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Evaluation of Red Cell Indices as Biomarkers in Rheumatoid Arthritis Patients

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Abstract

Inflammatory changes in rheumatological diseases encompass alterations in shape, number, and size of peripheral blood cells. Complete blood cell parameters may be used as an index of inflammation and disease activity. Assess the hematological parameters in rheumatoid arthritis (RA) and identify their relationship with disease activity. 141 patients with rheumatoid arthritis and 100 healthy controls were included in this study. Full medical history, general and musculoskeletal examination, assessment of disease activity using the DAS 28 score, markers of inflammation, rheumatoid factor (RF) titer, anti-cyclic citrullinated peptide (anti-CCP) titer and complete blood picture were done. RA patients had lower RBCs, Hb, MPV, PWD and Hb/RDW% ratio and higher RDW% than controls. Active RA patients had higher WBCs, neutrophils, and NLR. WBCs and neutrophils were positively correlated with DAS score and CRP titer. NLR ratio correlated positively with the DAS score, CRP and Anti CCP titers. Active RA had higher RDW% and lower HCT, Hb, Hb/PLT, RDW%/PLT, Hb/RDW% ratios. RDW% was positively correlated with DAS score, ESR, CRP, RF and Anti CCP titers. The RDW% differentiated active and inactive RA with best cut-off value >12. Active patients had higher platelets and PLR, which were positively correlated with DAS score. Changes in hematological parameters are significantly associated with disease activity in RA patients and they correlate positively with inflammatory markers. RDW%, platelets count and PLR are the most affected hematologic parameters in relation to DAS score and parameters of disease activity.

Keywords

Rheumatoid Arthritis, Red Cell Indices, Biomarkers.

Rheumatoid arthritis RA is an autoimmune disorder characterized by chronic inflammation that not only affects the joints but also has systemic manifestation Patients with RA face significant physical disabilities and a substantial financial burden as their disease progresses (1). According to previous studies, early detection and treatment can reduce the risk of RA-related decreased bone density and joint abnormalities, increasing the likelihood that RA patients would experience recovery. Thus, improving the prognosis of RA requires early diagnosis and treatment (2).

Recent studies investigated the association between the activity of RA and the hematological parameters. Some studies assessed the correlation between platelets (PLT), red blood cells (RBC), red blood cells-platelet ratio (RPR) and hemoglobin-platelet ratio (HPR) as regards the disease activity (3).

Little is known about the significance of the PLT and parameters of RBC in differentiating active from inactive disease (4). Studies found negative correlation between disease activity and hemoglobin (Hb) level and thrombocytosis with high disease activity, but results were not conclusive as regard the mean platelet volume (MPV) (5).

Another study revealed a presence of an increase in the number of platelets in patients with RA during disease activity, then a decrease in their number with remission. Consequently, a correlation between platelet indices and disease activity in RA has been proposed (6).

Red cell indices were previously only used in medical facilities to help in anemia differential diagnosis (7). In the last ten years, red cell indices—along with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)—have been utilized as markers of inflammation (8). It has been suggested that an increase in red cell indices is indication of systemic inflammation. Acute coronary syndrome, atrial fibrillation, heart failure, and hypertension are just a few of the cardiovascular diseases (CVD) for which recent research has shown elevated red cell indices levels. Additionally, it has been noted that higher red cell indices are linked to higher rates of morbidity and mortality in CVD patients (9).

In addition, studies have demonstrated that a number of parameters, including mean platelet volume (MPV), red cell indices, neutrophil/lymphocyte ratio (NLR), red blood cell distribution width/platelet ratio (RPR), RDW, and Platelet/lymphocyte ratio (PLR) can be utilized as indices of mortality in certain diseases as well as inflammatory markers in autoimmune diseases (10). However, there hasn't been much research done on the relationship between RA patients' RPR values and their disease activity (11).

Few studies have investigated the association between red cell indices, all the hematological parameters, markers of inflammation and disease activity in RA. The aim of this study is to evaluate red cell indices and their relation with the disease activity in patients with rheumatoid arthritis.

Materials and Methods

A case control study was conducted in Rheumatology department, Lady Reading Hospital (LRH), Peshawar on 141 rheumatoid arthritis patients diagnosed according to 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for RA, and 100 healthy controls who were matched according to age and sex (12).

Individuals with chronic kidney disease, chronic liver disease, blood disorders, malignancies, and other autoimmune diseases were excluded from our study. We obtained written consent in advance from each patient. A complete medical history was taken, along with a musculoskeletal and general examination, and the DAS 28 score-ESR was used to measure the disease activity. A score of less than 2.6 was regarded as inactive, 2.6–3.2 as low disease activity, >3.2–5.1 as moderate disease activity, and >5.1 as high disease activity, per the DAS 28 score. Individuals exhibiting mild, moderate, or severe activity were considered to be actively diseased.

Complete blood picture showing red blood cells (RBCs) count and indices, white blood cells (WBCs); both total and differential counts, and platelets parameters was done to all patients. Complete blood count was done using a Coulter Counter (T660; Beckman Coulter, Brea, CA). Markers of disease activity including Erythrocyte sedimentation rate (ESR) (Westergren method) was done, C reactive protein (CRP) titer [performed on Modular P auto analyzer (Roche Diagnostics, Mannheim, Germany)]., RF titer and anti-CCP titer (determination by a COBAS Autoanalyzer (Roche Diagnostics, Mannheim, Germany) were also done.

Comparison between active RA patients, inactive RA patients and healthy controls regarding the hematological parameters was done. Then a comparison between active and inactive groups regarding the WBCs, RBCs and platelet indices, and a correlation of the hematological parameters with DAS score and parameters of disease activity were assessed. Version 17.0 of SPSS was used to tabulate and statistically analyze the collected data. Variables such as range, mean ± standard deviation, and frequencies and percentages were utilized. For comparison, the Chi-square and Mann Whitney U tests were also used. P values of less than 0.05 were considered as significant.

Results

The mean age of RA patients was 50.404± 11.945 years. 77.3 % of them were females and 22.7 % were males. 91(64.54%) patients were active while 50 patients (35.46%) were inactive. RA patients showed statistically significant lower RBCs, Hb, MPV, PWD and Hb/RDW% ratio, while they had statistically significant higher RDW% compared with the controls (Table 1).

Table 1: Comparison Between RA Patients and Controls as Regard Wbcs, Rbcs and Platelet Parameters.

Hematological indices	Groups						T-Test	
	RA			Control				
	Mean	±	SD	Mean	±	SD	t	P-value
WBCs (10^9/L)	7.136	±	2.491	6.977	±	1.990	0.555	0.580
Neutrophils (10^9/L)	4.287	±	2.321	4.112	±	1.629	0.685	0.494
Lymphocytes (10^9/L)	2.283	±	0.690	2.294	±	0.768	-0.115	0.908
HCT (%)	36.149	±	2.364	36.099	±	2.453	0.165	0.869
RBCs(10^{12}/L)	4.786	±	0.523	5.480	±	4.096	-1.991	0.048*
Hb(g/L)	11.984	±	0.810	12.344	±	0.717	-3.729	<0.001*
MCV (fL)	78.865	±	7.346	80.477	±	5.782	-1.918	0.056
MCH (pg)	26.457	±	3.021	27.107	±	2.625	-1.814	0.071
RDW%	13.776	±	2.234	13.171	±	1.473	2.493	0.013*
PLT (10^9/L)	402.752	±	174.647	365.704	±	140.972	1.838	0.067
MPV/fl	9.177	±	1.009	10.921	±	2.043	-8.898	<0.001*
PDW%	10.445	±	1.655	12.282	±	1.882	-8.301	<0.001*
Hb/PLT ratio	0.037	±	0.020	0.040	±	0.017	-1.158	0.248
RDW%/PLT ratio	0.040	±	0.015	0.042	±	0.015	-0.912	0.363
RBCs/PLT ratio	0.015	±	0.008	0.017	±	0.013	-1.685	0.093
Hb/RDW% ratio	0.896	±	0.177	0.951	±	0.132	-2.719	0.007*
NLR ratio	2.093	±	1.508	1.977	±	1.136	0.682	0.496
PLR ratio	200.002	±	139.664	178.532	±	112.876	1.331	0.184

WBCs, neutrophil, RDW%, PLT, NLR and PLR were significantly higher in active RA patients while HCT, Hb, Hb/PLT, RDW%/PLT, Hb/RDW% and RBCs/PLT ratios were significantly lower compared to the inactive patients (Table 2).

Table 2: Comparison Between Active and Inactive RA Patients as Regard Wbcs, Rbcs and Platelet Parameters.

RA	DAS 28 Activity						T-Test	
	Inactive			Active				
	Mean	±	SD	Mean	±	SD	t	P-value
WBCs (10^9/L)	6.568	±	2.016	7.448	±	2.676	-2.028	0.044*
Neutrophils (10^9/L)	3.752	±	1.665	4.581	±	2.574	-2.053	0.042*
Lymphocytes (10^9/L)	2.288	±	0.573	2.280	±	0.750	0.063	0.950
HCT (%)	36.680	±	2.437	35.857	±	2.284	1.999	0.048*
RBCs(10^{12}/L)	4.833	±	0.499	4.760	±	0.536	0.787	0.432
Hb(g/L)	12.254	±	0.783	11.835	±	0.791	3.020	0.003*
MCV (fL)	78.432	±	8.032	79.103	±	6.975	-0.518	0.605
MCH (pg)	25.942	±	3.142	26.741	±	2.931	-1.509	0.134
RDW%	11.560	±	1.188	14.993	±	1.665	-12.883	<0.001*
PLT (10^9/L)	238.740	±	99.662	492.868	±	137.419	-11.511	<0.001*
MPV/fl	9.142	±	0.871	9.196	±	1.082	-0.302	0.763
PDW%	10.250	±	1.633	10.553	±	1.667	-1.039	0.301
Hb/PLT ratio	0.057	±	0.018	0.026	±	0.011	12.631	<0.001*
RDW%/PLT ratio	0.053	±	0.014	0.033	±	0.009	10.585	<0.001*
RBCs/PLT ratio	0.023	±	0.007	0.011	±	0.004	13.009	<0.001*
Hb/RDW% ratio	1.071	±	0.120	0.801	±	0.121	12.741	<0.001*
NLR ratio	1.701	±	0.761	2.308	±	1.758	-2.320	0.022*
PLR ratio	110.268	±	53.937	249.307	±	147.742	-6.415	<0.001*

The number of tender joints was significantly positively correlated with RDW%, PLT count, NLR and PLR. On the contrary, it was significantly negatively correlated with RBCs count, Hb levels, Hb/PLT, RDW%/PLT, RBCs/PLT and Hb/RDW% ratios. The number of swollen joints showed statistically significant positive correlations with RDW%, PLT count, PLR. On the other hand, it was negatively correlated with the Hb, Hb/PLT, RDW%/PLT, RBCs/PLT and Hb/RDW% ratios. DAS28 score was positively correlated with WBCs, neutrophils, PLTs, RDW%, NLR and PLR in RA patients. On the contrary, HCT, Hb levels, Hb/PLT, RDW%/PLT, RBCs/PLT and Hb/RDW% ratios were negatively correlated with DAS28 score (Table 3).

Table 3: Correlation Between Wbcs, Rbcs and Platelet Parameters with Clinical Parameters of the Disease Activity.

RA	Tender j		Swollen j		DAS 28	
	r	P-value	r	P-value	R	P-value
WBCs (10^9/L)	0.075	0.451	0.023	0.816	0.164	0.052*
Neutrophils (10^9/L)	0.112	0.256	0.019	0.849	0.180	0.033*
Lympho(10^9/L)	-0.152	0.125	-0.130	0.183	-0.073	0.392
HCT (%)	-0.068	0.492	-0.095	0.332	-0.206	0.014*
RBCs(10^{12}/L)	-0.236	0.016*	-0.023	0.813	-0.126	0.136
Hb(g/L)	-0.303	0.002*	-0.222	0.022*	-0.378	<0.001*
MCV (fL)	0.177	0.073	0.037	0.702	0.072	0.394
MCH (pg)	0.094	0.340	0.008	0.934	0.097	0.254
RDW%	0.745	<0.001*	0.634	<0.001*	0.876	<0.001*
PLT (10^9/L)	0.775	<0.001*	0.611	<0.001*	0.859	<0.001*
MPV/fl	-0.011	0.915	0.097	0.319	0.027	0.751
PDW%	0.105	0.291	0.162	0.096	0.109	0.199
Hb/PLT ratio	-0.654	<0.001*	-0.527	<0.001*	-0.753	<0.001*
RDW%/PLT ratio	-0.593	<0.001*	-0.474	<0.001*	-0.692	<0.001*
RBCs/PLT ratio	-0.544	<0.001*	-0.420	<0.001*	-0.704	<0.001*
Hb/RDW% ratio	-0.745	<0.001*	-0.588	<0.001*	-0.855	<0.001*
NLR ratio	0.199	0.043*	0.111	0.254	0.240	0.004*
PLR ratio	0.602	<0.001*	0.433	<0.001*	0.665	<0.001*

There was statistically significant positive correlation between ESR and RDW%, PLT count, PLR while it was significantly negatively correlated with HG levels, Hb/PLT ratio, RDW%/PLT ratio, RBCs/PLT ratio, Hb/RDW% ratio. Other significant correlations are shown in table3 and 4. Both RF and Anti CCP titres were positively correlated to RDW%, PLT count and PLR, but they were negatively correlated with HG levels, Hb/PLT, RDW%/PLT, RBCs/PLT and Hb/RDW% ratios. However, anti CCP titre was positively correlated with NLR (Table 4).

Table 4: Correlation Between Wbcs, Rbcs and Platelet Parameters with Laboratory Parameters of the Disease Activity.

RA	ESR		CRP		RF		ANTI CCP	
	r	P-value	r	P-value	r	P-value	r	P-value
WBCs (10^9/L)	0.125	0.139	0.265	0.001*	-0.036	0.675	0.059	0.487
Neutrophils(10^9/L)	0.143	0.090	0.294	<0.001*	0.019	0.819	0.102	0.227
Lymphocytes (10^9/L)	-0.002	0.981	-0.024	0.776	-0.212	0.012	-0.196	0.020
HCT (%)	-0.097	0.255	-0.085	0.314	-0.098	0.246	-0.065	0.445
RBCs(10^{12}/L)	-0.120	0.156	-0.056	0.509	-0.139	0.101	-0.118	0.164
Hb(g/L)	-0.376	<0.001*	-0.185	0.028*	-0.236	0.005*	-0.185	0.028*
MCV (fL)	-0.020	0.817	0.076	0.368	-0.117	0.168	0.000	0.999
MCH (pg)	0.062	0.468	-0.073	0.392	0.074	0.381	0.148	0.080
RDW%	0.577	<0.001*	0.396	<0.001*	0.283	0.001*	0.294	<0.001*
PLT (10^9/L)	0.551	<0.001*	0.325	<0.001*	0.272	0.001*	0.355	<0.001*
MPV/fl	-0.014	0.867	0.016	0.852	-0.039	0.644	-0.010	0.908
PDW%	0.145	0.087	0.102	0.231	-0.002	0.978	-0.069	0.417
Hb/PLT ratio	-0.476	<0.001*	-0.311	<0.001*	-0.268	0.001*	-0.326	<0.001*
RDW%/PLT ratio	-0.409	<0.001*	-0.252	0.003*	-0.226	0.007*	-0.299	<0.001*
RBCs/PLT ratio	-0.425	<0.001*	-0.304	<0.001*	-0.300	<0.001*	-0.308	<0.001*
Hb/RDW% ratio	-0.593	<0.001*	-0.375	<0.001*	-0.325	<0.001*	-0.316	<0.001*
NLR ratio	0.159	0.059	0.295	<0.001*	0.112	0.187	0.188	0.026*
PLR ratio	0.386	<0.001*	0.220	0.009*	0.341	<0.001*	0.393	<0.001*

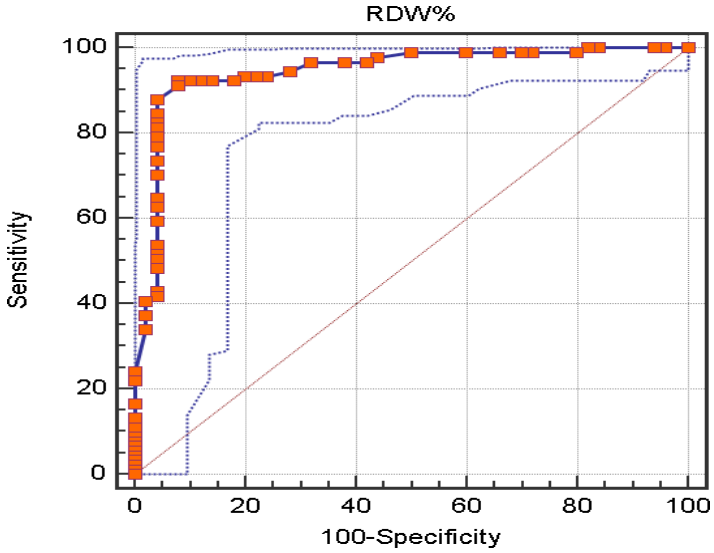

Figure 1: The ROC Curve Showed That the Best RDW% Cut-Off Value for Predicting Disease Activity in RA Patients Was >12.9 With A Sensitivity of 92.31% And A Specificity of 92.00%, With Positive Predictive Value Is 95.5%.

The best RDW% cut-off value for predicting disease activity in RA patients was >12.9 (Figure 1).

Discussion

Inflammatory process in rheumatic diseases causes changes in the peripheral blood cell counts, morphology and sizes. Therefore, blood cell indices were considered as indicators of inflammation and markers of disease activity. Studies proved a significant role of platelets in the inflammatory response (11). In addition, RBC-related parameters can be used as inflammatory markers in autoimmune diseases. Ratios among haematological indices have shown to be useful tools for evaluation of inflammatory activity in various autoimmune diseases including ulcerative colitis and Familial Mediterranean fever (13). Few studies investigated the relationship between the parameters of PLT, RBC, WBCs parameters and disease activity; especially their importance in differentiating active from inactive RA. Therefore, the current study aimed at assessing the association between all these blood biomarkers and rheumatoid arthritis disease activity (14).

To assess the difference concerning haematological parameters among RA patients and healthy controls, a comparison between both groups regarding the WBCs, RBCs and platelet parameters was done and results showed that the RA patients had higher WBCs, neutrophils and NLR while they had lower lymphocytes compared to healthy controls, but these results did not reach the statistical significance. These results partially agreed with study by Zinellu *et al.* whose results revealed that NLR increased significantly in RA patientscompared to controls. Similarly, Helal et al.,and Abd-Elazeem et al., found that theNLR and PLR were significantly higher in RA patients than that of the controls (15).

As regard the RBCs parameters, RA patients had statistically significant higher RDW% and lower RBCs count, Hb level and Hb/RDW% ratio than healthy controls. Orange *et al.,* also reported a significant higher RDW in patients with RA compared to controls (16). Interestingly, Mellors *et al*., found that a higher percentage of RDW was observed in patients with RA than in patients with osteoarthritis (17).

Similarly, results of Ustaoglu *et al.,* discerned that RA patients had significantly lower RBCs than control group. While assessing the parameters of platelets, although a high platelets count wasobserved, it was of no statistical significance. Yet there was a statistically significant lower value of MPV and PDW inpatients with RA than controls. These results were in accordance with the results of Ustaoglu *et al.,* which showedsignificantly higher platelet count in patients with RA than healthy controls (18). While these results disagreed with Khaled et al., results who found that patients with RA had significantly higher PDW values than those of controls (19).

In order to identify the relationship between different haematological parameters and DAS score and disease activity parameters, the patients with RA were divided into active RA [91 patients (64.6%)] and inactive RA [50 patients (35.46%)] groups. Then comparison between both groups as regards haematological parameters and correlation of haematological indices with parameters of disease activity were done.

Regarding WBCs parameters, there was significantly higher WBCs count, neutrophil count, and NLR in active patients. Also, WBCs and neutrophil counts correlated positively with both DAS score and CRP titer NLR ratio correlated significantly positively with the DAS score, number of tender joints, CRP and Anti CCP titers. Atwa *et al.,* reported a positive correlation between the DAS28 score and WBCs count, neutrophil count and NLR in RA patients as in this study (9). Also, Haitao et al., results also proved that high NLR values were positively associated with increase CRP, ESR, and DAS28 values in RA patients (20).

Remalante *et al.,* detected significant higher NLR in active disease and reported a significant relationship between NLR and PLR with the DAS-28 (10). Another

study by Conic *et al.,* found that the NLR was positively correlated with ESR and CRP and NLR increased with increasing the DAS28 score (21).

Deng *et al.,* found that the DAS28 positively correlated with the NLR and PLR. These studies support the present study and may reflect the importance of WBCs indices as a marker of inflammation and disease activity in patients with RA (22).

Current results showed that the RBCs parameters may give an idea about the inflammatory status and activity status in RA patients, and that the alterations in these parameters go hand in hand with alterations in the inflammatory markers. The current study found that active patients had significantly higher RDW%, while HCT value, Hb levels, Hb/PLT ratio, RDW%/PLT ratio, Hb/RDW% ratio and RBCs/PLT ratio were significantly lower than the inactive patients. Also, the RDW% was positively correlated with DAS score and other clinical and laboratory activity parameters "number of tender and swollen joints, ESR, CRP, RF and Anti CCP titres". These results are in concordance to Song *et al.,* who observed that the RDW was associated with the level of inflammatory markers andautoantibodies in RA patients (23). Ozisler et al., also supported the results and demonstrated that CRP and ESR correlated positively with RDW in patients with RA patients (24).

Moreover, a study found that RDW was positively correlated with DAS-28 and proposed its use as a marker of activity in RA and that RDW was positively correlated with ESR and CRP in reflecting the inflammatory state that go hand in hand with the current results (25).

The current results are in line with Mohamed et al., who observed that Patientswith high disease activity had a significantly lower Hb values. Active RA patients showed significantly lower levels of RBC counts, Hb, Red blood cell /platelets ratio and hemoglobin-platelet ratio compared toinactive RA and that Hb, RPR and HPR were negatively related with DAS28-CRP (26).

On the other hand, Lange et al., showed that there was no significant correlation between DAS28-ESR, RF, and ACPA with RDW. The study did not find correlation between RDW and DAS-28 (27).

Farrukh *et al.,* found that RDW could differentiate between RA and controls. Although the current study did not assess the diagnostic value of RDW in RA, but RDW% showed its value in differentiating active from inactive RA with best cut-off value >12.9% (28).

Platelet parameters in RA patients revealed that it could be a reflection of the inflammatory and activity status. Thepresent study found that active patients had significantly higher platelets count and PLR. Moreover, Platelet count and PLR were positively correlated with DAS score and all other clinical and laboratory activity parameters. These results are in accordance to other results Wang *el al.,* who showed that active RA patients had higher PLT counts, and that PLT count was positively correlated with DAS28 score (29). Similarly, Tekin *et al.* observed a relationship between plateletindices and disease activity in RA. Results of Tekin et al., agree with our results as they found significantly higherplatelet count and MPV in high disease activity patients. Although the higher MPV in active patients did not reach the statistical significance in the present results (30).

MPV showed significant importance as a marker of inflammation and disease activity. In one study by Gisondi *et al.,* MPV was significantly associated with RA disease activity. Although the currentresults found higher MPV in active patients than in inactive patients yet it did not reach statistical significance (31).

Yi *et al.,* also supported this study and concluded that parameters of the blood cells may be used in evaluation of disease activity in autoimmune inflammatory disorders generally (32).

Conclusion

Alterations in WBCs, RBCs and PLTs parameters proved to be significantly related to the disease activity in patients with RA, and these changes go hand in hand with inflammatory markers. Therefore, they can be used as indicators of the inflammation and activity in RA patients. RDW%, platelets count and PLR were among the most hematologic parameters connected with DAS score, parameters of disease activity followed by WBCs count, neutrophil count and NLR. CBC and haematological parameters are simple, available and cheap laboratory investigation that could be used in the future to assess and follow up RA patients. Larger prospective studies with huge number of patients are recommended to confirm and explain the importance of haematological parameters in RA patients in comparison with other autoimmune diseases.

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