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Correlation of Red Cell distribution width and Neutrophil to Lymphocyte ratio with Disease activity in Rheumatoid Arthritis

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Abstract

Background and objectives: The study investigated the relationship between red cell distribution width and neutrophil-to-lymphocyte ratio with disease activity in rheumatoid arthritis. These markers provide insights into inflammation and immune dysregulation, potentially aiding clinical decision-making, and patient management.

Methods: In the current cross-sectional study, 105 patients suffering from rheumatoid arthritis who were referred to the Rheumatology and Rehabilitation division in Sulaymaniyah, Kurdistan region from January 2023 to June 2023 were studied. To gather the required data, the patient's medical files and relevant examinations were used. Disease activity measured using disease activity score-28 and clinical disease activity.

Results: The study involved patients with an average age of 53.38 years. Eighty patients (76.2%) were females, and 25 (23.8%) were males. Patient and evaluator global disease activity mean were 5.38 and 4.52, respectively. Mean values for red cell distribution width, neutrophil/lymphocyte ratio, erythrocyte sedimentation rate, and hemoglobin were 15.4672, 2.3603, 31.611, and 12.773, respectively. Notably, clinical disease activity showed no significant correlation with age, Body mass index, disease duration, or various hematological parameters. Similarly, no significant associations were observed between Disease activity score-28 and demographic or clinical factors.

Conclusion: Neutrophil to lymphocyte ratio and red cell distribution width cannot be utilized as reliable biomarkers to assess disease activity in patients with rheumatoid arthritis.

Keywords: Neutrophil to lymphocyte ratio, Red cell distribution width, Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is characterized by systemic inflammation and joint destruction caused by synovitis. Its prevalence is around 1% of the global population, with a higher incidence in women.[1] The cardinal features of RA encompass swollen and tender joints accompanied by morning stiffness and fatigue. Severe cases may involve extra-articular manifestations such as rheumatoid nodules, interstitial lung disease, pericarditis, and vasculitis. The etiology of RA is multifaceted, involving genetic and environmental factors that disrupt immune tolerance, resulting in autoantibodies such as anti-cyclic citrullinated peptide antibodies and rheumatoid factor.[2] Immune complexes are formed by these autoantibodies which also activate the complement cascade and attract inflammatory cells to the synovium. Disease activity in RA can be evaluated through several composite indices, including C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), patient global assessment, and the disease activity score 28 (DAS28). Disease remission is shown with DAS28 scores below 2.6. Low, moderate, and high disease activities are indicated with DAS28 scores 2.6 to 3.2, >3.2 to 5.1, and over 5.1, respectively. Although ESR and CRP are acute-phase reactants reflecting systemic inflammation, they can also increase due to comorbidities. Therefore, interest in identifying novel biomarkers that correlate with RA disease activity is increasing.[3] Anisocytosis (defined as the size of circulating red blood cells) is measured through red cell distribution width (RDW) which is an integral part of a comprehensive blood count. Although RDW is mainly utilized to differentiate microcytic anemias, studies have indicated its association with systemic inflammation. The balance between innate immune response (due to neutrophils) and adaptive immunity (supported by lymphocytes) is shown by neutrophil-to-lymphocyte ratio (NLR). Both RDW and NLR are easily obtainable, cost-effective, and routinely reported parameters in a complete blood count.[4] Additionally, RDW and NLR positively correlate with conventional markers of inflammation like ESR and CRP and disease activity scores.[5] The precise pathophysiological mechanisms linking RDW and NLR to inflammation in RA are not completely understood, but potential factors include impaired iron metabolism, erythropoietin inhibition, decreased red blood cell survival, oxidative stress, and release of proinflammatory cytokines promoting neutrophilia and relative lymphopenia during active disease.[6] Existing studies on the application of NLR and RDW in evaluating disease activity in RA have yielded inconclusive findings, primarily due to variations in hemogram parameters among different ethnic groups and the failure to consider confounding factors such as anemia. Consequently, it is essential to conduct large-scale investigations that control for relevant comorbidities to obtain more reliable results. Hence, the current study was aimed at evaluating the relation between RDW and NLR and disease activity in RA within the local population.

Patients and methods

The present cross-sectional study was conducted in Rheumatology and Rehabilitation division in Sulaymaniyah, Kurdistan region, Iraq between January and June 2023. The study was conducted on 105 patients suffering from rheumatoid arthritis based on 2010 ACR /EULAR classification criteria. Patients who were 18 to 80 years old and had rheumatoid arthritis based on ACR /EULAR 2010 classification criteria system were included in the study, while patients who refused to give consent and those who had chronic liver disease, severe anemia, chronic renal injury, chronic infection, history of blood transfusion within 4 months, malignancy, pregnancy, and 6 months

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postpartum were excluded. The disease activity was assessed using DAS-28 and CDAI, and the patients were sent for investigations including ESR, CBC (five differential count), liver function test, Renal function test. The patient's medical files and relevant examinations were used to collect the required data which were analyzed using Statistical Package for Social Sciences (SPSS, version 24). The Ethics Committee of the Kurdistan Higher Council of Medical Specialties approved the study's protocol. In addition, the patients gave their informed consent.

Results

The collected data indicated that the patients aged from 21 to 80 years; with 31.4% of them being 41 to 50 years, 27.6% being 51 to 60 years, 18.1% being 61 to 70 years, 10.5% being 71 to 80 years, 7.6% being 31 to 40 years, and 4.8% being 21 to 30 years. In terms of their sex, most of them (76.2%) were females, and the rest (23.8%) were males, Table (1).

Table (1): The patients' age and sex

	Frequency (N)	Percentage (%)
Age group		
21 - 30	5	4.8
31 - 40	8	7.6
41 - 50	33	31.4
51 - 60	29	27.6
61 - 70	19	18.1
71 - 80	11	10.5
Total	105	100.0
Sex		
Male	25	23.8
Female	80	76.2
Total	105	100.0

According to the analysis of the collected data, normal weight, overweight, and obesity class I were observed among 23.8%, 39%, and 29.5% of the patients, respectively. Seropositive status was positive in 77.1% of the patients. The most frequently consumed drugs were steroid and conventional synthetic disease modifying Anti Rheumatic Drugs (csDMARD) (44.8%) and csDMARD alone (23.8%). Most of the patients (79%) did not smoke, and 12.4% were passive smokers. Most of them (99%) did not drink alcohol. Based on the results, the clinical disease activity was low in 25.7% of the patients, moderate in 37.1%, and high in 30.5%. Moreover, the score of DAS-28 (ESR) was low in 13.3% of the patients, moderate in 51.4%, and high in 23% of the patients, Table (2). The results of analyzing CDAI or DAS-28 scores using independent samples T-test are presented in Figure (1). As indicated, there was not a significant relation between clinical disease activity and RDW (p-value=0.4). As shown by the results of independent samples T-test presented in Figure (2), clinical disease activity and neutrophil/lymphocyte ratio were not significantly correlated (p-value=0.4), Figure (2). The results of Pearson correlation coefficient indicated that there was a significant correlation between RDW and total score of clinical disease activity (p-value=0.016), while the results of 2-tailed T-test did not show a significant correlation between them (p-value=0.874). As shown by the results of both Pearson correlation coefficient and 2-tailed T-test, neutrophil/Lymphocyte ratio (NLR) did not have significant correlations with total score of clinical disease activity index (p-value>0.05), See Table (3).According to the results of ANOVA test presented in Table (3), the total score of clinical disease activity had no significant correlation with RDW and neutrophil/lymphocyte ratio (p-value>0.05).

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Table (2): The patients' demographics and clinical characteristics

	Frequency (N)	Percentage (%)
BMI		
Underweight <18.5	1	1.0
Normal weight 18.5 - 24.9	25	23.8
Overweight 25 - 29.9	41	39.0
Obesity Class I 30.0 - 34.9	31	29.5
Obesity Class II 35.0 - 39.9	7	6.7
Total	105	100.0
Seropositive status		
Positive	81	77.1
Negative	24	22.9
Total	105	100.0
Drug history		
NSAID	1	1.0
csDMARD	25	23.8
bDMARD	7	6.7
Steroid, csDMARD and Other	47	44.8
Steroid and Other	8	7.6
csDMARD, bDMARD and Other	8	7.6
NSAID, Steroid, csDMARD, bDMARD and Other	9	8.6
Total	105	100.0
Smoking History		
Positive	9	8.6
Negative	83	79.0
Passive smoker	13	12.4
Total	105	100.0
Alcoholic History		
Negative	104	99.0
Ex-alcoholic	1	1.0
Total	105	100.0
Total score of clinical disease activity index		
Remission ≤2.8	7	6.7
Low 2.9 – 10	27	25.7
Moderate 10.1 – 22	39	37.1
High > 22.1	32	30.5
Total	105	100.0
Total score of DAS-28 (ESR)		
Remission <2.6	12	11.4
Low 2.6 - 3.2	14	13.3
Moderate 3.3 - 5.1	54	51.4
High > 5.2	25	23.8
Total	105	100.0

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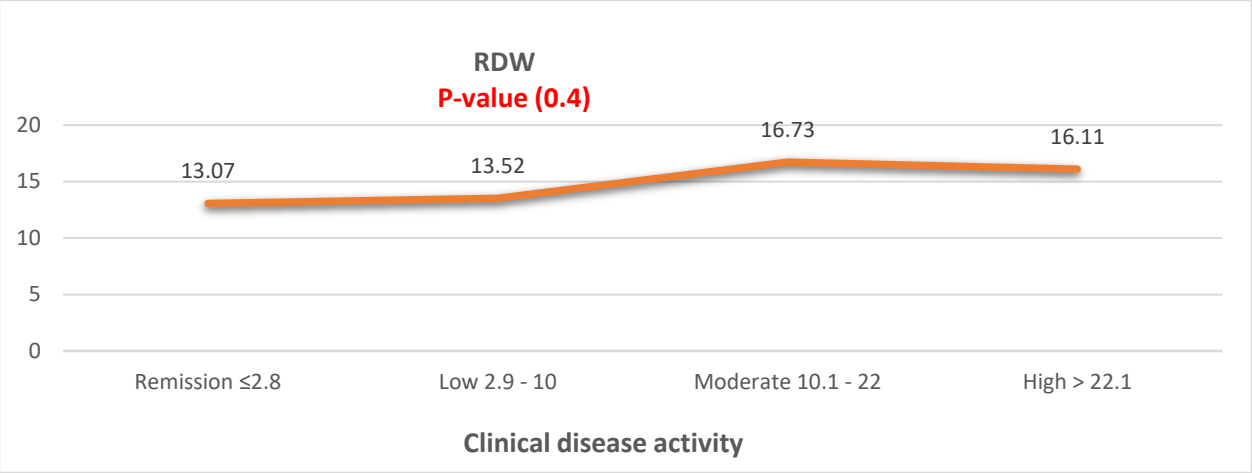

Figure (1): Relation between RDW and CDAI

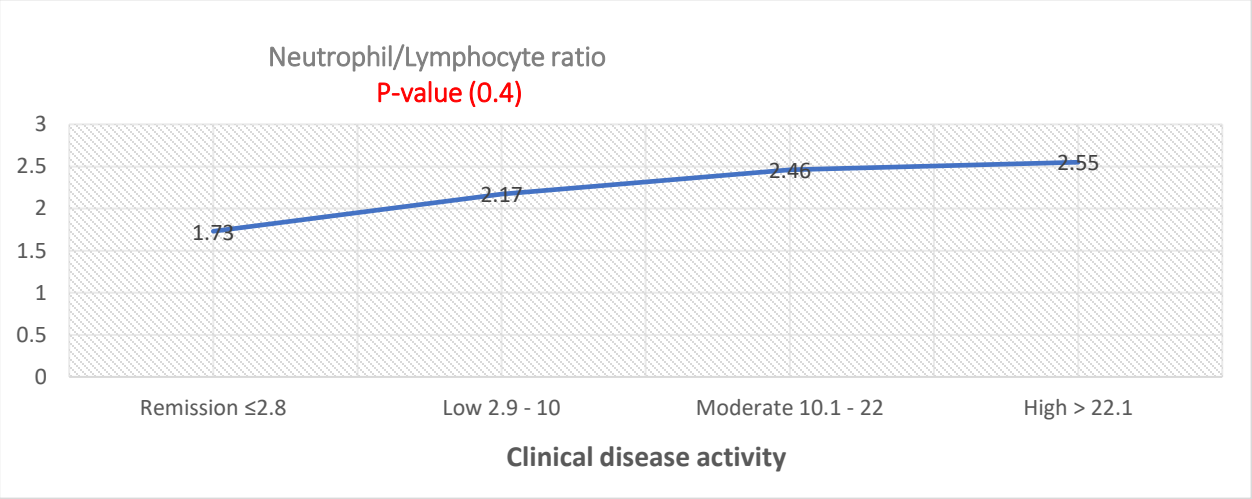

Figure (2): Relationship between NLR and CDAI

Table (3): Correlation between total score of clinical disease activity and the studied variables

Total score of clinical disease activity index		N	Mean ± Std. De	95% Cl	Mini – Maxi	p-value
RDW	Remission ≤2.8	7	13.0714 ± 0.61837	12.4995 - 13.6433	12.40 - 14.10	0.401
	Low 2.9 - 10	27	13.5185 ± 1.02208	13.1142 - 13.9228	12.10 - 17.00	
	Moderate 10.1 - 22	39	16.7256 ± 11.07426	13.1358 - 20.3155	11.80 - 53.10	
	High > 22.1	32	16.1019 ± 9.34175	12.7338 - 19.4699	11.20 - 47.10	
	Total	105	15.4672 ± 8.55549	13.8115 - 17.1229	11.20 - 53.10	
Neutrophil / Lymphocyte ratio	Remission ≤2.8	7	1.7286 ± 0.34503	1.4095 - 2.0477	1.20 - 2.10	0.624
	Low 2.9 - 10	27	2.1704 ± 1.01785	1.7677 - 2.5730	.70 - 4.50	
	Moderate 10.1 - 22	39	2.4572 ± 2.04495	1.7943 - 3.1201	.80 - 11.50	
	High > 22.1	32	2.5406 ± 1.69094	1.9310 - 3.1503	.40 - 9.80	
	Total	105	2.3603 ± 1.64191	2.0425 - 2.6780	.40 - 11.50	

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As can be seen from figure (3) the results demonstrated no significant relationships between RDW and DAS-28 (ESR) (p-value=0.5).

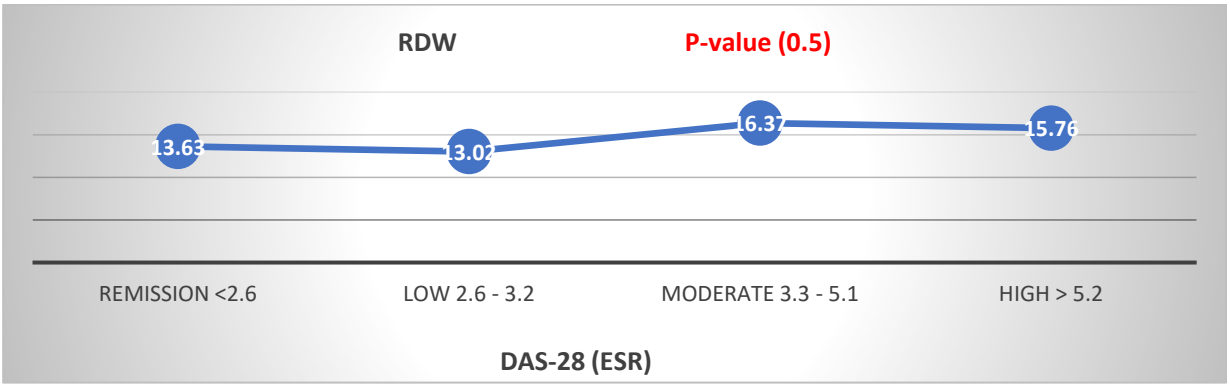

Figure (3): Relationship between RDW and DAS-28 (ESR)

According to the results presented in figure (4), DAS-28 (ESR) had no significant relationships with neutrophil/lymphocyte ratio (p-value=0.7).

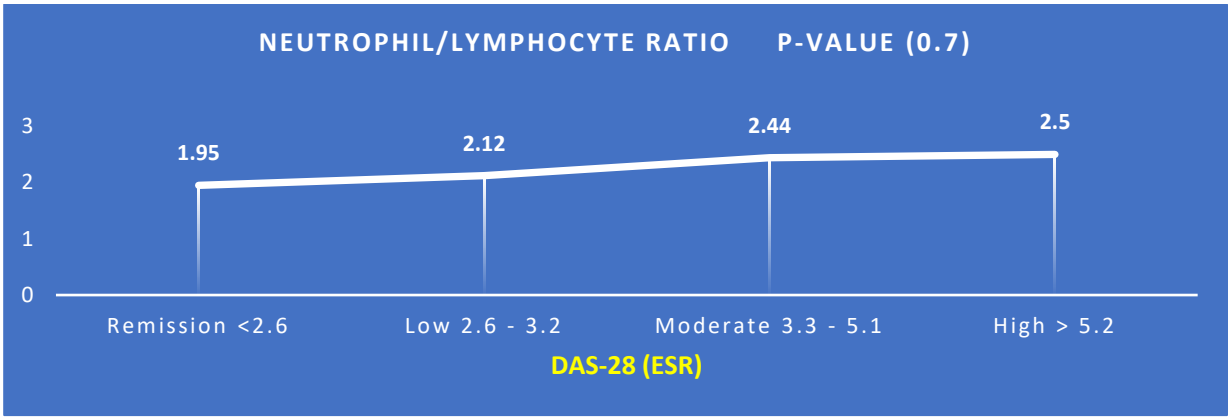

Figure (4): Relationship DAS-28 (ESR) and NLR

As indicated by the results presented in Table (4), the DAS-28 (ESR) total score had no significant associations with RDW, or neutrophil/lymphocyte ratio (p-value>0.05).

Table (4): Correlation between DAS-28 (ESR) total score and the studied variables

Total score of DAS-28 (ESR)		N	Mean ± Std. De	95% Cl	Mini – Maxi	p-value
RDW	Remission <2.6	12	13.6250 ± 1.20990	12.8563 - 14.3937	12.50 - 17.00	0.511
	Low 2.6 - 3.2	14	13.0214 ± 0.88420	12.5109 - 13.5320	12.00 - 14.80	
	Moderate 3.3 - 5.1	54	16.3752 ± 10.12274	13.6122 - 19.1382	11.80 - 53.10	
	High > 5.2	25	15.7600 ± 9.09240	12.0068 - 19.5132	11.20 - 47.10	
	Total	105	15.4672 ± 8.55549	13.8115 - 17.1229	11.20 - 53.10	
Neutrophil /Lymphocyte ratio	Remission <2.6	12	1.9500 ± 0.83720	1.4181 - 2.4819	0.90 - 4.00	0.719
	Low 2.6 - 3.2	14	2.1286 ± 0.69662	1.7264 - 2.5308	1.00 - 3.30	
	Moderate 3.3 - 5.1	54	2.4431 ± 1.88152	1.9296 - 2.9567	0.40 - 11.50	
	High > 5.2	25	2.5080 ± 1.76822	1.7781 - 3.2379	1.10 - 9.80	
	Total	105	2.3603 ± 1.64191	2.0425 - 2.6780	0.40 - 11.50	

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Discussion

The study revealed a significant correlation between Red Cell Distribution Width (RDW) and neutrophil-to-lymphocyte ratio (NLR) with disease activity in Rheumatoid Arthritis (RA). Most patients were female (76.2%), and the most common age group was 41-50 years (31.4%). The study population exhibited varying disease activity levels, with 25.7% and 13.3% of patients demonstrating low disease activity, respectively, according to CDAI and DAS-28 scores. Demographic and clinical factors, such as body mass index, seropositivity, comorbidities, and treatment regimens, were also heterogeneous and may impact disease activity and inflammatory markers. Lifestyle factors, including smoking status and alcohol consumption, were also noted. These diverse characteristics should be considered when interpreting the relationship between RDW, NLR, and disease activity in rheumatoid arthritis (RA) patients. A similar study reported that RDW can be influenced by several demographic and biological factors such as age, physical activity, hypertension, metabolic syndrome, renal and liver function, inflammation, and, last but not least, genetic factors.[7] Our data shows no significant relationship between RDW and CDAI in rheumatoid arthritis (RA) patients. While there appears to be a numerical difference in RDW values across the disease activity groups, with higher RDW values observed in patients with moderate and high disease activity, this difference was not statistically significant. This finding suggests that RDW may not be a reliable biomarker for assessing disease activity in RA patients. Unlike the current study's findings, a recent study in 2021 found a positive correlation between RDW and disease activity markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and DAS28, in patients with rheumatoid arthritis. Additionally, RDW was a better marker than (ESR) and (CRP) in detecting the level of disease activity. Based on their findings, it was suggested that RDW could be used in clinics to follow disease activity. In addition, RDW is widely available, as it's usually included in routine complete blood pictures, and there will be no need for a further cost.[8] The results showed no significant correlation between NLR and clinical disease activity in rheumatoid arthritis patients. This finding contradicts previous studies that suggested a positive association between elevated NLR and increased disease activity in rheumatoid arthritis.[9] In a similar study in 2020, the findings suggested that the neutrophil-lymphocyte ratio was increased in RA patients and positively correlated with CRP, ESR, and DAS-28, which are well-established and commonly used markers for evaluating disease activity in RA. Moreover, their study found that neutrophil counts were increased significantly, whereas the lymphocyte count was decreased significantly in RA patients. Further research is needed to investigate the relationship between these two parameters and their potential utility as biomarkers for disease activity monitoring in rheumatoid arthritis.[10] The results of our study indicate that there is no significant correlation between the clinical disease activity index and either RDW or NLR in patients with Rheumatoid Arthritis (RA). The Pearson correlation coefficients for RDW and NLR with the total score of clinical disease activity index were 0.016 ($p = 0.874$) and 0.073 ($p = 0.456$), respectively. These findings suggest that RDW and NLR may not be reliable markers for assessing disease activity in RA patients. This is contrary to some previous studies that have reported associations between these parameters and RA disease activity. The lack of correlation observed in our study could be due to various factors, including the heterogeneity of our patient population, the specific disease activity index used, or the

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influence of confounding variables not accounted for in this analysis. For instance, a study in 2020 reported that RDW and NLR are potential low-cost markers for detecting rheumatoid arthritis.[11] However, in another study, it was reported that the NLR is a valuable inflammatory marker in patients with RA, but RDW is not useful in this regard.[12] In another related study, it was reported that the NLR is a valuable inflammatory marker in patients with RA. Still, RDW was not found to be useful for this purpose.[12] Further research is needed to explore the potential utility of RDW in evaluating disease activity in rheumatoid arthritis, possibly in combination with other inflammatory markers or clinical assessments. Furthermore, a study in 2021 reported a significant correlation between RDW and disease activity in RA patients. According to their investigation, RDW performed better than Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) in detecting RA disease activity. Hence, RDW could be employed in clinical settings to monitor disease activity. An additional advantage of RDW is its widespread availability, as it is typically included in routine complete blood counts, eliminating the need for additional costs.[8] The findings showed no significant relationship between DAS-28 (ESR) and NLR. This suggests that NLR may not be a reliable marker for assessing disease activity in RA patients. Based on a similar study in 2023, although there was a highly significant positive correlation between NLR and RDW, no significant correlation was seen between NLR and disease duration, TJC, SJC, CRP, RF, ACPA, and DAS28–ESR.[12] The study found no significant correlation between DAS-28 ESR, RDW, and NLR, in rheumatoid arthritis patients. This suggests that these hematological parameters may not be reliable biomarkers for assessing disease activity in rheumatoid arthritis. In contrast to the data from this study, a study in 2024 reported a statistically significant correlation of RDW with the DAS28 score.[10]

Conclusion

The study found no significant correlations between clinical disease activity (CDAI) or disease activity score-28 (DAS-28) and red cell distribution width (RDW) or neutrophil-to-lymphocyte ratio (NLR) in rheumatoid arthritis patients. therefore, RDW and NLR cannot be reliably used as biomarkers to assess disease activity in rheumatoid arthritis patients. Further large-scale studies controlling for confounding factors are needed to clarify the relationship between these markers and RA disease activity.

Conflict of interest

None.

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