Thi-Qar Medical Journal (TQMJ):Vol.(26),No.(2),2023

Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq

ISSN (Print):1992-9218

Correlation of Red Cell Distribution Width and Neutrophil to Lymphocyte Ratio with Disease Activity in Rheumatoid Arthritis

Solin Nooruldeen Omar*1, Raouf Rahim Mirza*2

1 Shahid Dr. Hemn hospital

2 Kurdistan Board for Medical Specialties/Rheumatology Department /Sulaimanya Center

***Corresponding author:**

dr.solin1991@gmail.com

Abstract

Background: The neutrophil to lymphocyte ratio (NLR), which reflects the balance between neutrophils and lymphocytes, and red cell distribution width (RDW), which measures the variation in red blood cell size, have been used as biomarkers for assessing disease activity and treatment response in rheumatoid arthritis (RA). These markers offer insights into inflammation and immune dysregulation in RA and could aid in clinical decision-making and optimizing patient management. The present study was carried out to assess the relationship between RDW and NLR with disease activity in RA.

Materials and methods: The present cross-sectional study was conducted on 105 patients with rheumatoid arthritis in Rheumatology and Rehabilitation division in Sulaymaniyah, Kurdistan region-Iraq from January 2023 to June 2023. The patients' medical files and relevant examinations were used to collect required data. Statistical Package for Social Sciences (SPSS, version 24.0) was used to analyze the collected data.

Results: The patients aged 53.38 years on average. The mean patient and evaluator global disease activities were respectively 5.38 and 4.52. Moreover, the mean scores of RDW, neutrophil/lymphocyte ratio, ESR, HG, and RBC were respectively 15.4672, 2.3603, 31.611, 12.773, and 4.8798. clinical Disease activity had no significant relationship with the patients' age, BMI, disease duration, RDW, neutrophil/lymphocyte ratio, WBC count, HG, or RBC (p-value>0.05). Also, no significant relationships were found between DAS-28 (ESR) and the patients' age, sex, BMI, Sero, disease duration, PMH, RDW, neutrophil/lymphocyte ratio, WBC count, HG, RBC, drug history, smoking history, or alcoholic history (p-value>0.05).

Conclusion: Neutrophil to lymphocyte ratio (NLR) and red cell distribution width (RDW) cannot be utilized as reliable biomarkers to assess disease activity in patients with rheumatoid arthritis; therefore, further studies are required to understand rheumatoid arthritis progression.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease 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 (Kaur et al., 2012(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, leading to the production of autoantibodies like rheumatoid factor and anti-cyclic citrullinated peptide antibodies. These autoantibodies form immune complexes, activate the complement cascade, and attract inflammatory cells to the synovium. Consequently, a cytokine cascade involving proinflammatory molecules like tumor necrosis factor-alpha, interleukin-1, and interleukin-6 perpetuates persistent synovitis and joint damage (Bonfiglioli et al., 2023 (2).

Several composite indices evaluate disease activity in RA, such as the Disease Activity Score 28 (DAS28), which considers the number of tender and swollen joints, patient global assessment, and either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels. DAS28 scores below 2.6 signify disease remission, while scores between 2.6-3.2 indicate low disease activity, >3.2-5.1 suggest moderate disease activity, and scores exceeding 5.1 signify high disease activity. Although ESR and CRP are acute-phase reactants reflecting systemic inflammation, they can also increase due to comorbidities. Therefore, there is a growing interest in identifying novel biomarkers that correlate with RA disease activity (Nielung et al., 2015(3).

Red cell distribution width (RDW) measures the variation in the size of circulating red blood cells (anisocytosis) and is routinely reported as part of a complete blood count. Although RDW is mainly utilized to differentiate microcytic anemias, studies have indicated its association with systemic inflammation. Neutrophil-to-lymphocyte ratio (NLR) reflects the balance between innate (neutrophils) and adaptive immunity (lymphocytes). Both RDW and NLR are easily obtainable, cost-effective, and routinely reported parameters in a complete blood count (Weiss et al., 2012(4).

Several studies have observed higher RDW and NLR levels in RA patients compared to healthy individuals. Additionally, RDW and NLR positively correlate with conventional markers of inflammation like ESR and CRP and disease activity scores. 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 (Mercan et al., 2016(5).

However, conflicting reports have raised doubts about the reliability of RDW and NLR as markers of RA activity. The specificity of RDW in predicting disease activity in RA remains uncertain due to its susceptibility to be influenced by anemia, which frequently occurs in RA as a consequence of chronic inflammation. Additionally, variations in reported cutoff values for RDW

and NLR predicting inflammation may be attributed to heterogeneity among study populations and differences in cell counting techniques (Kushwaha et al., 2023(6).

Existing studies on the use of RDW and NLR in assessing 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. Prospective analyses that assess the temporal associations between RDW, NLR, and RA disease activity markers like flare-ups and treatment responses are needed to establish the clinical significance of these promising biomarkers. Gaining a better understanding of their utility in monitoring RA could support the development of standardized assessment approaches. However, before full implementation, further validation and robust evidence are necessary (Wu et al., 2023(7). Hence, the objective of this present study is to evaluate the relationship between RDW and NLR and disease activity in RA within the local population.

Materials and Methods

Study design and setting: The present cross-sectional study was conducted in Rheumatology and Rehabilitation division in Sulaymaniyah, Kurdistan region, Iraq from January 2023 to June 2023.

Study sample and sampling method: The study sample consisted of 105 patients who were diagnosed with rheumatoid arthritis according to 2010 ACR /EULAR classification criteria. The inclusion criteria were rheumatoid arthritis patients aged 18 to 80 years who were diagnosed according to 2010 ACR /EULAR classification criteria. The exclusion criteria were patients refused to give consent, chronic liver disease, severe anemia, chronic renal injury, chronic infection, history of blood transfusion within 4 months, malignancy, pregnancy and 6 months postpartum.

Data collection and analysis: Required data were collected from the patients' medical files and relevant examinations. The collected data were analyzed using Statistical Package for Social Sciences (SPSS, version 24.0).

Ethical considerations: The study's protocol was approved by the Ethics Committee of Kurdistan Board for Medical Specialties. Moreover, informed consent was obtained from the participants.

Results

Analyzing the collected data revealed that the patients' age ranged from 21 to 80 years; most of them (59%) were 41 to 60 years. Moreover, the results showed that most of them (80%) were females, married (92.4%), lived in Slemani (91.4%), and were housewives (67.6%)

(See Table 1).

Table (1). The patients' sociodemographics

	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**
Married		
Married	**97**	**92.4**
Unmarried	**8**	**7.6**
Total	**105**	**100.0**
Residency		
Slemani	**96**	**91.4**
Kalar	**4**	**3.8**
Darbandixan	**2**	**1.9**
Halabja	**2**	**1.9**
Qaladze	**1**	**1.0**
Total	**105**	**100.0**
Occupation		
Housewife	**71**	**67.6**
Employee	**23**	**21.9**
Retired	**8**	**7.6**
Driver	**2**	**1.9**
Student	**1**	**1.0**
Total	**105**	**100.0**

According to the results, 23.8% of the patients had normal weight, 39% were overweight, and 29.5% had obesity class II. Sero and comorbidities were found positive in 77.1% and 23.8% of the patients, respectively. The most frequently consumed drugs were steroid and csDMARD (44.8%) and csDMARD (23.8%). Most of the patients (79%) did not smoke, and 12.4% were passive smokers. Most of them (99%) did not drink alcohol. The results showed that the disease activity was low in 25.7% of the patients, moderate in 37.1%, and high in 30.5%. The score of DAS-28 (ESR) was low in 13.3% of the patients, moderate in 51.4%, and high in 23.8% (See Table 2).

Table (2). The patients' BMI and other medical variables

	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**
Sero		
Positive	**81**	**77.1**
Negative	**24**	**22.9**
Total	**105**	**100.0**
Co Morbidities		
Positive	**25**	**23.8**
Negative	**80**	**76.2**
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**

As indicated by the results, there were no significant relationships between the total scores of clinical disease activity index and the patients' age, BMI, or disease duration (p-value>0.05) (See Table 3).

Table (3). Relationship between clinical disease activity index and patients' age, BMI, and disease duration

Total Score Of Clinical Disease Activity Index		N	Mean ± Std. De	95% Cl	Mini - Maxi	P-Value
Age	Remission ≤2.8	7	50.86 ± 15.507	36.52 - 65.20	27 - 68	0.817
	Low 2.9 - 10	27	55.19 ± 12.357	50.30 - 60.07	29 - 75	
	Moderate 10.1 - 22	39	52.56 ± 13.094	48.32 - 56.81	24 - 76	
	High > 22.1	32	53.41 ± 12.944	48.74 - 58.07	21 - 73	
	Total	105	53.38 ± 12.890	50.89 - 55.88	21 - 76	
BMI	Remission ≤2.8	7	28.743 ± 5.6261	23.540 - 33.946	22.3 - 36.1	0.784
	Low 2.9 - 10	27	27.244 ± 4.2794	25.552 - 28.937	17.7 - 32.6	
	Moderate 10.1 - 22	39	28.103 ± 4.8839	26.519 - 29.686	19.8 - 40.0	
	High > 22.1	32	28.297 ± 4.1912	26.786 - 29.808	19.5 - 39.0	
	Total	105	27.984 ± 4.5357	27.106 - 28.862	17.7 - 40.0	
Disease Duration	Remission ≤2.8	7	10.14 ± 7.381	3.32 - 16.97	2 - 23	0.324
	Low 2.9 - 10	27	11.74 ± 8.681	8.31 - 15.17	2 - 33	
	Moderate 10.1 - 22	39	8.28 ± 7.089	5.98 - 10.58	1 - 35	
	High > 22.1	32	9.16 ± 7.044	6.62 - 11.70	1 - 32	
	Total	105	9.56 ± 7.554	8.10 - 11.02	1 - 35	

The results also indicated that there was not a significant relationship between clinical disease activity and RDW (p-value=0.4) (See Figure 1).

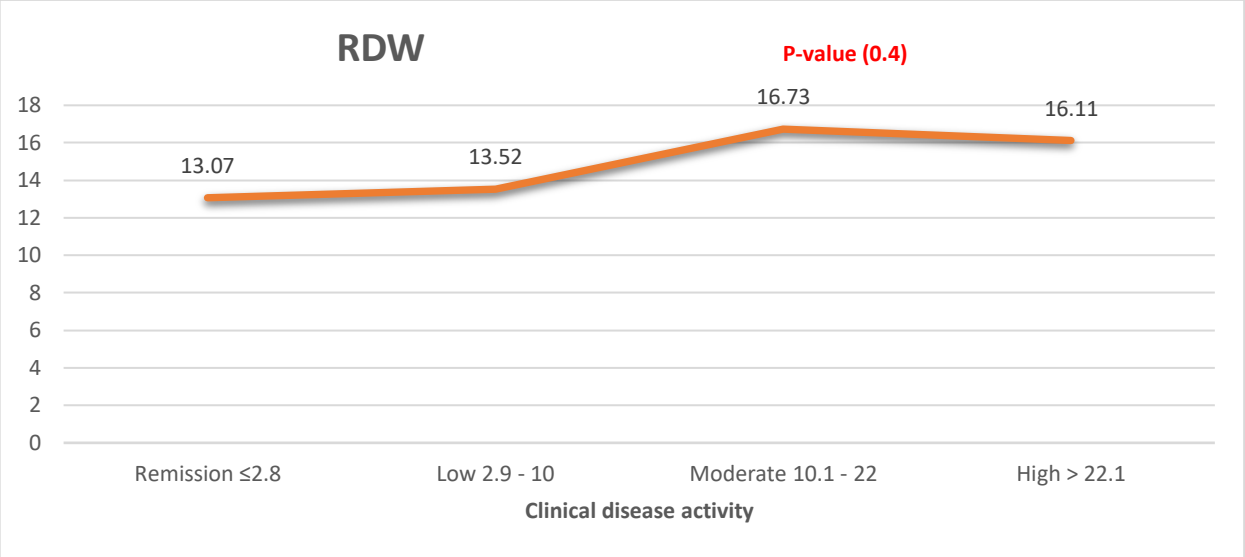

Figure (1). Relationship between RDW and clinical disease activity

According to the results, there was not a significant relationship between clinical disease activity and neutrophil/lymphocyte ratio (p-value=0.4) (See Figure 2).

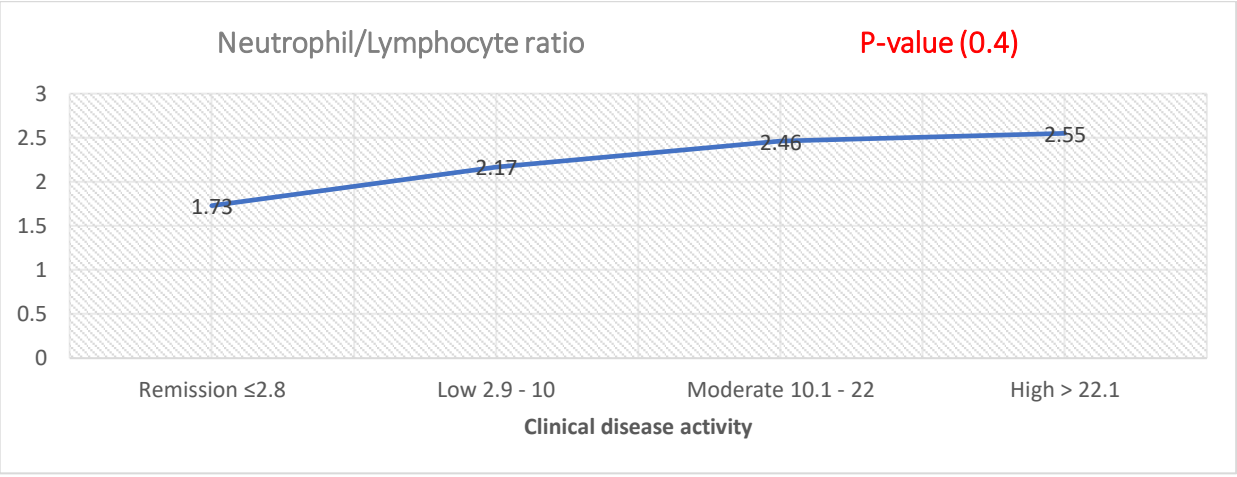

Figure (2). Relationship between clinical disease activity and neutrophil/lymphocyte ratio

The results revealed that the total score of clinical disease activity had no significant correlation with RDW, WBC count, neutrophil/lymphocyte ratio, HG, or RBC (p-value>0.05) (See Table 4).

Table (4). 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	
WBC Count	Remission ≤2.8	7	8.057 ± 3.1769	5.119 - 10.995	4.6 - 13.6	0.595
	Low 2.9 - 10	27	8.026 ± 2.6782	6.966 - 9.085	4.0 - 13.5	
	Moderate 10.1 - 22	39	7.256 ± 2.5512	6.429 - 8.083	4.3 - 17.9	
	High > 22.1	32	7.703 ± 2.1349	6.933 - 8.473	2.2 - 13.6	
	Total	105	7.644 ± 2.4938	7.161 - 8.126	2.2 - 17.9	
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	

HG	Remission ≤2.8	7	13.2857 ± 1.23346	12.1450 - 14.4265	11.00 - 14.90	0.779
	Low 2.9 - 10	27	12.9100 ± 1.16014	12.4511 - 13.3689	9.50 - 14.50	
	Moderate 10.1 - 22	39	12.5846 ± 2.52154	11.7672 - 13.4020	4.90 - 15.30	
	High > 22.1	32	12.7750 ± 1.38004	12.2774 - 13.2726	9.30 - 15.20	
	Total	105	12.7730 ± 1.83058	12.4188 - 13.1273	4.90 - 15.30	
RBC	Remission ≤2.8	7	4.7571 ± 0.44668	4.3440 - 5.1703	4.10 - 5.50	0.416
	Low 2.9 - 10	27	4.7104 ± .40341	4.5508\ - 4.8700	3.90 - 5.50	
	Moderate 10.1 - 22	39	5.1436 ± 1.94189	4.5141 - 5.7731	4.00 - 14.00	
	High > 22.1	32	4.7281 ± .34476	4.6038 - 4.8524	4.10 - 5.40	
	Total	105	4.8798 ± 1.22764	4.6422 - 5.1174	3.90 - 14.00	

As revealed by the results of the present study, total score of DAS-28 (ESR) had no significant relationships with the patients' age, BMI, or disease duration (p-value>0.05) (See Table 5).

Table (5). Relationship between total score of DAS-28 (ESR) and the patients' age, BMI, or disease duration

Total Score Of DAS-28 (ESR)		N	Mean ± Std. De	95% Cl	Mini - Maxi	P-Value
Age	Remission <2.6	12	53.00 ± 14.715	43.65 - 62.35	27 - 73	0.933
	Low 2.6 - 3.2	14	52.14 ± 11.628	45.43 - 58.86	33 - 72	
	Moderate 3.3 - 5.1	54	53.15 ± 13.128	49.56 - 56.73	23 - 76	
	High > 5.2	25	54.76 ± 12.801	49.48 - 60.04	21 - 73	
	Total	105	53.38 ± 12.890	50.89 - 55.88	21 - 76	
BMI	Remission <2.6	12	26.517 ± 3.1156	24.537 - 28.496	19.5 - 32.0	0.551
	Low 2.6 - 3.2	14	28.607 ± 4.4128	26.059 - 31.155	22.2 - 36.1	
	Moderate 3.3 - 5.1	54	27.835 ± 4.6533	26.565 - 29.105	17.7 - 40.0	
	High > 5.2	25	28.660 ± 4.9500	26.617 - 30.703	19.5 - 39.0	
	Total	105	27.984 ± 4.5357	27.106 - 28.862	17.7 - 40.0	
Disease Duration	Remission <2.6	12	10.25 ± 9.659	4.11 - 16.39	2 - 33	0.982
	Low 2.6 - 3.2	14	9.29 ± 6.776	5.37 - 13.20	1 - 23	
	Moderate 3.3 - 5.1	54	9.37 ± 7.656	7.28 - 11.46	1 - 35	
	High > 5.2	25	9.80 ± 7.053	6.89 - 12.71	1 - 26	
	Total	105	9.56 ± 7.554	8.10 - 11.02	1 - 35	

The results demonstrated no significant relationships between RDW and DAS-28 (ESR) (p-value=0.5) (See Figure 3).

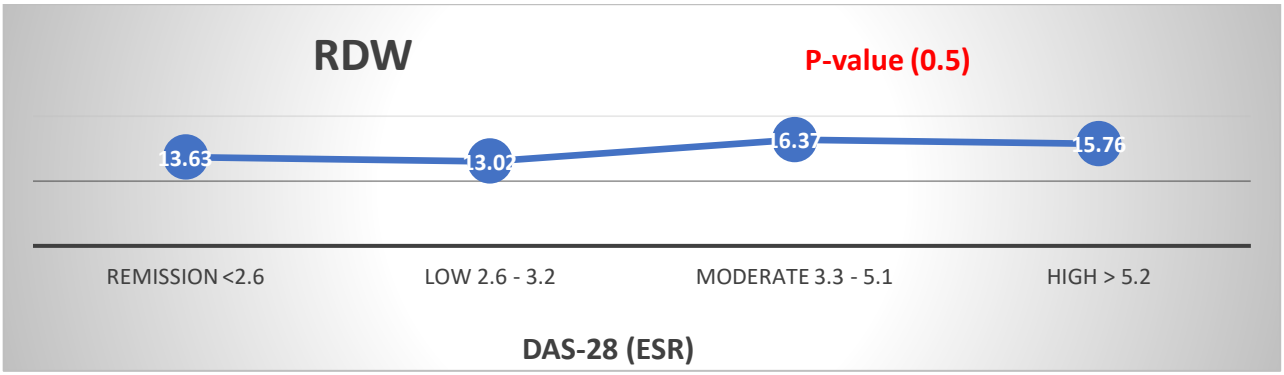

Figure (3). Relationship between RDW and DAS-28 (ESR)

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

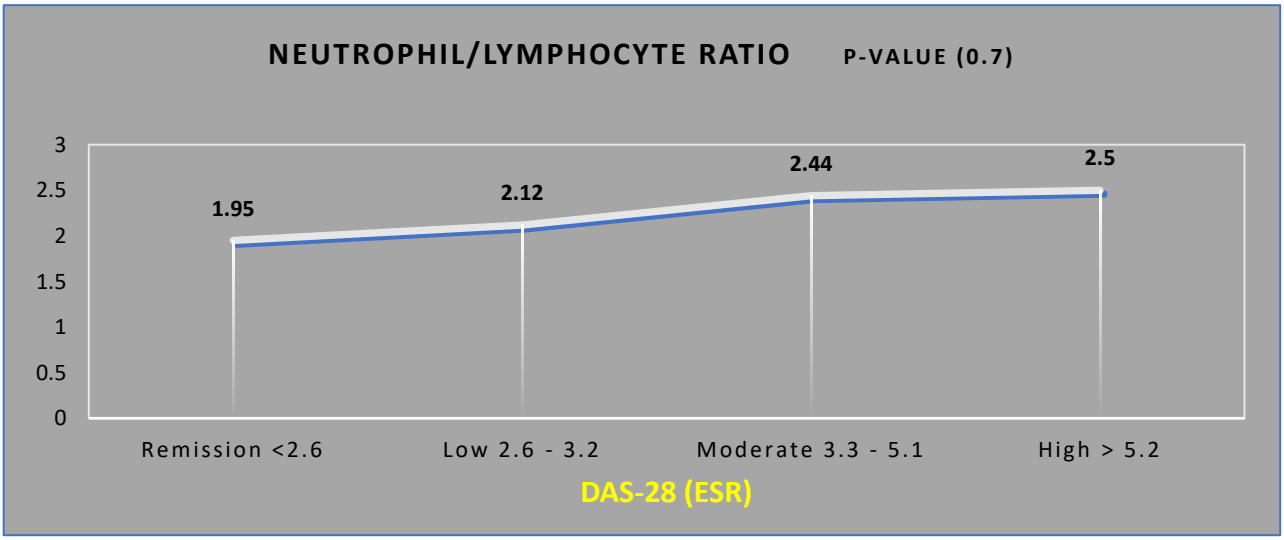

Figure (4). Relationship DAS-28 (ESR) and neutrophil/lymphocyte ratio

As indicated by the results of the present study, total score of DAS-28 (ESR) had no significant associations with RDW, WBC count, neutrophil/lymphocyte ratio, HG, or RBC (p-value>0.05) (See Table 6).

Table (6). Correlation between total score of DAS-28 (ESR) 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	
WBC Count	Remission <2.6	12	7.775 ± 2.5162	6.176 - 9.374	4.9 - 13.6	0.932
	Low 2.6 - 3.2	14	7.243 ± 2.2242	5.959 - 8.527	4.0 - 10.7	
	Moderate 3.3 - 5.1	54	7.722 ± 2.7730	6.965 - 8.479	2.2 - 17.9	
	High > 5.2	25	7.636 ± 2.0666	6.783 - 8.489	3.7 - 13.6	
	Total	105	7.644 ± 2.4938	7.161 - 8.126	2.2 - 17.9	
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	
HG	Remission <2.6	12	13.4333 ± 0.74508	12.9599 - 13.9067	12.10 - 14.90	0.488
	Low 2.6 - 3.2	14	12.5929 ± 2.38955	11.2132 - 13.9725	5.00 - 15.20	
	Moderate 3.3 - 5.1	54	12.8180 ± 2.00708	12.2701 - 13.3658	4.90 - 15.30	

	High > 5.2	25	12.4600 ± 1.39074	11.8859 - 13.0341	9.30 - 14.60	
	Total	105	12.7730 ± 1.83058	12.4188 - 13.1273	4.90 - 15.30	
RBC	Remission <2.6	12	4.9083 ± 0.31754	4.7066 - 5.1101	4.50 - 5.50	0.390
	Low 2.6 - 3.2	14	4.6000 ± 0.46410	4.3320 - 4.8680	3.90 - 5.50	
	Moderate 3.3 - 5.1	54	5.0644 ± 1.65690	4.6122 - 5.5167	3.90 - 14.00	
	High > 5.2	25	4.6240 ± 0.33823	4.4844 - 4.7636	4.00 - 5.20	
	Total	105	4.8798 ± 1.22764	4.6422 - 5.1174	3.90 - 14.00	

According to the results of the present study, total score of DAS-28 (ESR) had no significant relationships with the patients' age, sex, BMI, Sero, PMH, drug history, smoking history, or alcoholic history (p-value>0.05) (See Table 7).

Table(7). Relationship between total score of DAS-28 (ESR) and the patients' sociodemographics

		Total score of DAS-28 (ESR)				Total	P-Value
		Remission <2.6	Low 2.6 - 3.2	Moderate 3.3 - 5.1	High > 5.2		
Age group	21 - 30	2(16.7)	0(0.0)	2(3.7)	1(4.0)	5(4.8)	0.842
	31 - 40	0(0.0)	3(21.4)	4(7.4)	1(4.0)	8(7.6)	
	41 - 50	4(33.3)	3(21.4)	19(35.2)	7(28.0)	33(31.4)	
	51 - 60	2(16.7)	4(28.6)	15(27.8)	8(32.0)	29(27.6)	
	61 - 70	3(25.0)	3(21.4)	8(14.8)	5(20.0)	19(18.1)	
	71 - 80	1(8.3)	1(7.1)	6(11.1)	3(12.0)	11(10.5)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
Sex	Male	3(25.0)	3(21.4)	15(27.8)	4(16.0)	25(23.8)	0.734
	Female	9(75.0)	11(78.6)	39(72.2)	21(84.0)	80(76.2)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
BMI	Underweight <18.5	0(0.0)	0(0.0)	1(1.9)	0(0.0)	1(1.0)	0.675
	Normal weight 18.5 - 24.9	2(16.7)	3(21.4)	13(24.1)	7(28.0)	25(23.8)	
	Overweight 25 - 29.9	8(66.7)	5(35.7)	22(40.7)	6(24.0)	41(39.0)	

	Obesity Class I 30.0 - 34.9	2(16.7)	4(28.6)	15(27.8)	10(40.0)	31(29.5)	
	Obesity Class II 35.0 - 39.9	0(0.0)	2(14.3)	3(5.6)	2(8.0)	7(6.7)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
Sero	Positive	12(100.0)	11(78.6)	40(74.1)	18(72.0)	81(77.1)	0.206
	Negative	0(0.0)	3(21.4)	14(25.9)	7(28.0)	24(22.9)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
comorbidities	Positive	3(25.0)	6(42.9)	12(22.2)	4(16.0)	25(23.8)	0.300
	Negative	9(75.0)	8(57.1)	42(77.8)	21(84.0)	80(76.2)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
Drug history	NSAID	0(0.0)	0(0.0)	1(1.9)	0(0.0)	1(1.0)	0.080
	csDMARD	1(8.3)	2(14.3)	15(27.8)	7(28.0)	25(23.8)	
	bDMARD	2(16.7)	2(14.3)	3(5.6)	0(0.0)	7(6.7)	
	Steroid, csDMARD and Other	9(75.0)	6(42.9)	23(42.6)	9(36.0)	47(44.8)	
	Steroid and Other	0(0.0)	1(7.1)	1(1.9)	6(24.0)	8(7.6)	
	csDMARD, bDMARD and Other	0(0.0)	1(7.1)	5(9.3)	2(8.0)	8(7.6)	
	NSAID, Steroid, csDMARD, bDMARD and Other	0(0.0)	2(14.3)	6(11.1)	1(4.0)	9(8.6)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
Smoking History	Positive	1(8.3)	0(0.0)	5(9.3)	3(12.0)	9(8.6)	0.249
	Negative	9(75.0)	11(78.6)	46(85.2)	17(68.0)	83(79.0)	
	Passive smoker	2(16.7)	3(21.4)	3(5.6)	5(20.0)	13(12.4)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	
Alcoholi History	Negative	11(91.7)	14(100.0)	54(100.0)	25(100.0)	104(99.0)	0.114
	Ex-alcoholic	1(8.3)	0(0.0)	0(0.0)	0(0.0)	1(1.0)	
Total		12(100.0)	14(100.0)	54(100.0)	25(100.0)	105(100.0)	

Discussion

Dysregulated immune responses and persistent inflammation in chronic inflammatory conditions have detrimental effects on hematopoiesis. Modifications in the composition of peripheral blood cells can serve as indicators of the severity of rheumatoid arthritis. Chronic inflammation induces changes in the composition of blood cells through both immune and non-immune mechanisms, such as excessive production of cytokines and antibodies, deficiency in growth factors, reduced lifespan of cells, impaired neutrophil function, bleeding, and toxicity from medications. The disrupted balance of immune responses and the multifactorial nature of the disease process contribute to abnormal hematopoiesis in inflammatory disorders through various pathways. Analyzing peripheral blood samples can offer valuable clinical insights into immune dysregulation and the progression of the disease (Mercan et al., 2016(5).

The results indicate that the sample consisted mainly of married, middle-aged women residing in Slemani who worked as housewives. This highlights the importance of targeting outreach efforts to include other demographic groups in future studies. Furthermore, the rheumatoid arthritis patients included in this sample exhibited challenges related to overweight or obesity and moderate to high disease activity based on DAS28 scores. Targeted interventions focusing on weight management and optimizing pharmacotherapy may lead to improved outcomes. Additionally, gathering additional data on medication adherence and lifestyle factors could provide valuable insights for informing treatment recommendations. In a comparable investigation, Carbonell et al. (2022(8) documented that individuals with seropositive rheumatoid arthritis (RA) typically experience heightened pain when compared to those with seronegative RA. Additionally, they are more likely to present with nodules (swollen lumps beneath the skin), vasculitis (inflamed blood vessels), rheumatoid lung complications, and comorbidities such as cardiovascular disease. Notably, smokers also demonstrate an increased susceptibility to developing seropositive RA. In another similar study conducted by Studenic et al. (2023(9), it was found that the Disease Activity Score (DAS) provides a score ranging from 0 to 10, with higher scores indicating more active disease. A DAS-28 reduction of 0.6 indicates a moderate improvement, while a reduction of over 1.2 indicates a significant improvement. Scores below 2.6 suggest disease remission.

The findings revealed that there were moderate levels of disease activity overall, as indicated by the mean joint counts and total Disease Activity Score 28 (DAS28) score falling within the moderate range. Notably, the patient and evaluator global assessments were higher than the joint counts, underscoring the influence of subjective symptoms on patients' perceived health status. Similarly, in a study by Hammer et al. (2021(10), it was observed that tender joint count showed a stronger association with high scores of patient-reported outcome measures compared to swollen joint count. In contrast, the tender joint count was more closely related to the US synovitis scores. Patients with a higher number of tender joints compared to swollen joints exhibited higher scores across all recorded patient-reported outcome measures and the clinical disease activity index, while displaying lower US synovitis scores.

The results indicate increased levels of inflammatory markers, such as erythrocyte sedimentation rate (ESR), and impaired patient-reported assessments of global health. Furthermore, additional hematologic indices, including red cell distribution width (RDW) and neutrophil/lymphocyte ratio, were elevated, suggesting the presence of systemic inflammation. In a similar study conducted by Triaille et al. (2023(11), it was demonstrated that ESR and C-reactive protein (CRP) are commonly used laboratory assays to measure the acute-phase response and are valuable for monitoring disease activity in rheumatoid arthritis (RA). The ESR is influenced by various factors, primarily fibrinogen. Additionally, the study revealed that fibrinogen and CRP levels exhibited significant correlations with the Modified Stanford Health Assessment Questionnaire, while ESR did not. The authors suggested that fibrinogen could be a more accurate replacement for ESR in assessing RA, particularly for evaluating the slower component of the acute-phase response and establishing a variable that better correlates with disability. Nevertheless, Kay et al. (2014(12) documented that despite the elevation of specific components of the clinical disease activity index, such as tender and swollen joint counts, and assessments by both patients and physicians, some individuals with active rheumatoid arthritis (RA) may exhibit normal levels of erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Consequently, these patients may not meet the entry criteria for participation in clinical trials. Furthermore, Mirpourian et al. (2014(13) conducted a study to investigate the relationship between obesity/adiposity and disease activity, as well as the clinical response to combination therapy, in RA patients. They found that obesity and adiposity are associated with less severe disease activity in the early stages of RA. However, they did not find any association between obesity/adiposity and response to combination therapy involving methotrexate and hydroxychloroquine in RA patients.

The results of our study did not reveal a significant association between red cell distribution width (RDW) and clinical disease activity. In contrast to our findings, Atwa et al. (2022(14) reported a strong correlation between RDW and disease activity in rheumatoid arthritis (RA). They also found that RDW outperformed erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in detecting RA disease activity. Additionally, they suggested that RDW could be utilized in clinical settings to monitor disease activity. Furthermore, RDW is widely available as it is typically included in routine complete blood counts, eliminating the need for additional costs. Regarding the neutrophil/lymphocyte ratio, our study did not demonstrate a significant relationship with clinical disease activity. However, in contrast to our findings, Kushwaha et al. (2023(6) reported that the neutrophil/lymphocyte ratio is a valuable indicator of disease activity in RA. They highlighted that the neutrophil/lymphocyte ratio is a cost-effective and easily accessible marker of inflammation. It exhibits strong correlations with other inflammatory markers and disease activity indices. Furthermore, the neutrophil/lymphocyte ratio is significantly increased in individuals who do not respond to triple therapy for RA and demonstrates superior performance compared to conventional markers of disease activity.

However, the results of our study did not reveal any significant correlations between clinical disease activity and various hematologic parameters, including red cell distribution width (RDW), white blood cell count (WBC), neutrophil/lymphocyte ratio, hemoglobin (HG), and red

blood cell count (RBC). In a study conducted by Alghamdi (2023(14), a positive association between RDW and disease activity was observed in certain studies, suggesting a potential link between elevated RDW levels and systemic inflammation in rheumatic diseases. Similarly, Al-Rawi et al. (2018(15) examined RDW levels in individuals with rheumatoid arthritis (RA) and investigated the potential associations between baseline demographic and clinical factors. Their findings indicated a notable increase in RDW levels among RA patients. Additionally, Xue et al. (2022(16) mentioned the importance of platelet (PLT) and red blood cell (RBC) in inflammatory processes. Their study demonstrated significant associations between blood PLT and RBC-related indices and RA disease activity, suggesting these indices could be utilized to differentiate active RA from inactive RA. In our study, no significant associations were found between the Disease Activity Score 28 (DAS-28) and patient age, body mass index (BMI), or disease duration among rheumatoid arthritis patients. However, in contrast to our data, Coras et al. (2020(17) reported significant correlations between serum levels of acute-phase reactants and disease activity based on the DAS28 score in RA patients. Their study emphasized that serum C-reactive protein (CRP), among various acute-phase reactant tests, serves as the most useful biochemical marker for evaluating disease activity in RA patients.

The results of our study did not reveal a significant association between the Disease Activity Score 28 (DAS-28) based on erythrocyte sedimentation rate (ESR). Furthermore, no meaningful correlations were observed between the DAS-28 (ESR) score and red cell distribution width (RDW), white blood cell count (WBC), neutrophil/lymphocyte ratio, hemoglobin level, or red blood cell count. Consistent with our findings, Berso et al. (2022(18) highlighted the discrepancies that arise when using ESR and C-reactive protein (CRP) scores in assessing rheumatoid arthritis (RA) with the DAS28. They emphasized that although the DAS28-ESR and DAS28-CRP scores were highly correlated, they differed significantly in categorizing patients and should not be used interchangeably. Similarly, in another study conducted by Mercan et al. (2016(5), no significant association was found between the neutrophil-lymphocyte ratio and disease duration, tender joint count, swollen joint count, DAS28-ESR, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), or CRP levels. The findings of our study also demonstrated no meaningful correlations between the DAS-28 (ESR) total score and factors such as age, sex, body mass index (BMI), seropositivity, medical history, medication use, smoking, or alcohol consumption. However, contrasting findings were reported by Jawaheer et al. (2010(19), who observed that DAS28 scores increased with higher BMI categories among women but decreased among men. Regression analysis revealed associations between BMI (both continuous and categorical) and DAS28, with a more significant difference in mean DAS28 scores for obese individuals compared to those who were overweight. These relationships were more pronounced in women and could not be explained by any single component of the DAS28.

Conclusion

In summary, no significant associations were found between the total DAS-28 (ESR) score and various variables, including age, body mass index (BMI), disease duration, red cell distribution

width (RDW), neutrophil/lymphocyte ratio, hemoglobin (HG), or red blood cell count (RBC). These findings suggest that these factors may not significantly influence the disease activity as measured by DAS-28 (ESR). Furthermore, there were no significant associations observed between clinical disease activity and age, BMI, disease duration, RDW, or neutrophil/lymphocyte ratio. These results highlight the intricate nature of disease activity assessment and indicate the need for further exploration of alternative markers or factors that may contribute to a more comprehensive understanding of rheumatoid arthritis progression. Moreover, the lack of significant relationships between DAS-28 (ESR) and various demographic and clinical variables emphasizes the multifactorial aspects of the disease and underscores the importance of adopting a comprehensive approach to its management.

References

Alghamdi, M. (2023). Red blood cell distribution width: A potential inexpensive marker for disease activity in patients with rheumatic diseases; Scoping review. Open Access Rheumatology: Research and Reviews, 15, 173–180. https://doi.org/10.2147/oarrr.s424168.

Al-Rawi, Z., Gorial, F., & Al-Bayati, A. A. (2018). Red Cell Distribution Width in Rheumatoid arthritis. Mediterranean Journal of Rheumatology, 29(1), 38–42. https://doi.org/10.31138/mjr.29.1.38.

Atwa, E. T., Omar, H. M., Amin, A., & Hammad, M. (2022). Red cell distribution width and mean platelet volume in rheumatoid arthritis patients: Its association with disease activity. Reumatología Clínica (English Edition), 18(7), 399–405. https://doi.org/10.1016/j.reumae.2021.04.011.

Berso, J. de L., Montes, E. G., Vellosa, J. C. R., Mansani, F. P., Toledo Júnior, A. de O., & Schafranski, M. D. (2022). Comparison between DAS28-ESR and DAS28- CRPus for patients with rheumatoid arthritis: application in a population of southern Brazil. Brazilian Journal of Pharmaceutical Sciences, 58. https://doi.org/10.1590/s2175-97902022e19752.

Bonfiglioli, K. R., de Medeiros Ribeiro, A. C., Carnieletto, A. P., et al. (2023). Extra-articular manifestations of rheumatoid arthritis remain a major challenge: data from a large, multi-centric cohort. Advances in Rheumatology (London, England), 63(1). https://doi.org/10.1186/s42358-023-00318-y.

Carbonell-Bobadilla, N., Soto-Fajardo, C., Amezcua-Guerra, L. M., et al. (2022). Patients with seronegative rheumatoid arthritis have a different phenotype than seropositive patients: A clinical and ultrasound study. Frontiers in Medicine, 9. https://doi.org/10.3389/fmed.2022.978351.

Coras, R., Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain, Sturchio, G. A., Bru, M. B., Fernandez, A. S., Farietta, S., Badia, S. C., Diez, B. R., de Agustín de Oro, J. J., Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain, Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain, Unit of Rheumatology, Vall

d´Hebron University Hospital, Barcelona, Spain, Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain, Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain, Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain, & Unit of Rheumatology, Vall d´Hebron University Hospital, Barcelona, Spain. (2020). Analysis of the correlation between disease activity score 28 and its ultrasonographic equivalent in rheumatoid arthritis patients. European Journal of Rheumatology, 7(3), 118–123. https://doi.org/10.5152/eurjrheum.2020.20038.

Hammer, H. B., Jensen Hansen, I. M., Järvinen, P., Leirisalo-Repo, M., Ziegelasch, M., Agular, B., & Terslev, L. (2021). Rheumatoid arthritis patients with predominantly tender joints rarely achieve clinical remission despite being in ultrasound remission. Rheumatology Advances in Practice, 5(2). https://doi.org/10.1093/rap/rkab030.

Jawaheer, D., Olsen, J., Lahiff, M., Forsberg, S., Lähteenmäki, J., et al. (2010). Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA Study. Clinical and Experimental Rheumatology, 28(4), 454–461.

Kaur, S., White, S., & Bartold, M. (2012). Periodontal disease as a risk factor for rheumatoid arthritis: A systematic review. JBI Library of Systematic Reviews, 10(42), 1–12. https://doi.org/10.11124/jbisrir-2012-288.

Kay, J., Morgacheva, O., Messing, S.P. et al. (2014). Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year. Arthritis Res Ther 16, R40 (2014). https://doi.org/10.1186/ar4469.

Kushwaha, S., Kaushik, R., Kakkar, R., & Kaushik, R. (2023). Red cell distribution width and neutrophil-lymphocyte ratio as inflammatory markers in patients with rheumatoid arthritis. Reumatologia, 61(1), 13–20. https://doi.org/10.5114/reum/161286.

Kushwaha, S., Kaushik, R., Kakkar, R., & Kaushik, R. (2023). Red cell distribution width and neutrophil-lymphocyte ratio as inflammatory markers in patients with rheumatoid arthritis. Reumatologia, 61(1), 13–20. https://doi.org/10.5114/reum/161286.

Mercan, R., Bitik, B., Tufan, A., Bozbulut, U. B., Atas, N., Ozturk, M. A., Haznedaroglu, S., & Goker, B. (2016). The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis: Neutrophil to lymphocyte ratio in inflammatory arthritides. Journal of Clinical Laboratory Analysis, 30(5), 597–601. https://doi.org/10.1002/jcla.21908.

Mercan, R., Bitik, B., Tufan, A., Bozbulut, U. B., Atas, N., Ozturk, M. A., … Goker, B. (2016). The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis. Journal of Clinical Laboratory Analysis, 30(5), 597–601. doi:10.1002/jcla.21908.

Mercan, R., Bitik, B., Tufan, A., Bozbulut, U. B., Atas, N., Ozturk, M. A., Haznedaroglu, S., & Goker, B. (2016). The association between neutrophil/lymphocyte ratio and disease activity in

rheumatoid arthritis and ankylosing spondylitis. Journal of Clinical Laboratory Analysis, 30(5), 597–601. https://doi.org/10.1002/jcla.21908.

Mirpourian M, Salesi M, Abdolahi H, Farajzadegan Z, Karimzadeh H. (2014). The association of body mass index with disease activity and clinical response to combination therapy in patients with rheumatoid arthritis. J Res Med Sci. 2014 Jun;19(6):509-14. PMID: 25197291; PMCID: PMC4155704.

Nielung, L., Christensen, R., Danneskiold-Samsøe, B., Bliddal, H., Holm, C. C., Ellegaard, K., Slott Jensen, H., & Bartels, E. M. (2015). Validity and agreement between the 28-joint disease activity score based on C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. Arthritis, 2015, 1–6. https://doi.org/10.1155/2015/401690.

Studenic, P., Aletaha, D., de Wit, M., Stamm, T. A., Alasti, F., Lacaille, D., Smolen, J. S., & Felson, D. T. (2023). American College of Rheumatology/EULAR remission criteria for rheumatoid arthritis: 2022 revision. Annals of the Rheumatic Diseases, 82(1), 74–80. https://doi.org/10.1136/ard-2022-223413.

Triaille C, Tilman G, Sokolova T, et al. (2023). Disease activity drives transcriptomic heterogeneity in early untreated rheumatoid synovitisAnnals of the Rheumatic Diseases Published Online First: 28 July 2023. doi: 10.1136/ard-2023-224068

Weiss, D. J., & Tvedten, H. (2012). Erythrocyte Disorders. In Small Animal Clinical Diagnosis by Laboratory Methods (pp. 38–62). Elsevier. https://doi.org/10.1016/B978-1-4377-0657-4.00003-X.

Wu, H., Li, C., Liu, S., Yao, S., Song, Z., Ren, D., & Wang, P. (2023). Is neutrophil lymphocyte ratio, platelet lymphocyte ratio or red blood cell distribution width associated with risk of mortality in patients with necrotizing fasciitis. Infection and Drug Resistance, 16, 3861–3870. https://doi.org/10.2147/idr.s413126.

Xue, L., Tao, L., Sun, H., Wang, Y., Zhang, Y., et al. (2022). Association between blood PLT and RBC related indices and disease activity in patients with rheumatoid arthritis. International Journal of General Medicine, 15, 573–581. https://doi.org/10.2147/ijgm.s351505.