



## A Study of Correlation of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Lymphocyte-Monocyte Ratio with Disease Activity in Patients of Rheumatoid Arthritis

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### KEYWORDS

Rheumatoid arthritis, Disease Activity Score (DAS28), Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, Lymphocyte-Monocyte Ratio, Inflammatory markers.

### ABSTRACT:

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder characterized by synovial inflammation and joint destruction. Disease Activity Score in 28 joints (DAS28) is commonly used to monitor disease activity, but there is growing interest in simpler, cost-effective hematological markers such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) for disease monitoring.

Objective: To evaluate the correlation of NLR, PLR, and LMR with disease activity in patients with RA using DAS28 score.

Materials and Methods: This prospective observational cohort study included 135 RA patients diagnosed based on 2010 ACR/EULAR criteria. Clinical evaluation, DAS28 scoring, complete blood count, ESR, CRP, and calculation of NLR, PLR, and LMR were performed at baseline and after treatment during follow-up. Statistical analysis included paired t-tests and Pearson's correlation.

Results: A statistically significant decrease in DAS28 score was observed from baseline to follow-up ( $p = 0.001$ ), indicating clinical improvement. NLR and PLR values significantly increased from baseline to follow-up ( $p = 0.001$  and  $p = 0.029$  respectively), and both showed a significant positive correlation with DAS28 scores (NLR:  $r = 0.411$ ,  $p = 0.010$ ; PLR:  $r = 0.514$ ,  $p = 0.001$ ). LMR showed a nonsignificant decrease ( $p = 0.213$ ) and a weak, nonsignificant negative correlation with DAS28 ( $r = -0.197$ ,  $p = 0.233$ ).

Conclusion: NLR and PLR are significantly correlated with RA disease activity and may serve as convenient, cost-effective markers in routine clinical practice. LMR appears to have limited utility in assessing disease activity. Further studies with larger sample sizes and extended follow-up are warranted.



## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder that predominantly affects the synovial joints, leading to pain, swelling, stiffness, and progressive joint destruction. It affects approximately 0.5–1% of the global population and is associated with substantial morbidity, disability, and a reduced quality of life if not appropriately managed [1,2].

The assessment of disease activity in RA is crucial for guiding treatment decisions and monitoring therapeutic response. One of the widely used composite indices is the Disease Activity Score in 28 joints (DAS28), which integrates clinical parameters with laboratory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) [3]. However, these conventional markers may not always accurately reflect systemic inflammation, and there is growing interest in identifying simple, cost-effective, and readily available biomarkers for evaluating RA activity.

Recent studies have highlighted the utility of hematological indices derived from routine complete blood counts (CBC), such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), as potential inflammatory markers in various diseases, including RA [4,5]. These indices are not only accessible but may also reflect the balance between innate and adaptive immune responses, thus serving as indirect markers of systemic inflammation.

Elevated NLR and PLR have been associated with increased RA disease activity, while lower LMR values have been linked to worse clinical outcomes [6,7]. Several studies suggest that these ratios correlate with DAS28 scores and may be used to monitor disease progression and treatment response [8]. Despite growing evidence, variations in findings across populations necessitate further exploration to validate their clinical utility.

The present study aims to evaluate the correlation of NLR, PLR, and LMR with disease activity in patients with rheumatoid arthritis using DAS28 scoring and to determine their potential role as adjunct markers for disease monitoring.

## MATERIALS AND METHODS

### Study Design and Setting

This prospective observational cohort study was conducted in the Department of General Medicine at the Integral Institute of Medical Sciences and Research (IIMSR), Integral University, Lucknow. The study was carried out over 18 months from March/April 2023 to September 2024 for data collection, followed by 6 months for data analysis.

### Sample Size Calculation

The sample size was calculated using the formula for estimating a population mean:

$$n = \left( \frac{Z \cdot \sigma}{E} \right)^2 n = \left( \frac{Z \cdot \sigma}{E} \right)^2$$

Where:

- $Z = 1.96$  (Z-value for 95% confidence level),
- $\sigma = 39.57$  (standard deviation from a previous study),
- $E = 8\%$  (margin of error).

After accounting for a 10% non-response rate, the final sample size was determined to be **135** participants.

### Inclusion Criteria

- Adult patients ( $\geq 18$  years), of either gender.
- Diagnosed with Rheumatoid Arthritis (RA) according to the 2010 ACR/EULAR classification criteria.
- Patients attending the outpatient department (OPD) of IIMSR.

### Exclusion Criteria

- Severe organ dysfunction (heart, liver, or kidney).
- Presence of other autoimmune diseases.
- Hematological disorders.
- Known malignancy.



- Pregnancy.
- Sepsis or known infectious disease.

**Data Collection and Clinical Evaluation**

Upon recruitment, detailed clinical and demographic data were recorded, including:

- Age, gender, and occupation.
- Disease duration, morning stiffness, and tender/swollen joint counts.
- Presence of comorbidities.

The **Disease Activity Score in 28 joints (DAS28)** was calculated for all patients, and disease activity was categorized based on EULAR criteria. Laboratory investigations including **complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)** were performed at baseline and follow-up.

Each patient was followed longitudinally and re-evaluated for RA disease activity and any emerging comorbid or infective conditions. The DAS28 score and laboratory markers were reassessed at the follow-up visit. Correlations between DAS28 scores and inflammatory marker ratios were analyzed at both baseline and follow-up.

**Statistical Analysis**

All data were entered into Microsoft Excel and analyzed using **SPSS version 26.0** (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed:

- **Continuous variables** were expressed as **mean ± standard deviation (SD)** or as **range** where appropriate.
- **Categorical variables** were expressed as **frequencies and percentages**.

Comparative analyses were performed using the **Chi-square test** for categorical data. A **p-value < 0.05** was considered statistically significant.

**Statistical Tools and Formulae Used**

1. **Mean ( $\bar{x}$ ):**

$$\bar{x} = \frac{\sum X}{n}$$

2. **Standard Deviation ( $\sigma$ ):**

For large samples ( $n > 30$ ), standard deviation was computed using the formula:

$$\sigma = \sqrt{\frac{\sum (X - \bar{x})^2}{n}}$$

3. **Chi-square ( $\chi^2$ ) Test:**

Used for comparing proportions across groups.

4. **Level of Significance (p-value):**

- $p > 0.05$  – Not significant
- $p < 0.05$  – Significant
- $p < 0.01$  – Highly significant
- $p < 0.001$  – Very highly significant

**RESULTS AND OBSERVATIONS;**

**Table: 1 Demographic and Clinical Characteristics of the Study Population**

	NUMBER	PERCENTAGE
AGE	46.78±14.90	
<b>GENDER</b>		
Female	94	69.63%



Male	41	30.37%
<b>OCCUPATION</b>		
Clerk	13	9.63%
Professionals	13	9.63%
Farmer	17	12.59%
Housewife	52	38.52%
Laborer	28	20.74%
Teacher	12	8.89%
<b>HISTORY OF PRESENT ILLNESS</b>		
Fatigue	33	24.44%
Joint pain	38	28.15%
Morning stiffness	35	25.93%
Swelling of joints	29	21.48%

The demographic and clinical profile of the 135 patients in the study reveals a mean age of  $46.78 \pm 14.90$  years, with a significant female predominance (69.63%) compared to males (30.37%). The most common occupation among participants was housewife (38.52%), followed by laborers (20.74%), farmers (12.59%), and professionals such as clerks and

engineers (each 9.63%), while teachers accounted for 8.89%. Regarding presenting symptoms, joint pain was the most frequently reported complaint (28.15%), followed closely by morning stiffness (25.93%) and fatigue (24.44%), with swelling of joints reported by 21.48% of patients

**Table: 2 Past Medical History, Medication Usage, and Dietary Patterns of the Study Population**

	NUMBER	PERCENTAGE
<b>PAST HISTORY</b>		
Diabetes	42	31.11%



Hypertension	31	22.96%
No significant history	62	45.93%
<b>MEDICATIONS</b>		
Hydroxychloroquine	29	21.48%
Methotrexate	36	26.67%
No medication	35	25.93%
Sulfasalazine	35	25.93%
<b>DIET HISTORY</b>		
Mixed	44	32.59%
Non-vegetarian	40	29.63%
Vegetarian	51	37.78%

**Table: 3 Family History of Comorbidities Among the Study Population**

<b>FAMILY HISTORY</b>	<b>NUMBER</b>	<b>PERCENTAGE</b>
Diabetes	31	22.96%
Hypertension	40	29.63%
Rheumatoid arthritis	33	24.44%
None	31	22.96%

**Table: 4 Vital Parameters of the Study Population (Mean ± SD)**

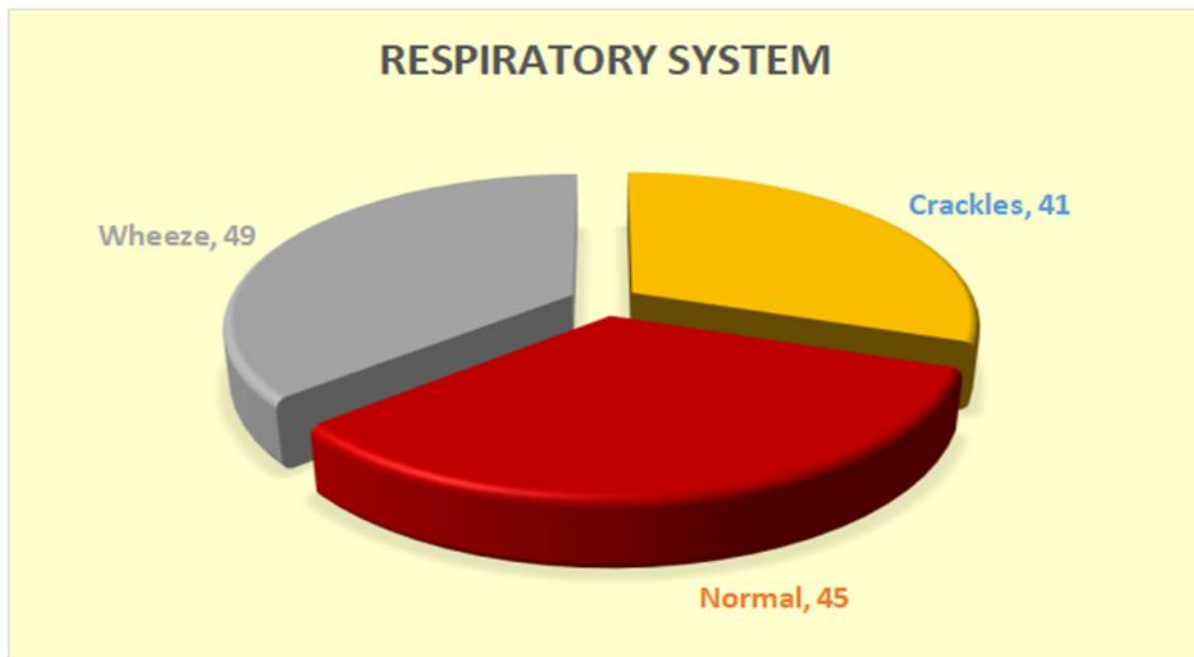
	<b>MEAN±SD</b>
HEART RATE	80.25±11.38



SBP	135.93±14.84
DBP	84.13±9.22

**Table: 5 General Physical Examination Findings of the Study Population**

		NUMBER	PERCENTAGE
EDEMA	Absent	135	100.00%
PALLOR	Present	102	91.85%
ICTERUS	Absent	135	100.00%
CLUBBING	Absent	135	100.00%
LYMPHADENOPATHY	Absent	135	100.00%
CYANOSIS	Absent	135	100.00%



**Figure: 1** Graphical representations of Respiratory System Examination Findings Among the Study Population

**Table 6: Systemic and Musculoskeletal Examination Findings Among the Study Population (N = 135)**

Examination System	Findings	Number	Percentage
Cardiovascular System (CVS)	Normal	135	100.00%
Central Nervous System (CNS)	Normal	135	100.00%
Abdomen & Genitourinary System	Normal	135	100.00%
Musculoskeletal System	Normal	41	30.37%
	Swollen joints	43	31.85%
	Tenderness	51	37.78%

**Table 7 Comparison of DAS28 Scores at Baseline and First Follow-Up Among the Study Population**

DAS28 SCORE	BASELINE		1st FOLLOW-UP		P-VALUE
	N	%	N	%	
Remission (<2.6)	0	0.00%	24	17.78%	X=51.67 p<0.0001*
A low level of disease activity (2.6-3.2)	14	10.37%	26	19.26%	
Active disease that may require change in medication (3.2-5.1)	57	42.22%	66	48.89%	
Very active disease that require careful monitoring and adjustment to medication (>5.1)	64	47.41%	19	14.07%	

The Disease Activity Score 28 (DAS28) evaluation revealed a statistically significant improvement in rheumatoid arthritis disease activity between baseline and the first follow-up (Chi-square = 51.67,  $p < 0.0001$ ). At baseline, none of the patients (0%) were in remission (<2.6 DAS28 score), whereas by the first follow-up, 17.78% of patients achieved remission, indicating marked disease control. The proportion of

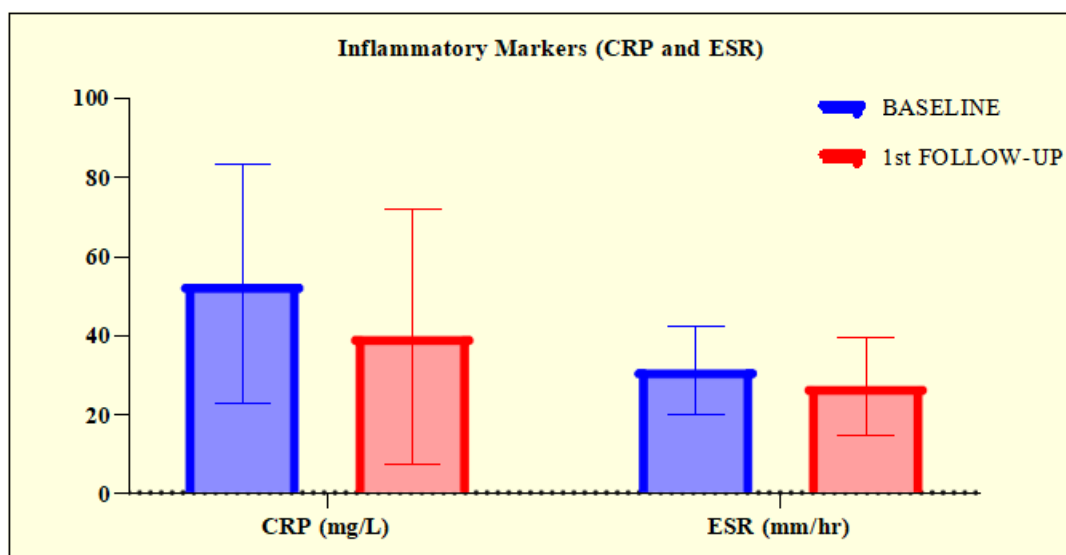
patients with low disease activity (DAS28 score 2.6–3.2) also increased from 10.37% at baseline to 19.26% at follow-up. Although the number of patients with moderate disease activity (DAS28 3.2–5.1) rose slightly from 42.22% to 48.89%, there was a significant decline in those with very active disease (DAS28 >5.1), decreasing sharply from 47.41% to 14.07%.

**Table 8 Comparison of Visual Analogue Scale (VAS) Scores at Baseline and First Follow-Up**

VAS	BASELINE		1st FOLLOW-UP		P-VALUE
	N	%	N	%	
Mild (1-3)	0	0.00%	44	32.59%	
Moderate (4-5)	0	0.00%	28	20.74%	



Severe (6-7)	48	35.56%	53	39.26%	X=134.0 p<0.0001*
Very Severe (8-9)	74	54.81%	10	7.41%	
Worst Pain Possible (10)	13	9.63%	0	0.00%	



**Figure: 2** Graphical representations of Comparison of Inflammatory Markers (CRP and ESR) at Baseline and First Follow-Up

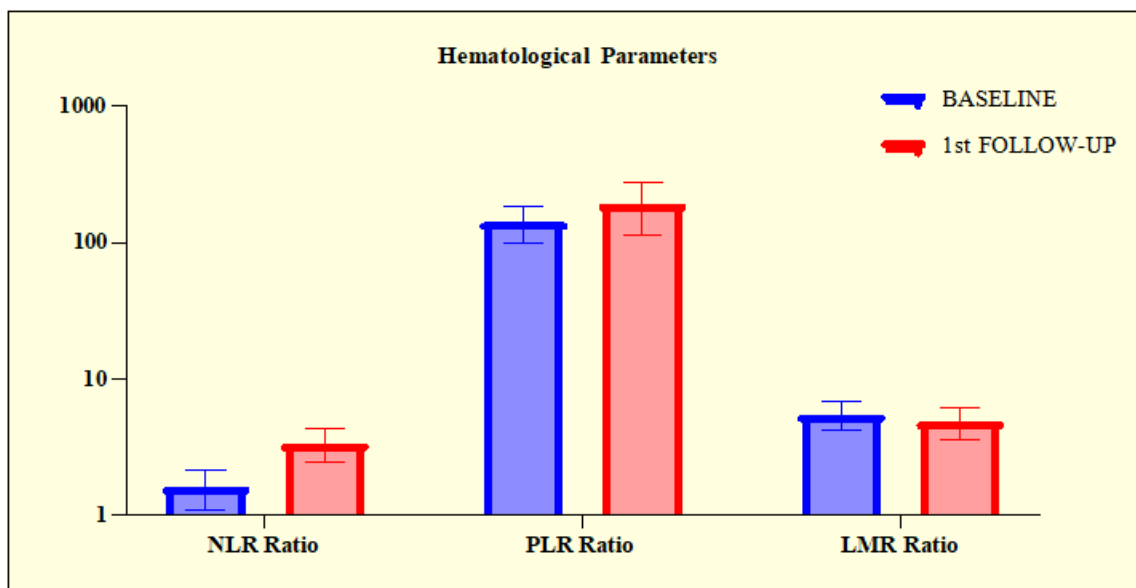
**Table: 9** Comparison of Hematological Parameters at Baseline and First Follow- Up

Parameter	Baseline		1st Follow-up		p-value
	Mean	SD	Mean	SD	
Hb (g/dL)	11.62	1.89	11.67	1.96	t=0.2134 p=0.8312
PCV (%)	39.75	5.19	40.01	5.86	t=0.3859 p=0.6999
MCV (fL)	85.75	8.87	85.92	9.27	t=0.1540 p=0.8778
MCH (pg)	28.94	2.75	28.92	3.13	t=0.0558 p=0.9556
MCHC (g/dL)	33.43	2.00	33.47	2.19	t=0.1567 p=0.8756
RBC Count (10 <sup>6</sup> /μL)	4.57	0.61	4.58	0.65	t=0.1303 p=0.8964
RDW-CV (%)	12.99	1.11	12.97	1.24	t=0.1396 p=0.8891
RDW-SD (fL)	44.40	5.91	44.35	6.48	t=0.0662 p=0.9472



**Table: 10 Comparison of Leukocyte Differential Counts, Platelet Indices, and Hematological Ratios at Baseline and Follow-Up**

Parameter	Baseline Mean (SD)	Follow-up Mean (SD)	Meant-value	p-value
WBC (cells/ $\mu$ L)	7069.41 (1937.20)	7744.20 (1968.09)	1.581	0.125
Neutrophils (%)	60.17 (8.57)	66.65 (7.02)	4.902	<b>0.000*</b>
Lymphocytes (%)	29.02 (7.34)	24.79 (6.07)	2.289	<b>0.030*</b>
Monocytes (%)	6.39 (2.19)	7.00 (2.62)	0.783	0.440
Eosinophils (%)	3.76 (1.05)	4.13 (1.64)	1.320	0.197
Basophils (%)	1.10 (0.44)	1.27 (0.70)	1.007	0.320
Platelet Count (cells/ $\mu$ L)	309204.66 (92592.46)	341017.78 (99709.61)	2.106	<b>0.045*</b>
Absolute Lymphocyte Count (cells/ $\mu$ L)	2051.58 (921.47)	1805.27 (879.26)	1.674	0.101
NLR Ratio	2.20 (0.51)	3.06 (1.00)	4.568	<b>0.001*</b>
PLR Ratio	174.27 (61.69)	204.99 (78.46)	2.362	<b>0.029*</b>
LMR Ratio	5.95 (2.14)	4.19 (2.63)	1.276	0.213



**Figure: 3** Graphical representations of Comparison of NLR, PLR, and LMR Ratios Between Remission and Disease Activity Groups

**Table: 11 Correlation of DAS28 Score with VAS, NLR, PLR, and LMR Ratios**

Parameter	Pearson r	95% Confidence Interval	R squared	P value
<b>DAS28 Score vs VAS</b>	<b>0.656</b>	0.656 to 0.787	0.478	<b>&lt;0.001*</b>
<b>DAS28 Score vs NLR Ratio</b>	<b>0.411</b>	0.452 to 0.568	0.257	<b>0.010*</b>
<b>DAS28 Score vs PLR Ratio</b>	<b>0.514</b>	0.336 to 0.735	0.385	<b>0.001*</b>
<b>DAS28 Score vs LMR Ratio</b>	<b>-0.197</b>	-0.578 to -0.239	0.202	<b>0.233</b>

The correlation analysis between the DAS28 score and various clinical and inflammatory parameters highlights significant positive relationships, particularly with pain and inflammatory ratios. A strong positive correlation was observed between DAS28 and VAS ( $r = 0.656$ ,  $p < 0.001$ ), indicating that higher disease activity is closely associated with increased pain perception, with nearly 48% of the variance explained ( $R^2 = 0.478$ ). NLR ( $r = 0.411$ ,  $p = 0.010$ ) and PLR ( $r = 0.514$ ,  $p = 0.001$ ) also showed

significant positive correlations with DAS28, suggesting that increases in these inflammatory ratios are reliably associated with higher RA disease activity. In contrast, LMR demonstrated a weak and non-significant negative correlation with DAS28 ( $r = -0.197$ ,  $p = 0.233$ ), indicating that it does not have a strong predictive value for disease activity in this cohort

## DISCUSSION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder primarily affecting synovial joints, leading to pain, swelling, and progressive joint destruction. Evaluating disease activity is crucial for the effective management of RA. Conventionally, composite scores such as the Disease Activity Score in 28 joints (DAS28) are used to assess disease activity. However, in recent years, attention has shifted to the utility of hematological parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) as accessible and cost-effective biomarkers of systemic inflammation.

In the present prospective observational cohort study of

135 RA patients, a significant improvement was observed in DAS28 scores between baseline and follow-up. This reduction in disease activity was paralleled by corresponding changes in inflammatory markers, including CRP and ESR, and hematological indices.

### Neutrophil-Lymphocyte Ratio (NLR)

The mean NLR increased significantly from baseline ( $2.20 \pm 0.51$ ) to follow-up ( $3.06 \pm 1.00$ ), and this change was statistically significant ( $p = 0.001$ ). A moderate positive correlation was observed between NLR and DAS28 scores ( $r = 0.411$ ,  $p = 0.010$ ), indicating that higher NLR values were associated with increased disease activity. These findings are consistent with previous studies demonstrating NLR as a potential marker of inflammation and disease activity in RA [1,2]. The rise in neutrophil count and concurrent lymphopenia, reflective of systemic inflammation, may underlie the clinical utility of NLR in this context [3].

### Platelet-Lymphocyte Ratio (PLR)

Similarly, PLR also showed a statistically significant increase from  $174.27 \pm 61.69$  to  $204.99 \pm 78.46$  ( $p = 0.029$ ). The Pearson correlation coefficient ( $r = 0.514$ ,  $p = 0.001$ ) revealed a strong positive association between PLR and DAS28 scores. Elevated PLR in RA patients has been reported by other researchers and is believed to reflect the pro-inflammatory state that characterizes active disease [4,5]. Thrombocytosis, often seen in active RA, along with lymphopenia, contributes to a raised PLR [6].

### Lymphocyte-Monocyte Ratio (LMR)

In contrast, LMR decreased slightly from  $5.95 \pm 2.14$  to



4.19 ± 2.63, but this change was not statistically significant ( $p = 0.213$ ). Moreover, its correlation with DAS28 scores was weak and statistically insignificant ( $r = -0.197$ ,  $p = 0.233$ ), suggesting limited utility in reflecting disease activity. Similar observations have been reported in prior studies, where LMR was found to be less sensitive compared to NLR and PLR [7].

### Pain Perception and Disease Activity

The Visual Analogue Scale (VAS) scores improved markedly during follow-up, with a shift from higher categories of pain (8–10) at baseline to mild and moderate levels at follow-up. A strong correlation was found between VAS and DAS28 ( $r = 0.656$ ,  $p < 0.001$ ), reaffirming that pain perception is a reliable subjective indicator of disease activity, in line with earlier findings [8].

### Clinical Implications

Our study supports the use of NLR and PLR as adjunct markers for evaluating RA disease activity. Their routine availability from complete blood counts adds a practical advantage, especially in resource-limited settings. However, LMR was not found to be a robust marker in our cohort, possibly due to varying monocyte counts and individual immune response variability.

### Limitations

This study has some limitations. It was a single-center study with a relatively moderate sample size, which may limit generalizability. Moreover, we did not evaluate longitudinal changes beyond one follow-up, and the effect of treatment regimens on hematological indices was not independently analyzed.

### CONCLUSION

The study demonstrates that NLR and PLR are significantly correlated with disease activity in RA patients and may serve as accessible, cost-effective inflammatory markers. LMR, on the other hand, lacks significant correlation and may have limited utility. Further multicentric studies with larger sample sizes and extended follow-up are recommended to validate these findings.

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