



Hematological Markers Associated with Rheumatoid Arthritis among Yemeni Patients in Sana'a City: A Case- Control Study

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ABSTRACT

Background: Rheumatoid arthritis (RA) is characterized by chronic inflammation and immune dysregulation affecting the hematopoietic system through multiple factors. Various inflammatory hematological markers, such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI), represent systemic inflammation and balance of the immune response.

Objective: This case-control study aimed to evaluate and compare the clinical utility of these novel, inflammatory ratios among Yemeni patients with rheumatoid arthritis.

Methods: 200 participants were enrolled in our study, including 100 cases with RA and 100 healthy controls. Peripheral blood samples were obtained from each participant for CBC and serological tests. The NLR, LMR, PLR, NMR, SIRI, and SII were calculated. A receiver operating characteristic (ROC) curve was plotted to evaluate the diagnostic value of RA.

Results: NLR, PLR, NMR, SIRI, and SII were significantly elevated in patients with rheumatoid arthritis, whereas LMR was significantly reduced compared with healthy controls ($p < 0.05$). Spearman's rho showed that the NLR ($r = .242, P = 0.015$; $r = 0.224, P = 0.025$), PLR ($r = 0.425, P < .001$; $r = 0.360, P < 0.001$), and SII ($r = 0.298, P = 0.003$; $r = 0.303, P = 0.002$) were positively correlated with both ESR and anti-CCP, while NMR ($r = 0.243, P = 0.015$) was only positively correlated with ESR. The AUC for SIRI equals to 0.658, NLR (AUC = 0.647), SII (AUC = 0.617), and PLR (AUC = 0.614) are statistically significant but modest discriminative power between patients with RA and healthy controls.

Conclusions: NLR, PLR, SIRI, and SII were significantly higher in RA patients than in control participants while LMR was significantly lower in RA patients. NLR, PLR, and SII were positively correlated with both ESR and anti-CCP, while NMR was only positively correlated with ESR. Therefore, these may be used as complementary diagnostic indicators in the diagnosis of RA, as they are simple, inexpensive, and objective markers. Further studies with larger sample sizes and extended follow-ups are warranted.

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1. INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic autoimmune disease characterized by inflammatory joint degeneration [1]. It affects various organs and systems, including the hematological system [2] with complex pathogenesis involving both the innate and adaptive immune systems[3].

Chronic inflammation and immune dysregulation, which are characteristic of RA, affect the hematopoietic system through multiple factors, such as immune complex formation, antibody production, cytokine-induced suppression of growth factors, drug toxicity, and the release of pro-inflammatory mediators [4–6]. Consequently, inflammatory changes in rheumatological dis-

eases lead to measurable changes in the number, morphology, and function of peripheral blood cells, which can be used to evaluate inflammatory activity [7]. In addition, B cell hyperactivation results in excessive autoantibody production, such as rheumatoid factor RF and anti-citrullinated protein antibodies, which not only serve as diagnostic and prognostic markers but also contribute to the perpetuation of immune-mediated articular destruction [8, 9].

Various inflammatory hematological markers, such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI), are calculated from complete blood count (CBC) to be used as inflammatory hematological markers, which represent systemic inflammation and balance of the immune response [6, 10, 11]. The cellular components underlying these indices are crucial, as they secrete cytokines, chemokines, proteases, and angiogenic factors during chronic inflammation [12]. CBC is a simple, inexpensive, and routine laboratory test commonly performed as part of a medical assessment in daily rheumatology practice [13, 14].

The hematological parameters in patients with RA are influenced by the underlying inflammatory disease, the level of inflammation, and the treatment regimen, and these parameters can serve as indices for monitoring inflammation, assessing disease activity and severity, and predicting potential complications, thereby aiding clinicians in making informed treatment decisions [7, 13, 15]. Regular monitoring of these parameters is important for the effective management of RA, minimization of complications, and improvement of patient outcomes [15].

In recent years, there has been increasing attention on these markers as potential prognostic tools for various inflammatory and autoimmune diseases [16]. This study aimed to assess hematological markers, including these novel inflammatory ratios, in Yemeni patients with RA. We assessed their diagnostic performance against established biomarkers (ESR and anti-CCP) and explored their correlations with disease-related inflammation.

2. MATERIALS AND METHODS

2.1. STUDY DESIGN AND PERIOD

This case-control study will be conducted from March 2024 to July 2025. The study included 100 Yemeni patients diagnosed with RA and 100 healthy controls matched for age and sex.

2.2. STUDY AREA AND POPULATION

Patients with RA were selected from hospitalized patients in the Medical and Orthopedic department of Al-Thawra General Hospital, Al-Sabeen Hospital for Women and

Children, Al-Kuwait University Hospital, and a rheumatological clinic in Sana'a city, with confirmation of RA diagnosis by a rheumatologist based on the criteria of the American College for Rheumatology/European League (2010ACR/EULAR) guidelines. Participants underwent comprehensive medical assessments, including a complete medical history, physical examinations, and laboratory investigations.

2.3. DATA COLLECTION

Data were collected through face-to-face interviews with the participants using a pre-designed questionnaire. The questionnaire, which included both closed and open-ended questions, covered demographic, social, and clinical characteristics, as well as laboratory results of RA.

2.4. SAMPLE COLLECTION

Peripheral blood samples (6 mL) were obtained from all study participants. Blood was allocated as follows: 2 mL was collected into an EDTA-containing tube, 2 mL was collected into a plain gel tube, and 2 mL was collected into a sodium citrate tube. EDTA-anticoagulated blood samples were used for the hematological assays. The plain gel tube was allowed to clot, and the serum was separated by centrifugation. Serum was transferred into Eppendorf tube, and stored at -20°C for measure anti-CCP. Sodium citrate-anticoagulated blood samples were used for estimating the erythrocyte sedimentation rate (ESR).

2.5. MEASUREMENT OF SERUM ANTI-CCP LEVELS

Serum was tested for the presence of cyclic citrullinated peptide (CCP) autoantibodies using a manual enzyme-linked immunosorbent assay (ELISA) with a commercial kit (INOVA Diagnostics, San Diego, CA, USA).

2.6. MEASUREMENT OF ESR

ESR was measured using the Westergren method on sodium citrate-anticoagulated whole blood samples, according to established clinical guidelines [17].

2.7. MEASUREMENT OF CBC PARAMETERS

Hematological markers, including white blood cell (WBC) count, red blood cell (RBC) count, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin (Hb) concentration, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), were analyzed using a Sysmex- XN-550 automated analyzer (Sysmex, Japan).



2.8. ASSESSMENT OF HEMATOLOGICAL INDICES

Hematological indices, including NLR, LMR, PLR, NMR, SIRI, and SII, were calculated using neutrophils, lymphocytes, monocytes, and platelets as follows:

NLR = neutrophil/lymphocyte ratio

LMR = lymphocyte/monocyte ratio

PLR = platelet/lymphocyte ratio

NMR = neutrophil / monocyte ratio

SIRI = (monocyte * neutrophil)/lymphocyte ratio

SII = (platelet * neutrophil)/lymphocyte ratio

2.9. STATISTICAL ANALYSIS

The data were coded and entered into the Statistical Package for the Social Sciences (SPSS, version 25; IBM Corp., 2017) for analysis. To compare continuous variables between the two groups, the independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. The strength and direction of the relationships between continuous variables were assessed using Spearman's rank correlation coefficient for non-normally distributed data. Receiver operating characteristic (ROC) curve analysis with estimation of the area under the curve. The optimal cutoff values of hematological indices for predicting the presence of RA were explored using ROC analysis based on the maximum Youden's index. A two-tailed p-value of < 0.05 was considered statistically significant.

2.10. ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethical Research Committee of the Faculty of Medicine and Health Sciences, Sana'a University.

3. RESULTS

A total of 100 (50%) cases and 100(50%) controls were included in this study. The majority of patients with RA were female (90%). The mean age \pm SD was 45 ± 13 years for cases and 44 ± 13 years for controls. The most affected age group among the cases was 40-49 years (34%). Approximately two-thirds of the patients were married (67%). Twenty% of patients with RA had hypertension, followed by diabetes mellitus (16%). The median disease duration was 4(0.1-24) years. The mean \pm SD of age at onset for cases was 39.7 ± 12 years (Table 1).

Table 2 showed monocyte, eosinophil, PLR, NLR, SIRI, SII, ESR and anti-CCP to be significantly higher in RA patients while Hb, hematocrit, lymphocyte, basophilic, RBCs, LMR ratios were significantly lower compared to healthy controls.

NLR, PLR, and SII had positively significant correlation with both ESR and anti-CCP while NMR had only positively significant correlation with ESR Table 3

ROC analysis

ROC analysis was performed to evaluate the potential of NLR, PLR, LMR, NMR, SIRI, SII, ESR, and anti-CCP as markers for distinguishing RA patients from healthy persons. The AUC of ESR was 0.988 and that of anti-CCP was 0.999, indicating near-perfect diagnostic accuracy. Both tests achieved 100% specificity, indicating that no healthy individuals were misclassified as patients with RA. Anti-CCP showed exceptional sensitivity (99%) compared to ESR (90%), making it the strongest individual predictor. The AUC for SIRI was 0.658, and for NLR (AUC = 0.647),SII(AUC, 0.617), and PLR (AUC = 0.614) were statistically significant but had modest discriminative power. Their sensitivities (50-69%) and specificities (62-73%) are balanced but suboptimal for standalone diagnosis compared to anti-CCP. LMR (AUC = 0.290) poorly performed. LMR had a remarkably low AUC (< 0.5), signifying that its values were inversely associated with RA status, and showed very low sensitivity (6%) despite high specificity (97%). However, NMR did not show a significant difference between the RA and healthy groups ($P = 0.139$). These parameters are shown in Fig. 1 and presented in Table 4.

4. DISCUSSION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, immune dysregulation, and multi-organ involvement [18].

This study aimed to evaluate changes in hematological parameters in patients with RA alongside with emerging inflammatory ratios in comparison to healthy controls to reveal their diagnostic and inflammatory relevance in RA [7].

The predominance of females (90%) among patients with RA in this study aligns with the well-established female bias of RA, attributed to hormonal influences, X-chromosome-linked immune regulatory genes, and heightened humoral immune responses in women [19].

The present study found significant reductions in hemoglobin, hematocrit, and RBC counts in patients with RA compared to healthy controls. These findings are in accordance with anemia of chronic disease driven by inflammatory cytokines, particularly IL-6, which suppresses erythropoietin production from the kidneys, inhibits iron mobilization through hepcidin upregulation, traps iron in macrophages, limits its availability for hemoglobin synthesis, and reduces erythrocyte lifespan[20–23].

Despite reduced Hb levels, MCV, MCH, and MCHC

Table 1. Demographic and clinical characteristics of patients with rheumatoid arthritis and control group, Sana'a, Yemen, 2025

Variables	Cases (n=100)		Control (n=100)		Total (n=200)	
	No.	(%)	No.	(%)	No.	(%)
Gender						
Female	89	89	90	90	179	90
Male	11	11	10	10	21	10
Age Group mean (\pmSD)	45(\pm 13)		44 (\pm 13)		45(\pm 13)	
<30	13	13	14	14	27	11
30-39	16	16	24	24	40	20
40-49	34	34	29	29	63	31.5
50-59	19	19	19	19	38	19
\geq 60	18	18	14	14	32	16
Marital status						
Single	18	16	19	19	37	18
Married	67	67	67	67	134	67
Widowed	11	11	10	10	21	11
Divorced	4	4	4	4	8	4
Residence						
Urban	78	78	93	93	171	85.5
Rural	22	22	7	7	29	14.5
Co-morbidities						
Hypertension	20	20	-	-		
Diabetes Mellitus	16	16				
Cardiovascular disease	6	6				
Periodontal	11	11				
Lung disease	2	2				
Allergy	10	10				
Anemia	16	16				
Viral disease	2	2				
Other autoimmune disease	4	4				
Disease duration (years)	4(0.1-24)		-			
Age at onset (years)	39.7 \pm 12					

SD, Standard deviation; ESR, erythrocyte sedimentation rate

results remained within the normal ranges and did not significantly vary between the two study groups, supporting a normocytic, normochromic anemia pattern, a characteristic of inflammation-mediated anemia rather than nutritional deficiency anemia [24].

Our study showed a decrease in lymphocyte counts in patients with RA than in healthy controls. Lower lymphocyte counts detected in patients with RA probably result from chronic immune activation, apoptosis of T lymphocytes, and redistribution of lymphocytes from peripheral blood to inflamed synovial tissue. This phenomenon has been described as a marker of immune exhaustion and chronic inflammatory burden [25, 26].

Patients with RA demonstrated significantly higher monocyte counts than healthy controls. Higher monocyte levels in RA reflect upregulation of myeloid lineage activation; such circulating monocytes serve as precursors to synovial macrophages and osteoclasts, driving pannus formation and joint erosion through

TNF- α , IL-1 β , and matrix metalloproteinase production. Increased monocyte counts in RA have been frequently associated with disease activity and radiographic progression [27–29].

In our study, the NLR was significantly higher in patients with positive correlations with ESR and anti-CCP. This result agrees with the previous studies reported by Elsayed *et al.* ., and Obaid *et al.* ., which showed a positive correlation with ESR among patients [10, 30]. Another study showed a significantly positive correlation with anti-CCP, as reported by Khan *et al.* [7]. However, this finding contrasts with those of other studies that found no significant correlation between NLR and ESR [7, 31–33]. Furthermore, another study reported no significant correlation between NLR and anti-CCP [10].

The inflammatory indices (NLR, SII, SIRI, and PLR) revealed moderate yet statistically significant



Table 2. Association of CBC parameters, LMR, NLR, PLR, NMR, SIRI, SII, ESR, and anti-CCP between the rheumatoid arthritis group and the control group, Sana'a, Yemen, 2025

Characteristic	Cases	Controls	P-Value
Hemoglobin level (g/dl) mean (±SD)	12.74±1.05	13.58±0.88	<0.001*
Hematocrit (%)	38.23±3.16	40.73±2.63	<0.001*
MCV (FL)	78.62±9.63	79.08±9.99	0.746*
MCH (Pg)	26.21±3.21	26.36±3.33	0.746*
MCHC (g/dl)	33.33±0.0	33.33±0.0	1.000*
WBC (×10⁹/L) mean (±SD)	6.70±2.20	6.45±1.52	0.337*
Neutrophil (×10⁹/L)	3.29(1.07-9.49)	2.87(0.91-7.89)	0.095**
Lymphocyte (×10⁹/L)	2.30(0.44-7.72)	2.65(1.17-4.12)	0.001**
Monocyte (×10⁹/L)	0.39(0.04-1.66)	0.33(0.07-0.79)	0.007**
Eosinophil (×10⁹/L)	0.21(0.0-2.20)	0.14(0.01-0.56)	0.001**
Basophil (×10⁹/L)	0.035(0.0-0.26)	0.042(0.01-0.12)	<0.001**
RBC (×10¹²/L) mean (±SD)	4.93±0.69	5.21±0.57	0.002*
Platelets (×10⁹/L) mean (±SD)	303.11±94.01	298.77±76.00	0.720*
LMR	5.33(2.23-22.43)	7.30(3.35-23.32)	<0.001**
NLR	1.39(0.28-8.81)	1.15(0.30-3.60)	<0.001**
PLR	127.42(50.72-797.27)	112.61(46.75-336.64)	0.005**
NMR	8.39(2.49-110.13)	9.12(3.16-26.79)	0.139**
SIRI	0.56(0.09-3.15)	0.39(0.08-1.68)	<0.001**
SII	426.90(61.01-3299.70)	312.42(107.64-1081.46)	0.004**
ESR (mm/1st hr) median (range)	38 (7.0-95)	4 (1-16)	<0.001**
Anti-CCP (U/mL) median (rang)	609.5(12.0-1939)	5.83(1.80-17.0)	<0.001**

*Independent t test, ** Mann Whitney test

Table 3. Correlation between NLR, PLR, LMR, NMR ratios SIRI, and SII with ESR and anti-CCP among rheumatoid arthritis patients

	ESR		Anti-CCP	
	Spearman coefficient	P-value	Spearman coefficient	P-value
NLR	0.242	0.015	0.224	0.025
PLR	0.425	<0.001	0.360	<0.001
LMR	-0.036	0.723	-0.087	0.387
NMR	0.243	0.015	0.166	0.098
SIRI	0.044	0.663	0.090	0.371
SII	0.298	0.003	0.303	0.002

ESR, erythrocyte sedimentation rate; Anti-CCP' anti-Cyclic citrullinated peptide NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte –monocyte ratio; NMR, neutrophil–monocyte ratio; SIRI, systemic immune response index; SII, systemic immune-inflammation index

Table 4. ROC curve analysis of NLR, PLR, LMR, NMR, SIRI, SII, ESR and anti-CCP as key factors in differentiating patients with RA from healthy controls

Variables	AUC	59%CI	Cut-off value	sensitivity	specificity	Youden-index	p-value
ESR	0.988	0.98-0.99	17.0	90%	100%	0.900	< 0.001
Anti-CCP	0.999	0.99-1.0	21.0	99%	100%	0.990	< 0.001
NLR	0.647	0.570-724	1.22	69%	63%	0.320	< 0.001
NMR	0.439	0.36-0.52	15.12	15%	88%	0.030	0.139
PLR	0.614	0.54-0.69	125.57	54%	69%	0.230	0.005
LMR	0.290	0.22-0.36	14.11	6%	97%	0.030	<0.001
SIRI	0.658	0.58-0.72	0.431	67%	62%	0.290	<0.001
SII	0.617	0.54-0.70	433.96	50%	73%	0.230	0.004

ESR, erythrocyte sedimentation rate; Anti-CCP' anti-Cyclic citrullinated peptide NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte –monocyte ratio; NMR, neutrophil–monocyte ratio

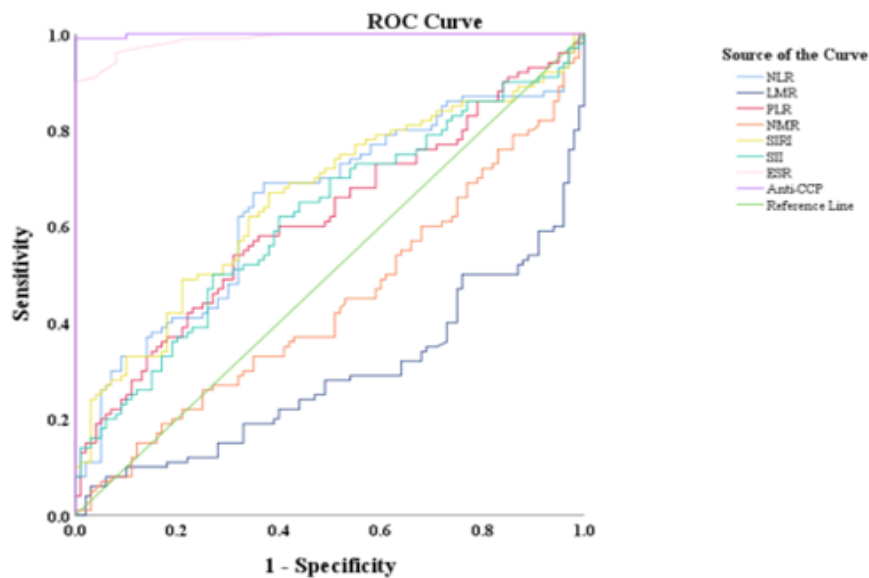


Figure 1. Receiver operating characteristic (ROC) curves analysis of NLR, PLR, LMR, MNR, SIRI, SII, ESR, and anti-CCP indices in the diagnosis of RA. Sensitivity and 1-specificity values are displayed.



AUCs. These ratios serve as integrative measures of innate immunity activation (neutrophils and platelets) in relation to adaptive immunity (represented by lymphocytes). Elevated NLR and SIRI support the role of neutrophil-mediated inflammation and the release of inflammatory citrullinating enzymes in the RA synovium [34]. Their modest performance suggests that they capture a general, non-specific inflammatory state that overlaps with, but is not exclusive to, RA.

PLR was significantly higher in patients with RA and showed strong positive correlations with ESR and anti-CCP. This result is similar to those of studies from Poland and Pakistan, which reported a significantly positive correlation [35] but dissimilar to those from studies from Egypt and Korea, which reported no significant correlation between PLR and ESR/anti-CCP [10]. Thrombocytosis in RA is driven by IL-6-mediated megakaryopoiesis. Studies reported that Elevated PLR has been associated with higher disease activity scores (DAS28) and increased cardiovascular risk in patients with RA [36–38].

LMR was significantly reduced in patients with RA and was inversely associated with disease presence. This finding reflects the combined effects of lymphocyte depletion and monocyte expansion. Although LMR correlated weakly with ESR and anti-CCP in this study, its markedly low AUC indicates limited diagnostic utility but has potential value as a marker of immune imbalance. This result agrees with other studies [39, 40]; however, this result disagrees with the study reported by Obaid et al. 2023, who showed a statistically significant increase in patients with high AUC and a significantly positive correlation with ESR [30].

The discrepancy in these inflammatory indices in different studies could be attributed to variations in the study populations, laboratory procedures, or treatment regimens.

5. CONCLUSION

NLR, PLR, MLR, SIRI, and SII were significantly higher in RA patients than in control group. NLR, PLR, and SII were positively correlated with both ESR and anti-CCP, while NMR was only positively correlated with ESR. Collectively, these findings suggest that these hematological inflammatory indices may serve as complementary biomarkers for disease screening and monitoring of inflammatory activity rather than for diagnosis.

6. RECOMMENDATIONS

The studied inflammatory indices are easy and cost-effective to measure. These indices may serve as ad-

junctive markers for the initial evaluation and monitoring of inflammatory activity in patients with RA. However, they should not replace established biomarkers (anti-CCP and RF) for RA diagnosis. Future studies should correlate these hematological markers with standardized clinical disease activity indices (e.g., DAS28-ESR) to investigate their role in assessing disease severity.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this study.

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