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Red Blood Cell Distribution Width as a Surrogate Marker of Disease Activity in Patients with Rheumatoid Arthritis

Saleha Farrukh[1], Fatima Khan[2], Wajahat Aziz[3], Uzma Rasheed[4], Shazia Zammarrud[5]

[1,2] Post-graduate trainee, [3]Professor [4]Associate Professor, [5]Assistant Professor
(Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad)

Author`s Contribution

[1] Manuscript writing
[2]Data Collection, data analysis
[3]Supervisor, Manuscript writing, Data Analysis, [4]Manuscript writing, [5]Data Analysis, Proofreading

Funding Source: None
Conflict of Interest: None

Received: May 07, 2021
Accepted: Sept 26, 2021

Address of Correspondent
Dr Saleha Farrukh
Department of Rheumatology, Pakistan Institute of Medical Sciences
Email: drsaleha@live.com.

ABSTRACT

Objective: To determine the association between red blood distribution width and disease activity in patients with rheumatoid arthritis and to compare the red blood distribution width in patients of rheumatoid arthritis with that in healthy subjects.

Methodology: This comparative case-control observational study was conducted at Pakistan Institute of Medical Sciences, on rheumatoid arthritis patients visiting the (Out Patient Departments) OPDs between September, 2020 and March, 2021. Study subjects were selected by non-probability convenient sampling and a control group comprising of healthy subjects was similarly selected from general medical OPDs. Complete blood picture and erythrocyte sedimentation rate were obtained for each patient and disease activity score was calculated for rheumatoid arthritis patients. Statistical Package for Social Sciences (SPSS) version 26 was used for data analysis. Data was checked for normality by using the Kolmogorov Smirnov test. An independent samples t-test was used for comparing means and Pearson's correlation coefficient for establishing an association between variables. P value less than 0.05 was considered significant.

Results: Of the total 140 patients, 60 (85.7%) in each group were female and 10 (14.3%) were male. The mean age was 39.23 years and 36.87 years in the case and control groups respectively. The mean disease duration of rheumatoid arthritis was 6.63 years. RDW was significantly elevated in patients with rheumatoid arthritis (16.82%) as compared to the control group (14.47%) and strong positively correlated with disease activity score (p 0.00038).

Conclusion: Red blood cell distribution width is strongly related to disease activity in patients of rheumatoid arthritis and may help in monitoring disease activity in rheumatoid arthritis patients.

Keywords: Rheumatoid arthritis, Red blood cell Distribution Width (RDW), Disease Activity Score – 28 joints (DAS-28).

Cite this article as: Farrukh S, Khan F, Aziz W, Rasheed U, Zammarrud S. Red Blood Cell Distribution Width as a Surrogate Marker of Disease Activity in Patients with Rheumatoid Arthritis. Ann Pak Inst Med Sci. 2021; 17(3):206-210.doi. 10.48036/apims.v17i3.507

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune multisystem inflammatory disorder primarily involving the joints, causing progressive cartilage destruction, joint space narrowing, joint deformities and a multitude of extra-articular morbidities. If left untreated, disability, intractable pain and poor quality of life are inevitable consequences. The global disease burden of RA has been estimated to be as high as 1% of the total world's population with an annual incidence of 50 to 100 new cases per 100,000 population.[1]

Red blood cell distribution width (RDW) is a parameter of the degree of variation in erythrocytic volume i.e. anisocytosis and is commonly analyzed by automated hemolysers, as one of the indices in the complete blood count, ranging between 12% and 16 % in healthy subjects. RDW is not influenced by acute infections, unlike the conventionally used inflammatory markers like

ESR and CRP, since it depends upon the red cell life span which averages to approximately120 days. Historically, it has been employed for differentiating between iron deficiency anemia and thalassemia.[2] Over the last decade, it has found innumerable other uses including serving as a viable prognostic factor in diverse cardiovascular and cerebrovascular disorders including Alzheimer's dementia.[3] Recent studies discovered an association between RDW and numerous autoimmune disorders including Systemic lupus erythematosus, Sjogren syndrome, Systemic sclerosis, Behcet's disease, RA, Psoriatic arthritis and Ankylosing spondylitis. These studies also found a positive correlation between RDW and various inflammatory markers like Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). Changes in RDW were found to be associated with the onset, disease activity and prognosis of these autoimmune disorders.[4]

Autoimmunity, the common pathogenesis underlying these diverse disorders, hypothetically triggered by autoantigens in a genetically predisposed host and perpetuated by epigenetic and environmental influences, is characterized by raised inflammatory makers like ESR and CRP. Increased RDW may also serve as a potential marker of disease flare in autoimmune disorders, as found in several studies.[5,6,7] Recent studies indicate a positive correlation between disease activity in patients with RA and an increased RDW.[8,9,10] Increase in RDW was also found to be associated with cytokines such as Tumor Necrosis Factor-alpha (TNF-a) and Interleukin-6 (IL-6). [11] Increased RDW was also discovered to positively associate with an increased incidence of premature cardiovascular morbidity and mortality in patients with RA.[12,13]

This study intends to ascertain the correlation between RDW and Disease Activity Score-28 joints (DAS-28) in patients with RA.[14] It compares the RDW in a sample of normal population compared to that in RA. It also compares ESR between case and control groups and aims to estimate the significance of RDW as a surrogate maker of active disease in RA.

Methodology

This case control study was carried out at Pakistan Institute of Medical Sciences (PIMS), Islamabad, from September, 2020 to March, 2021. Ethical approval for the study was granted by the Hospital Ethics Committee in August, 2020. Patients were selected for this study by employing non-probability consecutive sampling. A sample size of 140 patients (70 in each of the cases and control groups), was calculated by using the OpenEpi tool with a 95% Confidence level, 80% power of the study and a mean RDW of 14.5 ± 2.8% for study group and 12.4 ± 1.1% for control group, according to a previous study.[15] 70 cases of RA were selected from the Rheumatology inpatient facility and outpatient clinics. After apprising the patients of the nature of the study and obtaining a consent, patients were consecutively included in the study. Similarly,70 age and gender-matched patients who consulted the general medical outpatient clinic at PIMS for minor complaints were selected for the study after obtaining an informed consent.

RA was diagnosed according to the ACR/ EULAR 2010 classification criteria for RA.[16] Patients with previous history of blood transfusions, thalassemia, malignancy, liver disease, renal disease, cardiovascular disorders, metabolic syndrome, cerebrovascular disease, thyroid dysfunction and pregnancy were excluded from the study. A detailed history and clinical examination were carried out for each patient. Hospital ID, name, age, gender and disease duration were recorded for each patient. Blood samples were submitted to hematology laboratory, where automated hemolysers were used for estimation of complete blood count including hemoglobin and RDW and ESR. DAS-28 was calculated for each RA patient and duly recorded. A threshold value less than 2.6 was considered dormant disease and DAS-28 > 2.6 was considered as active disease.[14]

Data was analyzed by utilizing IBM SPSS version 26. Gender was assessed by descriptive statistics. Means and standard deviations were calculated for quantitative statistics. Normal distribution of quantitative variables was assessed by using the Kolmogorov Simirnov and Shapiro Wilk tests. For normally distributed quantitative variables, an independent samples t-test was applied. Significance was set at a p value <0.05. Correlation between RDW and DAS-28 was established with Pearson's correlation coefficient. Sensitivity and specificity of RDW for disease activity in RA was determined by using a ROC curve. A one way between groups ANOVA will be applied to compare subgroups of patients with active and inactive disease and normal and low hemoglobin levels.

Results

A total of 140 patients were included in the study with 70 patients in each of the cases and control groups. Each group had 60 (85.7%) female patients and 10 (14.3%) male patients. No statistically significant difference was found between the two study groups regarding age and gender distribution (p > 0.05). The mean duration of disease was 6.63 years in the RA group. Other demographic and clinical variables are depicted in Table I.

Table I: Demographic and clinical variables

Variable	Rheumatoid arthritis (70)	Control group (70)	P value *
Female N (%)	60 (85.7%)	60 (85.7%)	
Male N (%)	10 (14.3 %)	10 (14.3 %)	
Age (years)	39.23 ± 8.830	36.87 ± 9.228	0.125
ESR in mm/hour	39.83 ± 17.395	21.83 ± 5.853	0.000
Hemoglobin (mg/dl)	11.309 ± 1.4684	12.316 ± 1.1815	0.007
RDW (%)	16.821 ± 2.1994	14.471 ± 1.6691	0.000
Disease duration (years)	6.63 ± 3.993		
DAS-28	4.371 ± 1.6442		

*p <0.05 considered significant.

The RDW in the RA group was significantly higher as compared to the control group i.e. 16.821 ± 2.1994 % vs 14.471 ± 1.6691 % (p <0.05). (Figure 1)

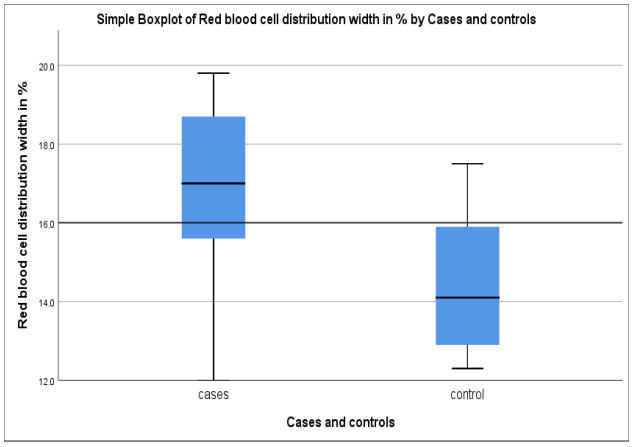

Figure 1: Comparison of RDW in the two groups.

RDW was found to have a strong positive correlation with DAS-28 in RA patients (p<0.000), with an R^2 Linear value of 0.750. (Figure 2).

The Area under the Curve (AUC) for RDW for predicting an active disease in RA patients, was 0.982 with 95% CI 0.954 - 1.000 (p < 0.000). The optimal cut-off value of

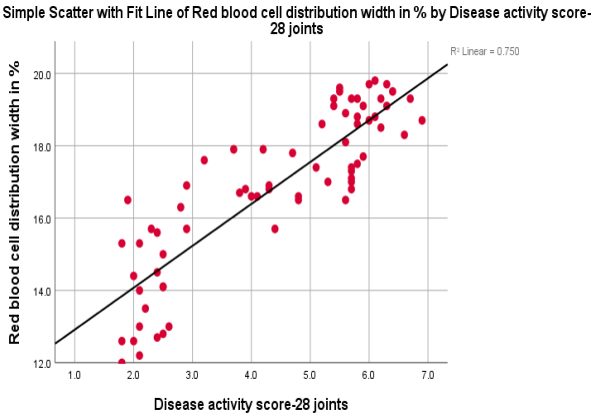

Figure 2: Correlation between RDW and DAS-28 in RA patients.

RDW for ascertaining disease activity in RA was > 16% with a sensitivity of 94.1% and a specificity of 94.7%. (Figure 3)

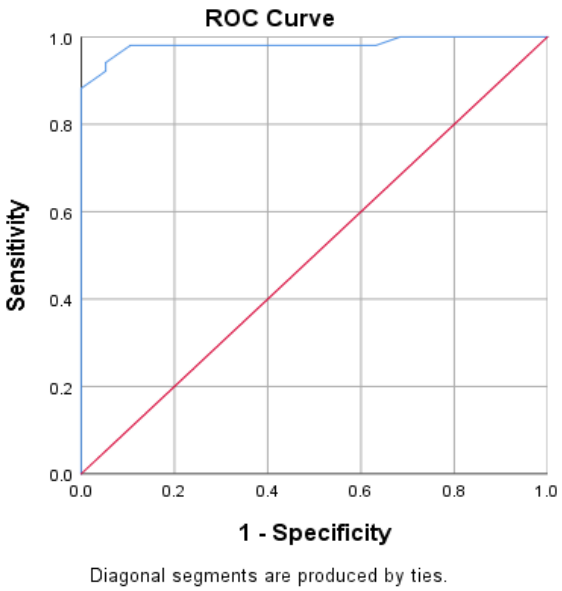

Figure 3: ROC curve for RDW in active Rheumatoid arthritis.

A one way between groups ANOVA showed significant differences between active, inactive disease and control subgroups with the maximum difference observed between the low hemoglobin, active disease and the normal hemoglobin, control subgroup. A comparison between subgroups of cases and controls regarding RDW is shown in figure 4.

Doi. 10.48036/apims.v17i3.507

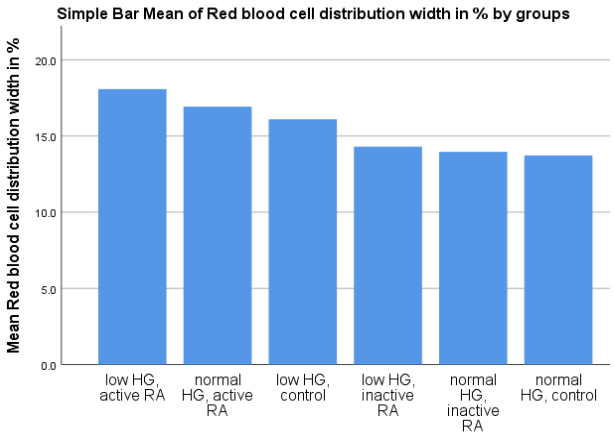

Figure 4: Comparison between subgroups of cases and controls regarding RDW.

Discussion

Our study found that RDW was significantly increased in patients with active RA as compared to healthy control group and that this increase was directly proportional to an increase in ESR. RDW, a measure of erythrocytic anisocytosis, may be raised in RA either due to a low hemoglobin level or as a result of oxidative stress that develops in inflammatory disorders and interferes with erythrocyte maturation. Different studies have found a significant increase in RDW in several other inflammatory disorders including Systemic lupus erythematosus, Systemic sclerosis and Behcet's disease.[5,6,7]

In our study, RDW was also increased in patients with low hemoglobin levels in the control group but it was increased even further in patients with RA. We also found that low hemoglobin or anemia was found in 43 (61.42%) of RA patients and 23 (32.85%) of the healthy control group. In our study, we found that in patients of RA, with or without anemia, RDW strongly positively correlated with DAS-28. These findings are in sharp contrast to a similar study conducted by Feng Lin et al, which found that the low hemoglobin level was responsible for the increase in RDW in patients of RA and when this confounding factor was controlled, no significant correlation was found between RDW and disease activity in RA.[17]

Furthermore, our study found that at a cut-off value of 16%, RDW was highly sensitive and specific for predicting disease activity in RA. Several studies published over the last decade explored the relevance of RDW as a marker of inflammation in autoimmune disorders. A retrospective case control study conducted by Cakir et al, including 81 patients diagnosed with RA and 80 healthy control subjects, compared RDW and mean platelet volume (MPV) in the two groups and correlated these indices with inflammatory markers. They found that RDW and MPV were significantly higher in the RA group as compared to the control group and had a potential for predicting disease activity in RA patients.[18] Tecer et al observed that RDW was significantly elevated in patients with RA and positively correlated with increases in inflammatory markers like ESR and CRP in disease flares.[8] Yunchun et al found an association between increased levels of inflammatory markers, titers of autoantibodies and RDW in patients of RA and accorded a diagnostic and prognostic significance to RDW.[10] Other studies discovered that RDW may serve as a convenient indicator of premature atherosclerosis and development of cardiovascular disorders in patients with RA.[12,13] Rodriguez Carrio et al also found similar implications of RDW in RA patients.[19] A more recently published study including 699 patients of RA, ankylosing spondylitis and non-inflammatory disorders like osteoarthritis and fibromyalgia, compared RDW and inflammatory makers between the various disorders and concluded that RDW was a useful tool for identifying a disease flare in inflammatory disorders, with a maximum sensitivity and specificity of 95%.[20] Al Rawi et al studied 111 patients with RA and found conflicting results indicating that although RDW was a sensitive and specific marker of disease activity in RA, it wasn't found to be associated with inflammatory markers.[15]

After an intensive research of local studies, we concluded that our study is unique in being a case control study comparing RDW in RA and healthy control groups and correlating it with disease activity. The limitations of our study are the small sample size and failure to compare with RDW in other autoimmune rheumatic disorders like systemic lupus erythematosus, systemic sclerosis, Sjogren syndrome and seronegative spondyloarthropathies and non-inflammatory rheumatic disorders like osteoarthritis and fibromyalgia. However, it may serve as a template for more extensive research for exploring the potential of RDW in various inflammatory disorders.

Conclusion

Our study found that RDW is strongly related to disease activity in patients of RA and may serve as a reliable

surrogate inflammatory marker for monitoring disease activity in RA patients.

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