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Original Article

# Neutrophil Lymphocyte Ratio as an Inflammatory Marker in Rheumatoid Arthritis

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## ABSTRACT

***Objective:*** To determine the role of Neutrophil Lymphocyte Ratio as an inflammatory marker in Rheumatoid Arthritis.
***Study Design:*** Cross-sectional analytical study.
***Place and Duration of Study:*** Rheumatology Department, National Hospital and Medical Center, Lahore Pakistan, from Mar to Sep 2021.
***Methodology:*** After approval from Institutional Ethical Review Board, 160 patients diagnosed with rheumatoid arthritis, aged 21-80 years, were enrolled. Demographic information and medical history were obtained and divided into two groups: Active disease (DAS-28 score>3.2) and LDA/remission (DAS-28 score<3.2). Clinical parameters of the DAS-28 score and CBC, including NLR, were assessed and recorded.
***Results:*** Out of 160 patients, there were 132(82.5%) females. The duration of disease was 8.4±6.8 years. Mean VAS score, tender joint count, swollen joint count, and DAS-28 score were 3.8±2.6, 4.2±4.1, 2.4±2.7 and 4.0±1.6 respectively. RA Factor was positive in 121(75.6%) and Anti-CCP antibody in 102(63.8%). Anaemia was found in 45(28.1%). Mean platelet and TLC were 357.1+99.3 ×109/L and 9.0+2.9 ×109/L respectively. On division into groups, the mean NLR in LDA/Remission-Group and Active Disease-Group were 2.5±1.4 and 3.9±2.1, respectively. High NLR was seen in 46 (57.5%) with Active Disease-Group compared with 13 (16.3%) in LDA/Remission-Group ($p$-value<0.001).
***Conclusion:*** High NLR was more common in active RA than LDA/remission, and NLR is useful in indicating disease activity.

**Keywords:** Disease activity score (DAS) 28 score, Neutrophil lymphocyte Ratio (NLR), Rheumatoid arthritis (RA),

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## INTRODUCTION

Rheumatoid arthritis (RA) is a commonly seen inflammatory arthritis, globally occurring in up to 1% of the population.[1] RA, primarily a joint disease, can have extra-articular features and abnormal immune responses. Due to chronic inflammation, abnormalities in the composition and quality of circulating blood cells can cause lymphopenia with raised neutrophils, thrombocytosis and normochromic anaemia,[2] which are useful as markers of inflammation.[3] Neutrophil lymphocyte ratio (NLR) is the proportion of absolute neutrophil count to lymphocyte count in CBC,[4] and is often employed to see inflammation in ulcerative colitis, cardiovascular disorders, neoplasm and familial Mediterranean fever.[5,6] CRP and ESR, the commonly tested markers for determining acute phase response because of their cost-effectiveness and reliability, can be affected by non-inflammatory factors such as sex, age, and haemoglobin level, but these factors do not affect NLR.[4] To assess the role of NLR in RA, the study by Uslu *et al*.[7] enrolled 50 RA patients and further divided them into two groups: active disease with DAS-28 ≥2.6 and remission with DAS-28 <2.6. The study showed a marked difference in NLR between active patients and controls (2.1±0.59 and 1.27±0.46, respectively). CBC is routinely done in RA patients to monitor the adverse effects of medicines and other disease-associated abnormalities. However, the link between NLR disease severity and chronic arthritis is not strongly established. Thus, the purpose of the present study was to document alterations in NLR with disease severity in RA and to determine the role of NLR as a marker of inflammation in RA.

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## METHODOLOGY

The cross-sectional analytical study was carried out at the Rheumatology Department, National Hospital and Medical Center, Lahore Pakistan, from March to September 2021. Approval from the Institutional Ethical Review Board (Ref: NHMC/1033) was taken, and patients were enrolled using a non-probability consecutive sampling technique.

**Inclusion Criteria:** Patients aged 21-80 years, of either gender, with Rheumatoid Arthritis as per 2010 ACR Diagnostic Criteria were included.

**Exclusion Criteria:** Patients currently on steroids and biologic DMARDS; patients with a history of steroid or

biologic DMARD use in the last 12 weeks; patients with chronic diseases including hypertension, diabetes mellitus, coronary artery disease, chronic renal failure, chronic obstructive pulmonary disease, hematologic diseases & malignancy; & patients with pregnancy or breastfeeding were excluded from the study.

Rheumatoid Arthritis was defined according to the 2010 ACR Diagnostic Criteria,[8] (Table-I), and the DAS-28 score,[9] (Table-II) was employed to determine disease activity. Neutrophil Lymphocyte Ratio was defined as an absolute number of neutrophils divided by an absolute number of lymphocytes. The normal range of NLR is up to 3%.[10] After informed consent, demographic information was obtained from each participant. Patients were then divided into two groups with 80 participants each. In the Active Disease-Group, patients having DAS-28 score >3.2 were included who were either treatment naïve or had stopped taking conventional DMARDs for more than 12 weeks. In the Low Disease Activity/Remission Group, patients taking conventional DMARDs with DAS-28 score <3.2 were included. All clinical parameters of the DAS-28 score and CBC report, including the NLR of each participant, were assessed and recorded. Standard treatment as per hospital protocol was given to all patients.

**Table-I: ACR Diagnostic Criteria-2010 for Rheumatoid Arthritis**

| ACR Diagnostic Criteria-2010 For Rheumatoid Arthritis | |
|---|---|
| **Clinical Parameters** | **Score** |
| **A. Joint involvement** | |
| 1 large joint | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints (with or without involvement of large joints) | 2 |
| 4-10 small joints (with or without involvement of large joints) | 3 |
| More than 10 joints (at least 1 small joint) | 5 |
| **B. Serology** | |
| Negative RA Factor and negative Anti-CCP Antibody | 0 |
| Low-positive RA Factor or low-positive Anti-CCP Antibody | 2 |
| High-positive RA Factor or high-positive Anti-CCP Antibody | 3 |
| **C. Acute-phase reactants** | |
| Normal CRP and normal ESR | 0 |
| High CRP or high ESR | 1 |
| **D. Duration of symptoms** | |
| Less than 6 weeks | 0 |
| More than 6 weeks | 1 |
| Interpretation: Add score of categories A–D. A score of 6 or more is diagnostic for Rheumatoid Arthritis. | |

**Table-II: DAS-28 Score to assess disease severity in Rheumatoid Arthritis**

| DAS-28 Score to assess disease severity in Rheumatoid Arthritis |
|---|
| Scoring items: |
| Tender joint count: 0-28 joints |
| Swollen joint count: 0-28 joints |
| ESR: in mm/h |
| Patient global assessment (VAS): 0-10 |
| Interpretation: |
| Remission: <2.6 |
| Low Disease Activity: 2.7 to 3.2 |
| Moderate Disease Activity: 3.3 to 5.1 |
| High Disease Activity : More than 5.1 |

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

## RESULTS

Out of the 160 patients enrolled in our study, 132(82.5%) were females, and 28(17.5%) were males, having a mean age of 42.6±14.2 years. The mean duration of the disease was 8.4±6.8 years. The mean ESR was 32.4±23.6 mm/hr. Mean VAS score, tender joint count, swollen joint count, and DAS-28 score were 3.8±2.6, 4.2±4.1, 2.4±2.7 and 4.0±1.6 respectively. RA Factor was positive in 121(75.6%), and Anti-CCP antibody was positive in 102(63.8%). The mean Hemoglobin level was 12.2±1.5 g/dl, and anaemia was found in 45(28.1%) patients. Mean platelet count and TLC were 357.1±99.3×109/L and 9.0±2.9 ×109/L respectively. The mean NLR was 3.2±1.9%, and high NLR was seen in 59(36.9%) patients, as shown in Table-III.

**Table-III: Comparison of Clinical Parameters according to Disease Activity (n=160)**

| Clinical Parameters | Groups Assigned According to Disease Activity | |
|---|---|---|
| | LDA/Remission-Group (n=80) | Active Disease-Group (n=80) |
| Mean age (years) | 44.3±15.4 | 40.8+12.7 |
| Mean Duration of disease (years) | 8.4±7.4 | 8.4±6.2 |
| Mean ESR (mm/hr) | 15.2±4.8 | 49.6±22.3 |
| Mean VAS score | 1.3±1.2 | 6.4±1.5 |
| Mean Tender joint count | 1.2±1.0 | 7.2±3.8 |
| Mean Swollen joint count | 0.3±0.7 | 4.4±2.3 |
| Mean DAS-28 score | 2.5±0.5 | 5.5±0.9 |
| Mean Hemoglobin (g/dl) | 12.7±1.8 | 11.7±1.1 |
| Mean Platelet Count (×109/L) | 335.8±109.1 | 378.4±83.9 |
| Mean TLC (×109/L) | 9.1±3.4 | 8.8±2.3 |
| Mean NLR (%) | 2.5±1.4 | 3.9±2.1 |

Patients were divided into two groups of 80 each depending on disease activity (active Vs LDA/ remission), and a comparison of clinical parameters of both groups is shown in Table-IV. High NLR was seen in 46 (57.5%) patients with active disease compared with 13(16.3%) patients with LDA/remission, showing a statistically significant association (*p*-value <0.001). On further stratification, sex (*p*-value 0.044) had a statistically significant association. The treatment regime of the patients with LDA/remission is shown in Table-V.

**Table-IV: Comparison of Clinical Parameters according to Disease Activity (n=160)**

| Clinical Parameters | Groups Assigned according to Disease Activity | | *p*-value |
|---|---|---|---|
| | LDA/Remission-Group (n=80) | Active Disease-Group (n=80) | |
| Gender: | | | 0.044 |
| Female | 64(80.0%) | 68(85.0%) | |
| Male | 16(20.0%) | 12(15.0%) | |
| **RA Factor status** | | | 0.813 |
| Positive | 65(81.3%) | 56(70.0%) | |
| Negative | 15(18.7%) | 24(30.0%) | |
| **Anti-CCP Antibody status** | | | 0.116 |
| Positive | 57(71.2%) | 45(56.3%) | |
| Negative | 23(28.8%) | 35(43.7%) | |
| Anemia: | | | 0.561 |
| Present | 17(21.3%) | 28(35.0%) | |
| Absent | 63(78.1%) | 52(65.0%) | |

**Table-V: Treatment Regime of Patients with LDA/Remission (n=80)**

| Current Treatment Regime of Patients with LDA/Remission | |
|---|---|
| Methotrexate Alone | 26(32.5%) |
| Leflunamide Alone | 20(25.0%) |
| Sulfasalazine Alone | 6(7.5%) |
| Methotrexate + Leflunamide Combination | 8 (10.0%) |
| Methotrexate + Sulfasalazine Combination | 5(6.3%) |
| Methotrexate + Hydroxychloroquine Combination | 15(18.8%) |

## DISCUSSION

The current study comprising 160 patients showed a significant association of NLR with disease activity in patients with RA. In addition, there was a strong association of NLR with gender. The DAS-28 score generally assesses disease severity in RA at baseline and follow-up, calculated by the swollen joint count, tender joint count, and patient global assessment on VAS and ESR.[10] The positive correlation of NLR with DAS28 will aid in estimating disease severity in RA. The association of NLR with DAS28 in our study is concordant with previous international studies.[10,11] The meta-analysis by Lee *et al*.[11] showed NLR to be significantly raised in RA patients. Boulos *et al*.[12] conducted a study with 222 patients with newly diagnosed RA having a mean age of 54.2±15.4 years and a mean disease duration of 22.3±25.0 weeks. On follow-up at 1 year, 45(20%) participants suffered treatment failure with triple therapy consisting of methotrexate, sulfasalazine and hydroxychloroquine. An NLR>2.7 at baseline was found to be an independent predictor of failing treatment, unlike ESR, CRP and DAS-28.12 These results are similar to our study in which mean NLR in the LDA/remission group and active disease group were 2.5±1.4 and 3.9±2.1 respectively. In the present study, high NLR was seen in 46(57.5%) with active disease compared with 13(16.3%) with LDA/remission, showing a statistically significant association (*p*-value<0.001) showing that there was a highly significant increase in NLR in RA patients depending on disease activity. These results are equivalent to three recent studies that demonstrate high NLR in RA.[4,13,14]

In our study, a significant association was depicted between NLR and the gender of patients (*p*-value=0.04). This was in contrast to the results of Fawzy *et al*.[15] and Kweon *et al*.[16] who showed no significant difference between gender and NLR. Our study found no significant correlation of NLR with age, haemoglobin, RA Factor and Anti-CCP Antibody status. However, Gökmen *et al*.[17] elevated NLR in RA patients with positive anti-CCP antibodies. Moreover, in addition to RA, Yolbas *et al*.[18] demonstrated NLR to be raised in other chronic rheumatologic disorders like Lupus, Scleroderma and Behcet's disease as compared to healthy controls, highlighting the role of NLR in other rheumatologic diseases also. Furthermore, in non-rheumatologic diseases, NLR is a beneficial marker for prognosis in patients with ulcerative colitis with active disease on infliximab therapy.[19] For more than half of total leukocytes, neutrophils have a vital role in the pathogenesis of inflammatory conditions by many lytic enzymes and the generation of free oxygen radicals and cytokines.[20]

However, data on the relationship of NLR to radiologic progression is scarce, and subsequently, more studies are required to elaborate on this. In conclusion, the present study shows NLR to correlate significantly with disease activity in RA patients. Thus, NLR, an easily available, objective, inexpensive, and readily reproducible clinical marker, should be considered in managing RA.

## LIMITATION OF STUDY

This study has a few limitations that are required to be considered. This was a single-centre study with a relatively small sample size and included the patients taking outpatient care only. For establishing the exact association between NLR and RA, case-control or cohort studies would be better options, but they involve more time and resources.

## CONCLUSION

Our study demonstrates that a raised Neutrophil Lymphocyte Ratio was seen more commonly in patients with active rheumatoid arthritis than in patients with LDA/remission. We recommend that NLR, an economical and easily available inflammatory marker, should be used for indicating disease activity in RA so that treatment may be modified accordingly to control and reduce disease morbidity and disability.

**Conflict of Interest:** None.

**Author's Contribution**

Following authors have made substantial contributions to the manuscript as under:

MQKT: & NIB: Conception, study design, drafting the manuscript, approval of the final version to be published.

SK: & SK: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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