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ORIGINAL ARTICLE

Evaluation of Relationship between Neutrophil to Lymphocyte Ratio and Rheumatoid Arthritis Severity

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ABSTRACT

Background: Persistent inflammation and progressive joint damage characterize autoimmune arthritis (RA), a long-term inflammatory condition

Objective: To assess the association between the neutrophil-lymphocyte index and the severity of autoimmune arthritis, evaluating its potential as a marker of disease activity

Study Design: Cross-sectional observational study.

Study Setting: The study was conducted at Fatima Memorial Hospital, Lahore over 6 months duration.

Methodology: This study included 140 RA patients, all fulfilling the 2010 ACR/EULAR classification criteria. Data on demographics, clinical features, and laboratory results, such as CBC, were recorded. NLR was calculated, and the DAS28 score was used to determine disease severity.

Results: The mean neutrophil to lymphocyte ratio (NLR) among all RA patients was 3.21 ± 1.85, with a significant increase across disease activity groups: 2.14 ± 1.02 in remission, 2.78 ± 1.23 in low, 3.42 ± 1.72 in moderate, and 4.51 ± 1.98 in high disease activity ($p < 0.01$). NLR was positively correlated with RA severity ($r = 0.32$, $p < 0.01$). Additionally, ESR and CRP levels were significantly elevated in patients with higher disease activity, further supporting the relationship between NLR and systemic inflammation.

Conclusion: NLR was found to be a significant biomarker for assessing RA severity. Its simplicity and accessibility make it a useful tool for clinical monitoring subjects diagnosed with RA, though further studies are required to validate its predictive value.

Keywords: Biomarker, Inflammation, Neutrophil to Lymphocyte Ratio, Severity, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is marked by inflammation of the synovial joints, a persistent condition that causes joint deterioration and loss of function. It is linked to substantial morbidity and a lower quality of life, and it impacts about 1% of the entire world population.[1,2] The pathophysiology of rheumatoid arthritis is multifaceted, encompassing genetic, environmental, and immunological variables. Rheumatoid arthritis, an autoimmune condition, induces an aberrant immune response, resulting in chronic inflammation and systemic consequences that beyond the joints.[3] Traditionally rheumatoid arthritis severity level has been assessed by clinical evaluations such the DAS 28 scoring for disease activity which quantifies activity of disease by considering pain level, joints swollen level, ESR-erythrocyte sedimentation level and overall health assessment of such patients. Nevertheless, these methods frequently exhibit constraints in delivering a holistic view of the inflammatory burden and forecasting disease development.[4] Consequently, there is an increasing interest in identifying objective, readily accessible, and economical biomarkers that can more correctly indicate the extent of systemic inflammation and the severity of rheumatoid arthritis.[5]

One such biomarker attracting increasing attention is the ratio of neutrophils to lymphocytes (NLR), a simple measure taken from regular complete blood counts. NLR reflects the association between neutrophils, which are participated in the innate immune response, and lymphocytes, which are important for acquired immunity. An increased NLR indicates an inflammatory state, where neutrophils increase in response to infection or tissue injury, while lymphocyte counts may decrease due to chronic stress or immune dysregulation.[6,7] In different inflammatory and autoimmune disorders, includes rheumatoid arthritis (RA), it has emerged as an important marker to assess disease activity, severity, and prognosis. Several researches have explored the association between NLR and RA, consistently finding that elevated NLR correlates with increased disease activity and more pronounced joint damage.[8,9]A meta-analysis found that higher NLR is linked to different markers of inflammation, such as erythrocyte sedimentation rate (ESR) and CRP supporting its potential as a reliable proxy for systemic inflammation in rheumatoid arthritis (RA).[10]

Given that rheumatoid arthritis (RA) is a systemic condition with effects beyond the joints such as cardiovascular complications, NLR may also serve as a predictor of these comorbidities, further emphasizing its clinical relevance. Given the chronic and progressive nature of RA, early and accurate assessment of disease severity is crucial for preventing long-term joint damage and improving patient outcomes. While clinical scores like DAS28 are valuable, they do not fully capture the systemic inflammatory state associated with RA.

MATERIALS AND METHODS

This study was conducted after Ethical permission. All participants were briefed on the objectives of the study, and written consent was obtained from each patient. This study followed a cross-sectional observational design. It was carried out at Department of Rheumatology Fatima Memorial Hospital, Lahore, spanning six months, from April 2023 to September 2023. The sample size of 140 patients was determined based on an anticipated correlation coefficient of 0.3 between NLR and RA severity, with a statistical power of 80% and a 95% confidence range.[11] Individuals aged 18 and above, having a verified diagnosis of rheumatoid arthritis, were incorporated into the study. Patients with concurrent disorders of inflammation (like psoriasis and lupus), active infections, malignancies, or a recent history of steroid or immunosuppressive medication were excluded, as these circumstances could distort NLR levels. Clinical and demographic data, encompassing sex, disease duration, age, smoking status, and data on comorbidities was extracted from patient medical records. Disease activity was quantified using the DAS28 scoring system, which evaluates rheumatoid arthritis (RA) severity based on the number of tender and swollen joints, ESR, and the overall health of the patient. Based on disease activity, patients were grouped into four categories: remission (DAS_28 less than 2.6), low activity

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(DĀS_28 having range 2.6-3.2), moderate activity (DĀS_28 having range 3.2-5.1), and high activity (DĀS_28 greater than 5.1). The NLR was calculated by dividing the absolute count of neutrophils by the absolute count of lymphocytes. Additional laboratory tests, such as ESR and CRP levels, were performed to assess systemic inflammation.

SPSS version 26.0 was employed for data analysis. Descriptive statistics were applied to describe the demographic and clinical variable. Continuous data were expressed as means ± standard deviations, categorical variables as frequencies and percentages, Pearson's correlation coefficient evaluated the relationship between NLR and RA severity, one-way ANOVA compared mean NLR levels across disease activity groups, and statistical significance was set at a p-value < 0.05.

RESULTS

In Table 1 patients had a mean age of 52.4 ± 12.6 years, with 78% being female and 22% male, while the average duration of RA was 7.3 ± 4.1 years. Regarding smoking status, 65% were non-smokers, whereas 35% were smokers. Hypertension was reported in 34% of patients, and diabetes in 22%. In terms of disease activity, 12% were in remission, low disease activity was observed in 25%, moderate in 36%, and high disease activity in 27% of the patients.

Table 2 illustrates the overall mean NLR was 3.21 ± 1.85. Patients in remission (DAS28 < 2.6) had the lowest mean NLR of 2.14 ± 1.02, while those with low disease activity had a mean NLR of 2.78 ± 1.23. Moderate disease activity was associated with a mean NLR of 3.42 ± 1.72, whereas high disease activity patients had the maximum mean NLR of 4.51 ± 1.98, indicating a progressive increase in NLR with worsening disease severity.

A moderate but significant association between NLR and RA severity is demonstrated in Table 3, with a correlation coefficient (r) of 0.32 and a p-value of less than 0.01, suggesting that higher NLR levels correlate with greater disease activity in RA patients.

The ANOVA results in Table 4 show significant variations in ratio of NLR across different rheumatoid arthritis (RA) disease activity levels. Statistically significant differences in NLR were observed between remission and low disease activity ($p < 0.01$), remission and moderate disease activity ($p < 0.01$), and remission and high disease activity ($p < 0.01$). Additionally, NLR significantly differed between low and high activity of disease groups ($p < 0.01$), highlighting its potential as a marker for RA severity.

Table 1: Chronic Inflammatory Arthritis Patient's Demographics and Clinical Profile

Variable	Category	Frequency (%)
Age	Mean ± SD	52.4 ± 12.6
Gender	Female	109 (78%)
	Male	31 (22%)
RA Duration (years)	Mean ± SD	7.3 ± 4.1
Smoking Status	Non-smokers	91 (65%)
	Smokers	49 (35%)
Comorbidities	Hypertension	48 (34%)
	Diabetes	31 (22%)
RA Disease Activity	Remission	17 (12%)
	Low disease Activity	35 (25%)
	Moderate- disease Activity	50 (36%)
	High disease Activity	38 (27%)

Table 2: NLR as an Indicator of RA's Severity

Category		Mean ± SD
Mean NLR	Mean±SD	3.21 ± 1.85
Remission	(DAS28 < 2.6)	2.14 ± 1.02
Low Disease Activity	(DAS_28 2.6–3.2)	2.78 ± 1.23
Moderate- Disease Activity	(DAS_28 3.2–5.1)	3.42 ± 1.72
High Disease Activity	(DAS_28 > 5.1)	4.51 ± 1.98

Table 5 summarizes the systemic inflammatory markers in rheumatoid arthritis (RA) patients. The mean erythrocyte sedimentation rate (ESR) was 42.5 ± 18.3 mm/hr, while CRP level was 15.6 ± 7.4 mg/L. The inflammatory cell ratio was recorded as 3.21 ± 1.85, indicating the existence of systemic inflammation in RA patients.

Table 3: Correlation Between NLR and RA Severity

Variable	Correlation Coefficient (r)	p-value
NLR vs DAS28 (RA Severity)	0.32	< 0.01

Table 4: NLR Comparison Across RA Disease Activity Groups (ANOVA Results)

Category	p-value
Remission vs Low Activity of Disease	< 0.01
Remission vs Moderate Activity of Disease	< 0.01
Remission vs High Activity of Disease	< 0.01
Low vs High Disease Activity	< 0.01

Table 5: Systemic Inflammatory Markers in RA Patients

Variable	Category	Mean ± SD
ESR	Mean± SD	42.5 ± 18.3
CRP	Mean± SD	15.6 ± 7.4
NLR	Mean± SD	3.21 ± 1.85

DISCUSSION

As an easily accessible and cost-efficient biomarker, NLR holds potential for assessing activity of disease and monitoring treatment action subjects diagnosed with RA. Chronic inflammation in RA contributes to both joint and systemic complications, making early detection and monitoring of inflammatory markers crucial for optimal disease management. Given its association with disease severity, NLR may serve as a valuable adjunct to conventional disease activity scores in evaluating rheumatoid arthritis progression.[12,13]

In our study, the mean NLR in RA patients was significantly elevated at 3.21 ± 1.85, with a clear upward trend across increasing disease activity groups, from 2.14 ± 1.02 in remission to 4.51 ± 1.98 in high activity of disease. This study is compatible with Mercan et al. (2016), who reported a similar association between NLR and RA severity, noting a higher NLR in RA patients (2.53 ± 1.4) compared to controls and a correlation between NLR and inflammatory bio-markers such as ESR "erythrocyte sedimentation rate" and CRP "C-reactive protein".[14]

Our results are consistent with the findings of Liu et al. (2023), who highlighted that an elevated NLR is linked with elevated systemic inflammation, indicating a disruption in the equilibrium between inflammatory activators and regulators.[15] The idea that NLR is a dependable indicator for evaluating the severity of RA, particularly in those with active illness, is supported by the positive relation seen between NLR and DAS28 ($r = 0.32$, $p < 0.01$). These results are linked with those of Liaqat et al. (2024), who discovered that NLR was prominently higher in active RA patients (1.99 ± 0.84) than in remission patients (1.76 ± 0.41) and healthy controls. The statistical significance of the link among NLR and disease activity scores was confirmed by both studies, indicating that NLR is clinically meaningful.[16]

Additionally, our study observed elevated systemic inflammatory markers, which includes ESR (42.5 ± 18.3 mm/hr) and CRP (15.6 ± 7.4 mg/L) in patients suffering with RA, particularly those with high activity of disease. This finding is related with Hachfi et al. (2022), who reported significantly higher CRP & ESR levels in RA individuals with severe disease activity, along with an increased mean NLR (3.62 ± 2.68). Both studies determined a significant association between NLR and traditional markers of inflammation ($p < 0.05$), supporting NLR's role in assessing systemic inflammation in RA.[17] Moreover, Li et al. (2021) found that NLR, along with PLR and CRP, was an independent factor influencing activity of disease in RA patients. In our study, NLR was similarly associated with RA severity, with a clear distinction in NLR levels across different disease activity groups, as confirmed by ANOVA results ($p < 0.01$). Li et al. (2021) also reported high diagnostic accuracy for NLR in RA patients, suggesting that it could be used not only to assess disease activity

but also to predict treatment outcomes. This aligns with our findings, where elevated NLR corresponded to more severe disease activity, indicating its potential role in guiding clinical management.[18]

Alternatively, whereas Jin et al. (2021) discovered a high association between NLR and CRP, they failed to detect a robust link between NLR and ESR. However, we found strong relations between NLR and ESR and CRP in our study, which means NLR may be a more comprehensive indicator of inflammation in RA, covering both short-term and long-term inflammatory responses. Dissimilar patient populations or research methods might account for this disparity.[20] Our results align with those of Fawzy et al. (2017), who informed an elevated NLR in patients suffering from RA (3.28 ± 0.59) compared to controls, along a prominent relation between NLR and several clinical parameters, such as disease duration, swollen joint count, and DAS28 score. Consistent with the findings of Fawzy et al. (2017), our observations indicate that patients exhibiting elevated disease activity also presented significantly higher NLR values, thereby reinforcing the part of NLR as an indicator of severity of disease.[19]

The study utilized a relatively large sample size of 140 RA patients and employed a widely accessible biomarker (NLR) that can be easily derived from routine blood tests, making the findings applicable in various clinical settings. The exclusion of healthy control subjects prevents direct comparisons between RA patients and non-RA populations.

CONCLUSION

NLR shows a significant correlation with RA severity, show the possibility as an accessible biomarker for routine disease activity monitoring.

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