

Haematological Parameters as Associate Marker of Disease Activity in Rheumatoid Arthritis: A Cross-Sectional Study from West Bengal Region of India

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder that affects synovial joints. Monitoring the disease activity is essential for effective treatment and remission. While the Disease Activity Score 28 (DAS28) is commonly used, recent studies have suggested that haematological parameters from a complete blood count (CBC) may also indicate disease activity. This study evaluated parameters such as haemoglobin (Hb), red and white blood cell counts, platelets, and ratios (NLR, PLR, and MPV) across different levels of RA activity and assessed their predictive accuracy using ROC analysis.

Methods: A cross-sectional study was conducted from January to April 2024 in patients with RA meeting the ACR/EULAR 2010 criteria. Patients with coexisting autoimmune diseases, infections, or hematologic disorders were excluded from the study. The CBC and DAS28 scores were reviewed. The patients were classified into four groups: remission, low, moderate, and high disease activity. Statistical analyses involved Kruskal-Wallis tests and multivariate logistic regression analyses. Receiver operating characteristic (ROC) curves were used to determine diagnostic performance.

Result: Multivariate analysis identified Hb level, NLR, and MPV as independent predictors of RA activity. ROC analysis showed AUCs of 0.717 for Hb, 0.608 for NLR, and 0.679 for MPV, indicating moderate diagnostic value. CBC-derived parameters, particularly Hb level, MPV, and NLR, are correlated with RA disease activity. Their integration into routine assessment can enhance disease monitoring, cost-effectiveness, and wide accessibility.

Conclusion: CBC-derived markers low haemoglobin with elevated NLR and MPV reflect increased inflammatory burden in RA. As these tests are inexpensive and widely available, they can complement DAS28 to improve accessible and cost-effective RA disease monitoring.

Keywords: rheumatoid arthritis; disease activity score 28 (DAS28); neutrophil to lymphocyte ratio (NLR); mean platelet volume (MPV); haemoglobin (Hb)

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterised by synovial inflammation, joint damage, and extra-articular manifestations. The main objective of RA treatment is to achieve remission or low disease activity by consistent monitoring. Traditionally, disease activity is measured using the Disease Activity Score in 28 joints (DAS28), which involves erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). However, both ESR and CRP levels can be

inaccurately elevated in various conditions, often resulting in an additional financial burden during routine practice. Regular monitoring of adverse drug reactions necessitates a complete blood count (CBC) at every appointment. This standard, cheaper test can indicate inflammatory changes through fluctuations in haemoglobin (Hb) levels, white blood cell (WBC) counts, neutrophil-to-lymphocyte ratio (NLR), platelet indices, and mean platelet volume (MPV). These factors are regulated by cytokines, such as TNF- α , IL-1, IL-6, and IFN- γ , which play a role in the pathogenesis of RA. As a result, growing evidence has emphasized the relevance of haematological markers as additional indicators of systemic inflammation in RA.[1]

This study sought to investigate whether haematological indices could independently predict RA disease activity and aid in clinical decision-making. We also sought to assess their predictive accuracy as composite scores to determine whether CBC-derived indices can be reliably integrated into routine clinical practice in this resource-constrained setting.

Materials and Methods

A cross-sectional study was conducted at the rheumatology outpatient clinic from January to April 2024, following ethical approval (EC no-IEC/AIIMS/Kalyani/certificate/2024/182). The study included adult patients aged 18 years or older who were diagnosed with RA according to the ACR/EULAR 2010 criteria[2]. For this study, we included patients with early disease (duration of less than 5 years). Patients were excluded if they had overlap with other autoimmune diseases, such as systemic lupus erythematosus (SLE), vasculitis, scleroderma, or seronegative spondyloarthritis; hematologic disorders, including thalassemia or immune thrombocytopenic purpura (ITP) or an active infection. Patients who were pregnant or lactating during the study were also excluded.

Study variables

Data collected included demographic details, disease duration, anti-cyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF) status. Disease activity was measured using DAS28 scores, which were calculated based on the number of tender joints, swollen joints, physician global assessment score (0–10), and ESR/CRP at the time of data collection.[3] Patients were categorized into remission (<2.6), low (2.6–3.2), moderate (3.2–5.1), and high (>5.1) disease activity groups based on DAS28-ESR/CRP scores.[4] Complete hemogram parameters included Hb, red blood cell (RBC) count, WBC count with differential, platelet count, MPV, NLR, RDW, and platelet-to-lymphocyte ratio (PLR). DAS28 scoring was double verified by two investigators to prevent any bias in the global assessment calculation. Study size was calculated from the previously conducted studies with adjustment of the power of the study and effect size in the previous result.

Statistical analysis was performed using SPSS version 22.0. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized as medians with interquartile ranges (IQR). Kruskal-Wallis and Chi-square tests were used to compare differences across the disease activity groups. Multivariate analysis was conducted using logistic regression, and receiver operating characteristic (ROC) curves were generated to assess the predictive value of the haematological markers. Statistical significance was set at $P < 0.05$.

Results

100 patients with RA were screened, and 90 patients with RA were included in the final analysis. They were categorized into four disease activity groups based on the DAS28 ESR/CRP scores: remission ($n = 20$), low activity ($n = 4$), moderate activity ($n = 21$), and high activity ($n = 45$). The mean age of the study population was 42.95 ± 9.79 years, with 33 ± 2.9 years in the remission groups and 44.13 ± 9.42 years in the severe disease activity group ($p = 0.360$). Among the 90 patients, 78 were female and 12 were male, with no statistically significant sex distribution among the groups ($p = 0.211$). Anti-CCP antibody positivity was observed in 54 patients and rheumatoid factor positivity was observed in 40 patients, with no significant difference across disease activity categories ($p = 0.610$ and 0.321 , respectively). (Table 1)

Extra-articular manifestations were reported in 43 patients with no significant variation across the groups ($p = 0.654$). The duration of RA significantly differed among groups, with the highest duration in the low disease activity group (52 ± 15.4 months) and the lowest in the remission group (25.75 ± 31.3 months) ($p < 0.001$). DAS28 scores were significantly different across the groups ($p < 0.001$), with mean values increasing from 1.77 in remission to 6.61 in the high disease activity group. (Table 1)

Haemoglobin levels decreased with increasing disease activity, from 12.0 ± 1.1 g/dL in remission to 10.6 ± 1.54 g/dL in high disease activity ($p < 0.001$). Total leukocyte counts showed an increasing trend, from $7.45 \pm 1.5 \times 10^9/L$ in remission to $9.11 \pm 2.5 \times 10^9/L$ in high disease activity ($p < 0.001$). NLR rose from 1.8 ± 0.52 in remission to 3.0 ± 1.13 in high disease activity ($p < 0.001$). Platelet counts also increased from 2.70 ± 0.70 to $3.3 \pm 1.10 \times 10^5/\mu L$ across the groups ($p < 0.001$). MPV increased from 10.68 ± 1.53 fL in remission to 12.77 ± 1.43 fL in high disease activity ($p < 0.001$). The

Table 1: Demographic characteristics of study population with status of disease activity.

| Characteristics | Total | Remission | Low disease activity | Moderate disease activity | Severe disease activity p value |
|-------------------------------|---------------|---------------|----------------------|---------------------------|---------------------------------|
| Number of patients | 90 | 20 | 4 | 21 | 45 |
| Age in years (mean) | 42.95 ± 9.79 | 33 ± 2.94 | 33 ± 14.31 | 43.6 ± 10.63 | 44.13 ± 9.42 0.360 |
| Male / Female | 12 /78 | 3 /17 | 0 /4 | 5 /16 | 4 /41 0.211 |
| Anti-CCP antibody | 54 | 13 | 2 | 12 | 27 0.610 |
| RA factor | 40 | 9 | 1 | 11 | 24 0.321 |
| Extra-articular manifestation | 43 | 9 | 2 | 10 | 24 0.654 |
| Duration of RA (in months) | 30.63 ± 21.68 | 25.75 ± 31.30 | 52 ± 15.40 | 31.14 ± 18.32 | 29.6 ± 21.65 <0.001 |
| DAS28 score | 4.85 ± 2.10 | 1.77 ± 0.54 | 2.71 ± 0.50 | 4.40 ± 0.51 | 6.61 ± 0.93 <0.001 |

mean RDW was 15.16 ± 1.79, which did not differ significantly across the groups. Although numerically more prevalent in the high disease group (Table 2).

Table 2: Haematological parameters in different groups of RA.

| Characteristics | Total | Remission | Low disease activity | Moderate disease activity | Severe disease activity P value |
|-----------------|--------------|--------------|----------------------|---------------------------|---------------------------------|
| No. of patients | 90 | 20 | 4 | 21 | 45 |
| Haemoglobin | 11.8 ± 1.32 | 12.0 ± 1.1 | 12.5 ± 1.21 | 11.7 ± 1.42 | 10.6 ± 1.54 <0.001 |
| TLC | 8.00 ± 1.94 | 7.45 ± 1.5 | 7.2 ± 1.4 | 8.21 ± 2.34 | 9.11 ± 2.5 <0.001 |
| NLR | 2.4 ± 0.81 | 1.8 ± 0.52 | 1.6 ± 0.75 | 2.42 ± 0.83 | 3.0 ± 1.13 <0.001 |
| Platelets | 2.6 ± 0.74 | 2.70 ± 0.70 | 2.73 ± 0.51 | 3.0 ± 0.63 | 3.3 ± 1.10 <0.001 |
| MPV (fL) | 11.4 ± 1.42 | 10.68 ± 1.53 | 10.21 ± 1.23 | 11.66 ± 1.51 | 12.77 ± 1.43 <0.001 |
| RDW cv | 15.16 ± 1.79 | 13.7 ± 0.54 | 14.7 ± 0.25 | 14.7 ± 1.24 | 15.5 ± 2.0 >0.05 |

Association with disease activity

Multivariate logistic regression analysis revealed that haemoglobin (OR: 0.52, $p < 0.001$), NLR (OR: 1.23, $p < 0.010$), and MPV (OR: 0.62, $p < 0.001$) were significantly associated with disease activity. Rest all parameters were not significantly associated (Table 3).

Table 3: Multivariate analysis to determine significant haematological parameters associated with RA disease severity.

| Parameter | Adjusted OR | p value |
|------------------------|-------------|---------|
| Hb (g/dl) | 0.52 | <0.001 |
| WBC count (cells/ul) | 0.88 | 0.213 |
| Neutrophils | 1.12 | 0.651 |
| Lymphocytes | 0.99 | 0.185 |
| NLR ratio | 1.23 | <0.010 |
| Platelet count (10/ul) | 1.17 | <0.071 |
| MPV | 0.62 | <0.001 |

ROC analysis showed AUCs of 0.717 for Hb, 0.608 for NLR, and 0.679 for MPV, indicating moderate diagnostic value (Figure 1).

ROC curve analysis indicated that haemoglobin had a sensitivity of 88%, specificity of 22.22%, positive predictive value (PPV) of 53.3%, negative predictive value (NPV) of 66.67%, and positive likelihood ratio of 1.14. The NLR exhibited a sensitivity of 89.13%, specificity of 77.78%, PPV of 80.39%, NPV of 87.50%, and positive likelihood ratio of 4.01. MPV demonstrated a sensitivity of 93.48%, specificity of 51.43%, PPV of 71.67%, NPV of 85.71%, and positive likelihood ratio of 1.92.

The combination of Hb <12.05 g/dL, NLR >2.63, and MPV >11.80 fL yielded a sensitivity of 97.83%, specificity of 91.11%, PPV of 91.84%, NPV of 97.62%, and a positive likelihood ratio of 11.01 (Table 4).

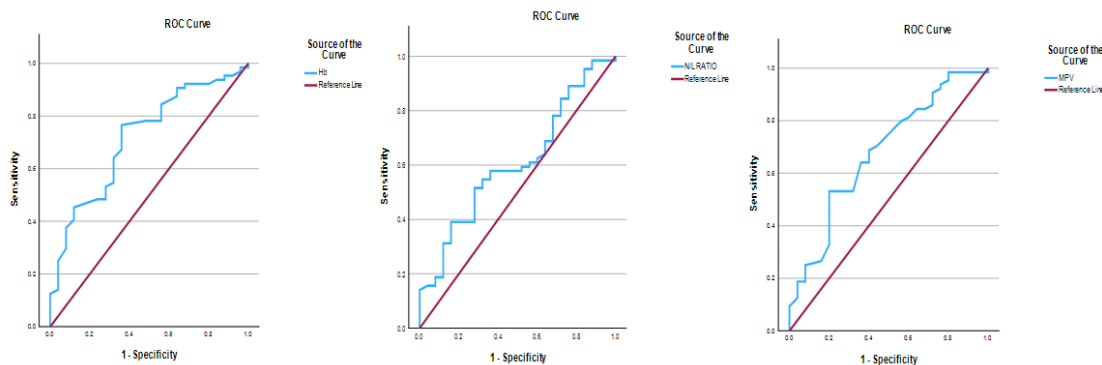


Figure 1: ROC analysis showing AUCs of 0.717 for Hb, 0.608 for NLR, and 0.679 for MPV, indicating moderate diagnostic value.

Table 4: Specificity, sensitivity of combined haematological parameters for disease severity for severe DAS28 activity.

| Haematology parameter | Sensitivity (%) | Specificity (%) | PPV | NPV | Positive likelihood ratio (%) |
|-----------------------|------------------------|------------------------|------------------------|------------------------|-------------------------------|
| Haemoglobin | 88 (75.95 to 96.29) | 22.22 (11.20 to 37.09) | 53.3 (48.66 to 57.95) | 66.67 (42.61–84.34) | 1.14 (0.95 to 1.38) |
| NLR | 89.13 (76.43 to 96.38) | 77.78 (62.91 to 88.80) | 80.39 (70.16 to 87.73) | 87.50 (75.10 to 94.20) | 4.01 (2.30 to 6.99) |
| MPV | 93.48 (82.10 to 98.63) | 51.43 (33.99 to 68.62) | 71.67 (64.08 to 78.20) | 85.71 (65.73 to 94.94) | 1.92 (1.36 to 2.73) |
| HB+NLR+MPV | 97.83 (88.47 to 99.94) | 91.11 (78.78 to 97.52) | 91.84 (81.52 to 96.63) | 97.62 (85.48 to 99.65) | 11.01 (4.31 to 28.07) |

Hb <12.05 gm%, NLR >2.63 and MPV > 11.80 fL
 PPV – positive predictive value, NPV – Negative predictive value

The ROC analysis reinforced the role of Hb and MPV as relatively strong and statistically significant predictors of RA disease activity, while NLR suggested a trend that may gain importance in larger or more diverse populations.

Discussion

This study highlights the importance of haematological parameters, specifically haemoglobin level, MPV, and NLR, as readily available and cost-effective indicators for assessing disease activity in RA. Haemoglobin had the strongest predictive value for disease activity, followed by MPV. These markers indicate that inflammatory processes are influenced by cytokine-mediated changes in haematopoiesis. By integrating these haematological metrics into routine assessments, we can enhance early identification of disease flares, track treatment effectiveness, and guide timely therapeutic strategies, particularly in resource-limited environments.

We have conducted a narrative review of various studies examined thus far regarding the correlation between disease activity and haematological parameters in RA, as presented in Table 5.[1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14] In acute or high-grade inflammation (e.g., flares of rheumatoid arthritis), MPV tends to decrease. This is thought to occur due to rapid consumption and migration of large, reactive platelets to the sites of inflammation, reducing their numbers in circulation.[15] The cause of low haemoglobin in inflammation is a complex interplay of immune-mediated marrow suppression and iron-restricted erythropoiesis driven by inflammatory cytokines and hepcidin dysregulation.[16] Neutrophils are primed and activated in active RA, secreting pro-inflammatory mediators like proteases, reactive oxygen species, and cytokines that worsen joint inflammation. Lymphopenia in RA is associated with lymphocyte migration into the inflamed synovium and increased lymphocyte apoptosis, which correlates with disease severity. The imbalance of elevated neutrophils and reduced lymphocytes results in increased NLR, which correlates with RA disease activity.[17]

Mercan et al.[8] reported a positive correlation between NLR and RA disease activity, suggesting its usefulness in evaluating treatment response. A recent meta-analysis by Lee et al.[18] established positive associations between NLR, PLR, and RA activity, as measured by DAS28. Findings by Chandrashekhara et al.[5] revealed a lower area under the curve (AUC) for NLR (0.584) in an Indian population, emphasising the need to account for population-specific variations. Similarly, recent studies[19, 20] noted that while the NLR had moderate diagnostic value in predicting disease flares, its accuracy improved when assessed in conjunction with other haematological markers.

Table 5: Comparative analysis of different studies on the correlation of haematological parameters with RA disease activity.

| Study | Population with outcome variable | Haematological parameters | Result |
|--|---|---------------------------|---|
| Chandrashekhara S et al[5] India 2015 | 124 RA based on relapse and remission (based on DAS 28 CRP) | NLR | The ROC analysis indicated that NLR was consistent in predicting remission. |
| Uslu AU et al[6] 2015 Turkey | 104 RA – group 1 & 2 based on DAS28 | NLR, PLR | A correlation was observed between NLR and PLR by DAS-28 |
| Peng Y F et al[7] 2015 China | 104 RA, compared with healthy control irrespective of disease activity | PLR, NLR | PLR is associated with RA, and PLR may be an underlying indicator indicating the chronic subclinical inflammation in patients with RA. |
| Mercan et al[8] 2015, Turkey | 136 RA-DAS28 CRP | NLR | NLR strong association with disease activity |
| Tekeoglu et al[9] Turkey 2016 | 102 patients with RA based on DAS28 | NLR & MPV | High NLR with high disease while low MPV with high disease |
| Talukdar et al[10] India 2017 | RA (80) – two group (low to moderate disease, DAS28 < 5.1 versus high disease, DAS28 > 5.1) | Hb, Platelet count, MPV | High disease active group had higher MPV, platelet count & low HB (p < 0.01, for all) |
| Abd-Elazeem, et al[11] 2018 Egypt | 50 RA – Active and Remission group | NLR, PLR | The NLR and PLR significantly correlated with the patients age (p = .02 and p = .006) and with the DAS-28 (p = .001 and p = .03 respectively) |
| Remalante PPM et al[12] 2020 Philippines | 134 RA – based on DAS28 ESR | NLR & RDW | Weak positive correlation between NLR & disease activity, no correlation between RDW & disease activity |
| Dechanuwong P et al[1] Thailand 2021 | 325 patients - 4 groups according to disease activity: disease remission or low, moderate or high disease activity. | Hb, MPV, NLR | Hb, NLR, MPV - independent factors associated with disease activity. Combination – sensitivity 95%, specificity 24%, PPV 37% NPV 91% in predicting remission |
| Lijuan, W et al[13] 2021 China | 547 RA patients – remission & disease activity based on DAS28 | NLR, PLR, LMR | Statistically significant difference in the NLR (4.2 ± 3.2 vs 3.4 ± 2.4 , $P=.034$) and PLR (222.3 ± 136.4 vs 176.9 ± 89.8 , $P=.006$) between the two groups |
| Masoumi, M et al[14] Iran 2024 | 305 RA patients – remission, LDA, moderate disease, active disease | PLR, NLR, LMR | ROC analysis showed ESR, CRP, NLR, and PLR distinguish active from remission RA AUC – NLR 0.66, PLR – 0.64 |

Abbreviation – DAS28 – Disease activity score 28, ESR – erythrocyte sedimentation rate, CRP – C reactive protein, Hb – Hemoglobin, MPV – mean platelet volume, NLR – neutrophil-lymphocyte ratio, PLR – platelet-lymphocyte ratio, LMR – lymphocyte-monocyte ratio, RDW – red cell distribution width, ROC – Receiver operator statistics

Our results are consistent with those of Khaled et al.[21] and Dechanuwong et al.,[1] who found significantly elevated MPV in RA patients with active disease, as well as by Uslu et al.[6] who advocated the use of both NLR and MPV as inflammatory indicators in RA and additional autoimmune disorders.

ROC analysis in the current study indicated that Hb is the most dependable haematological predictor of disease activity, followed by MPV. This finding is supported by many recent studies,[22, 23, 24] which show that lower Hb levels are strongly linked to active RA and unfavourable functional outcomes. Furthermore, several studies have highlighted the effectiveness of MPV and RDW as early indicators of systemic inflammation and treatment response among patients with RA taking disease-modifying anti-rheumatic drugs (DMARDs).

Our study demonstrated that the combination of Hb, MPV, and NLR significantly enhanced the diagnostic performance, with high sensitivity and specificity in identifying high disease activity. This aligns with recent conclusions that argue that composite haematological scores offer superior clinical benefits for monitoring RA progression and facilitating timely therapeutic adjustments. Integrating these parameters into standard RA monitoring protocols could enhance the early detection of disease flare-ups or treatment failures, particularly in resource-limited clinical settings.

The limitations of this study include the small sample size and the absence of follow-up data. The low disease activity group contains only four patients, which poses a restriction for subgroup analysis. Including additional RA activity measures, such as CDAI and SDAI, would strengthen the study. Further multicentre and longitudinal research is required to confirm the prognostic value of these findings across different populations. Incorporating more haematological parameters will improve the study's results. A comparative analysis of various serum biomarkers alongside haematological parameters will assist in identifying more specific multiparameter predictors for the treatment of difficult-to-treat RA.

Conclusion

This study highlights the importance of haematological parameters, specifically haemoglobin, MPV, and NLR, as readily available and cost-effective associate variables for assessing disease activity in RA. Further longitudinal studies are needed to use them as predictive markers in RA disease activity assessment.

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