kurtosis. The data were shown to be non-parametric using the Shapiro-Wilk test of normality, which revealed that none of the variables

followed a normal distribution (p-value less than 0.001). Consequently, the hypothesis was suitably tested using non-parametric statistics (Table 3).

Table 3: Evaluation of Clinical Indicators for Normalcy and Descriptive Statistics (n=230)

Variables	Mean ± SD	Median	Skewness	Kurtosis	Shapiro-Wilk, p-value
NLR	2.06 ± 0.93	1.92	1.34	3.05	<0.001
PLR	130.01 ± 55.62	114.65	1.49	4.16	<0.001
ESR (mm/hr)	42.99 ± 24.92	39.00	0.42	-0.71	<0.001
CRP (mg/L)	19.96 ± 12.71	18.70	0.34	-0.76	<0.001
DAS28	4.40 ± 1.53	4.20	0.43	-0.91	<0.001

Spearman's rank correlation analysis confirmed significant positive associations among all inflammatory markers and disease activity (DAS28). The results showed a substantial positive correlation involving NLR and DAS28 ($\rho = 0.772$, $p < 0.001$), and a comparably robust correlation between PLR and DAS28 ($\rho = 0.768$, $p < 0.001$). Disease activity was even more strongly correlated with standard inflammatory markers including ESR ($\rho = 0.912$, $p < 0.001$) and CRP ($\rho = 0.917$, $p < 0.001$). Additionally, NLR and PLR were strongly correlated with each other ($\rho = 0.824$, $p < 0.001$), indicating consistency between hematological inflammatory indices (Figure 1).

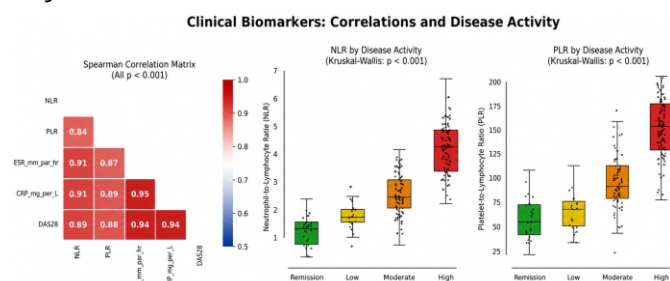


Figure 1: Correlation and Distribution of Inflammatory Biomarkers Across Disease Activity Categories

There were notable variations in both NLR and PLR across disease activity groups, as shown by Kruskal-Wallis analysis ($\chi^2 = 122.507$ and 124.589 , respectively; $df = 3$; $p < 0.001$ for both). When comparing the groups using moderate and high disease activity to those with remission and low activity, post hoc pairwise comparisons with Bonferroni correction showed that NLR and PLR were substantially greater in the former two categories (adjusted $p < 0.005$). Regarding NLR (adjusted $p = 0.237$) and PLR (adjusted $p = 1.000$), there was no statistically significant difference seen between the groups in remission and those with minimal disease activity. According to these results, inflammatory markers tend to rise as illness severity increases (Figure 2).

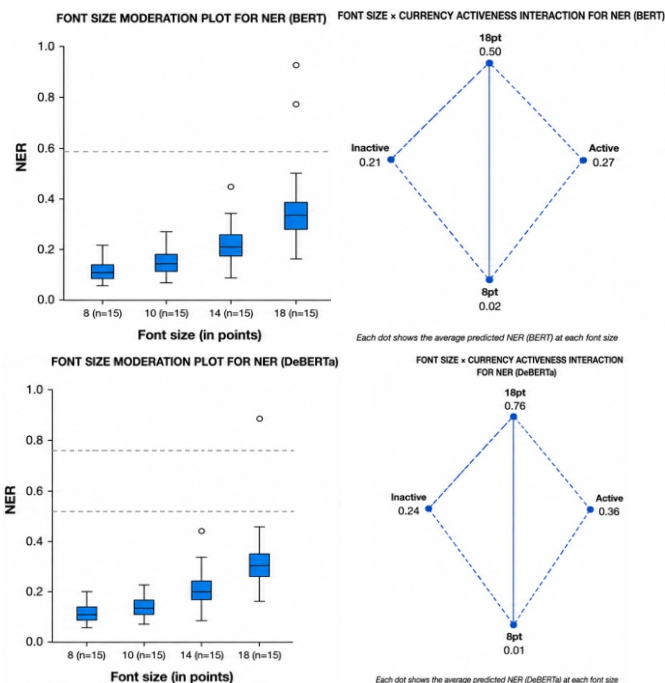


Figure 2: Comparison of NLR and PLR Across Disease Activity Categories Using Kruskal-Wallis analysis

The multivariate linear regression model as a whole was significant in statistical terms ($F = 549.71$, $p < 0.001$) and explained a large amount of variation in DAS28 ($R^2 = 0.937$; adjusted $R^2 = 0.935$). Out of all the measures that were considered, the two that stood out as the most reliable indicators of disease activity were CRP ($\beta = 0.454$, $p < 0.001$) and ESR ($\beta = 0.423$, $p < 0.001$). Furthermore, NLR showed a statistically significant correlation with DAS28 ($\beta = 0.116$, $p = 0.001$), suggesting that it plays a function as an indicator of inflammation. Statistical significance was lost by PLR in the multivariable model ($\beta = 0.054$, $p = 0.112$). In contrast. Neither age ($p = 0.844$) nor illness duration ($p = 0.291$), two demographic factors, were substantially linked to DAS28 (Table 4).

Table 4: Multivariable Linear Regression Analysis for Predictors of DAS28 (n=230)

Variables	B	Std. Error	β (Standardized)	t	p-value
Constant	1.612	0.144	—	11.204	<0.001
Age	0.000	0.002	0.003	0.197	0.844
Disease duration	-0.006	0.006	-0.018	-1.058	0.291
NLR	0.192	0.055	0.116	3.515	0.001
PLR	0.001	0.001	0.054	1.596	0.112
ESR	0.026	0.002	0.423	12.742	<0.001
CRP	0.055	0.004	0.454	13.585	<0.001

ROC curve analysis was performed to assess the ability of NLR and PLR to discriminate high disease activity. NLR demonstrated good diagnostic performance with an AUC of 0.892, demonstrating strong discriminatory ability. Similarly, PLR showed slightly higher performance with an

AUC of 0.898, also reflecting good accuracy in identifying patients with high disease activity. By assessing the sensitivity and specificity of optimal cut-off, it was concluded that an NLR threshold of about 2.0 had a balanced diagnostic performance, corresponding to a sensitivity of approximately 90% and an acceptable specificity. For PLR, a cutoff value of about 120-130 resulted in a sensitivity greater than 80% and moderate specificity, which means that it could be used in clinical screening (Table 5).

Table 5: ROC Analysis of NLR and PLR for Predicting High Disease Activity (n=230)

Variables	AUC	Interpretation	Suggested Cut-off	Sensitivity	Specificity
NLR	0.892	Good	~2.0	~0.90	~0.75
PLR	0.898	Good	~125	~0.85	~0.70

AUC = Area under the curve; values >0.8 indicate good discriminatory ability

DISCUSSION

In their study of rheumatoid arthritis (RA) patients, researchers noticed a positive relationship between neutrophil to lymphocyte ratio (NLR) and a disease activity score 28 (DAS28), and platelet to lymphocyte ratio (PLR). Our results corroborated the usefulness of NLR and PLR as inflammatory markers in RA, as previously reported. The NLR and PLR in patients with more active illness were significantly elevated, suggesting a possible correlation with systemic inflammation [10, 11]. In the current study, NLR and PLR were significantly elevated with the progression of illness, suggesting that these markers are sensitive to the inflammatory changes in RA. Similarly, Wen *et al.* and Xu *et al.* determined that high NLR and PLR values were associated with the active phases of the disease, and that both these markers can be used separately as markers of disease severity. The positive correlations found in this study between DAS28 and NLR ($p = 0.772$, $p < 0.001$) and PLR ($p = 0.768$, $p < 0.001$) is also in support of these previous findings [12, 13]. The current study revealed that DAS28 correlated better with the conventional inflammatory markers, ESR ($p = 0.912$, $p < 0.001$) and CRP ($p = 0.917$, $p < 0.001$), than with the markers NLR and PLR [14]. This is in line with the results of Rashid *et al.* who found that ESR and CRP are the most useful markers of disease activity in RA [15]. Likewise, Hu *et al.* found that hematological ratios like NLR and PLR are helpful, but not as effective as CRP and ESR [16]. In addition, the present study shows that NLR and PLR are not as good as the conventional biomarkers in the context of disease activity. This is consistent with the findings of Ronai and Griffiths stating that although the neutrophil indices are markers of inflammation, they are not primary markers [7]. Furthermore, Oude Voshaar *et al.* pointed out that in clinical practice, the other two

measurements (CRP and ESR) are more powerful independent predictors of inflammatory burden [17, 18]. In the present study, the diagnostic performance analysis using ROC curves showed good discriminatory powers of both NLR (AUC = 0.892) and PLR (AUC = 0.898) in high disease activity. Erre *et al.* reported similar results, with both ratios having moderate to high diagnostic accuracy for RA [10]. Similar cut-off values for NLR and PLR were reported by Chen *et al.* confirming their clinical usefulness to monitor disease activity [19]. There were various limitations to this study. As a cross-sectional study, it was not possible to draw causal inferences. The same has been reported by Chen *et al.* who pointed out that cross-sectional analyses are not helpful for predictions [19]. Further, due to the single-center design, generalizability of the results may be limited, as noted by Masoumi *et al.* [14]. The absence of external validation of cut-off values further restricts the clinical application. The multi-center, longitudinal, external validation studies recommended by Sun *et al.* should be conducted in the future to confirm the utility of NLR and PLR as a prognostic marker for RA [20]. Several limitations are included in this investigation. To begin with, it can only conclude associations between inflammatory indicators and disease activity based on a cross-sectional design. The second limitation is that the research only used data from one location; thus, the results may not apply elsewhere. Third, the suggested cut-off values were not externally validated, even though NLR and PLR showed substantial relationships. Furthermore, the findings might have been impacted by possible confounding variables such as drug side effects and variations in illness duration. To further validate these biomarkers and determine their predictive and clinical use in RA, future research should involve multiple cohorts, innovative longitudinal approaches, and external review.

CONCLUSIONS

Disease activity was positively associated with NLR ($p = 0.772$) and PLR ($p = 0.768$), although ESR ($p = 0.912$) and CRP ($p = 0.917$) exhibited greater connections. Multivariable analysis revealed that CRP ($\beta = 0.454$) and ESR ($\beta = 0.423$) remained the most robust independent predictors, with NLR also demonstrating a notable impact ($\beta = 0.116$). According to ROC analysis, NLR and PLR both performed well as diagnostic tools (AUC = 0.892 and AUC = 0.898, respectively). This work adds to the growing body of data suggesting that NLR and PLR could potentially be cost-effective supplemental markers for assessing RA disease activity.

Authors' Contribution

Conceptualization: HH

Methodology: HH, N, Z

Formal analysis: HH, MA, N, Z, AZ

Writing and Drafting: HH, MA, M, AZ

Review and Editing: HH, MA, N, M, Z, AZ

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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