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Red blood cell distribution width-to-platelet ratio inversely correlates with indicators of disease activity status in rheumatoid arthritis patients

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Introduction. Present study was performed to verify red blood cell distribution width-to-platelet ratio (RPR) level in rheumatoid arthritis (RA) patients and to examine its correlation with clinical and biochemical indicators of disease activity status.

Methods. In this cross-sectional analytical study, 67 patients with RA and 34 age- and gender-matched healthy control subjects were enrolled. Based on the disease activity score 28-ESR (DAS28-ESR), RA patients were divided into subgroups: low disease activity (n = 20), moderate disease activity (n = 22) and high disease activity (n = 25). Laboratory tests included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration, platelet count (PLT), red blood cells count (RBC), red blood cells distribution width (RDW) and fibrinogen concentration. Statistical analyses were carried out using SPSS 13 software. Statistical significance was set at a p-value less than 0.05.

Results. There was statistically significant difference ($p = 0.006$) between RPR in RA patients with different stages of disease activity, with higher values in patients with low disease activity. The RPR showed statistically significant negative correlations with ESR (rho = –0.309; $p = 0.012$), CRP (rho = –0.421; $p = 0.001$), swollen joint count – SJC (rho = –0.368; $p = 0.002$) and tender joint count – TJC (rho = –0.355; $p = 0.003$), DAS28-ESR (rho = –0.409; $p = 0.001$), DAS28-CRP (rho = –0.422; $p < 0.0005$) and Visual analogue scale – VAS (rho = –0.260; $p = 0.033$) in RA patients.

Conclusion. The present study provided evidence that the lower RPR values in RA patients are significantly associated with the disease activity indicators.

Key words: blood cells, red cell distribution width, blood platelet count, autoimmune diseases, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects the peripheral diarthroidal joints and leads to their destruction. It is associated with malaise, morning stiffness and fatigue and, depending on the severity, may be accompanied with systemic manifestation including effects on the blood cells [1].

Pathogenesis of RA is associated with an infiltration of the synovium by pro-inflammatory immune cells. These cells secrete multiple cytokines and matrix degrading enzymes which are crucial for maintenance of chronic inflammation and are causing the destruction of joint tissue in RA patients. The inflammatory processes and proinflammatory cytokines alter the attributes and functions of platelets (PLTs) and induce changes in erythroid progenitor cells, erythropoietin and red blood cells (RBCs) resulting in the development of many features of the disease.

Multiple evidence points towards involvement of PLTs in rheumatoid inflammation. It has been previously demonstrated that inflammation is accompanied with peripheric thrombocytosis in RA [2]. Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) in the serum of RA patients can activate platelets [3]. Activated platelets in RA patients release a wide range of soluble platelet activation markers, CD40L, P-selectin and highly active membranous vesicles – platelet-derived microparticles (PMPs), whose levels could be useful in monitoring the disease activity.

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Red blood cell distribution width (RDW) is a simple, easily measured parameter of circulating red blood cells (RBCs) heterogeneity in the size or volume. As a part of the routine haemogram test, RDW is widely used for the differential diagnosis of anemia. Recent studies have demonstrated that elevated RDW indicates the degree of heterogeneity in the size of circulating RBCs, but it also might be an indicator of a chronic inflammation stress and impaired iron metabolism [4]. It has been suggested that increased levels of inflammatory cytokines might suppress erythropoietin-induced erythrocyte maturation, shorten the lifespan of RBCs and accelerate the entry of newer, larger reticulocytes into the peripheral circulation, leading to an increased RDW [5].

A red cell distribution width-to-platelet ratio (RPR), as the proportion of red blood cell distribution width to platelet count, combines the prognostic advantages of RDW and PLT. It has been considered as a novel, simple, cost-effective biomarker which reflects inflammation severity [6]. Further, RPR has been shown to be an independent serum predictor of significant fibrosis and cirrhosis in patients with chronic hepatitis [7]. The aim of this study was to evaluate RPR level in RA patients and to investigate its correlation with clinical and biochemical indicators of disease activity status.

MATERIALS AND METHODS

Study design and participants

This cross-sectional, analytical study comprised 67 RA patients (male/female: 4/63; mean age: 54.7 ± 11.9 years), who fulfilled the criteria of the American College of Rheumatology/European League Against Rheumatism Collaborative initiative for the classification of RA [8], hospitalized in the Clinic for Heart Disease, Blood Vessels and Rheumatism, University Clinical Centre Sarajevo (UCCS). Patients were divided into the following groups according to stage of disease activity evaluated by Disease Activity Score 28-ESR (DAS28-ESR score): group I included 20 RA patients with low stage of disease activity (DAS28-ESR ≤ 3.2), group II included 22 RA patients with moderate stage of disease activity (3.2 < DAS28-ESR ≤ 5.1) and group III included 25 RA patients with high stage of disease activity (DAS28-ESR > 5.1).

The exclusion criteria for the studied group of RA patients included age younger than 18 years or older than 70 years, other rheumatic diseases or other acute or chronic local or systemic diseases of any etiology, malignancy, pregnancy and use of platelet aggregation inhibitors or anticoagulant drugs. The control group consisted of 34 healthy control individuals, age and gender matched to the patients. Subjects of the control group had no history of RA or other rheumatic, autoimmune and inflammatory diseases. After careful explanation of the study procedure, written informed consent for answering the questionnaire and providing blood for analysis was obtained. The study protocol was evaluated and approved by the Ethical Committee of the University Clinical Centre Sarajevo (registered number: 0305–33957). The study was carried out in accordance with the Declaration of Helsinki.

Physical examination and laboratory analysis

All patients underwent gathering of demographic information and clinical examination, with special attention to articular examination, on the same day as venous blood sample was collected. Patients were asked to assess their global assessment of disease activity on a Visual Analogue Scale (VAS), ranging from 0 (very well) to 100 (very poorly). The VAS scores were measured in millimeters [9]. The disease activity in RA patients was determined by competent medical doctor with the use of disease activity score 28-ESR [10].

DAS28-ESR is a mathematical formula with four variables:

DAS28-ESR = $0.56x\sqrt{(TEN28)} + 0.28 \times \sqrt{(SW28)} + 0.70 \times \ln(ESR) + 0.014 \times (GH)$.

(TEN28: 28 tender joint count; SW28: 28 swollen joint count; ln (ESR): natural logarithm of Westergren's erythrocyte sedimentation rate (ESR-mm/h); GH: general health or patient's global assessment of disease activity on the visual analogue scale (VAS) of 100 mm).

The DAS28-CRP considered C-reactive protein (CRP – mg/l) and was calculated as follows:

DAS28 (CRP) = $0.56 \times \sqrt{(TEN28)} + 0.28 \times \sqrt{(SW28)} + 0.014 \times GH + 0.36 \times \ln(CRP + 1) + 0.96$ [10].

Peripheral venous blood samples were collected using vacutainer technique from all patients and control subjects between 6:30 and 8:00 AM, after an overnight fast for at least 8 to 12 h. All hematological and biochemical analyses were conducted at the Organizing Unit for Clinical Chemistry and Biochemistry at the UCCS.

The blood platelet count (PLT), red blood cell count (RBC) and red cell distribution width

(RDW) were determined as part of the automated complete blood count on an automatic hematology analyzer (CELL-DYN Ruby; Abbott Laboratories, USA). Serum CRP concentration was measured by the immunoturbidimetric assay (Beckman Synchron LX System).

ESR was determined by the Westergren technique using venous blood, with added 3.2% sodium citrate as anti-coagulant. Blood sample was placed in an upright graduated pipette (Westergren tube), and the rate of RBCs faling was measured and reported in mm/h. Plasma fibrinogen was measured by standard clot method using the BCS Coagulation System (Dade Behring).

From obtained values of RDW and PLT, the RPR was calculated as: RPR = RDW (%)/platelet count (10^9/L) [11].

Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 13.0 for Windows (Chicago, IL, USA). The normality and variance homogeneity of data for quantitative variables were tested using the Kolmogorov-Smirnov or Shapiro-Wilk test.

Categorical variables were demonstrated as numbers and percentages and differences between them were assessed using Chi-square test.

Results of descriptive statistics for quantitative variables are presented as arithmetic mean ± standard deviation (SD) for normally distributed variables or as median with interquartile range (25–75 percentile) for skewed variables.

The significance of the mean differences between two groups was assessed by independent two-sample Student t test and by one-way analysis of variance (ANOVA) for more than two groups. The difference in values of parameters which showed a non-normal distribution was assessed by Mann-Whitney U-test or Kruskal-Wallis test. Correlation coefficient between two quantitative variables was assessed using the Spearman's rank correlation test. Statistical significance of the obtained results was set at $p < 0.05$.

RESULTS

The average age of healthy subjects in the control group was 51.1 ± 7.4 years and 94.0% were females, whereas average age of RA patients in RA group was 54.7 ± 11.9 years and 85.3% of them were females. There was no statistically significant differences between the control subjects and the patients with RA when comparing gender ($p = 0.145$) or age ($p = 0.067$) (Table 1). Increase in median values of CRP concentrations and ESR in the RA patients were found to be highly significant ($p < 0.0005$) compared to those observed in the control group. Also, median platelet count in the peripheral blood was significantly ($p < 0.0005$) higher, while average EBC was significantly ($p = 0.04$) lower in the RA group compared to the values recorded in the control group. The average fibrinogen concentrations ($p = 0.011$) and RDW values ($p < 0.0005$) were also significantly higher in the RA group than those in the control group (Table 1).

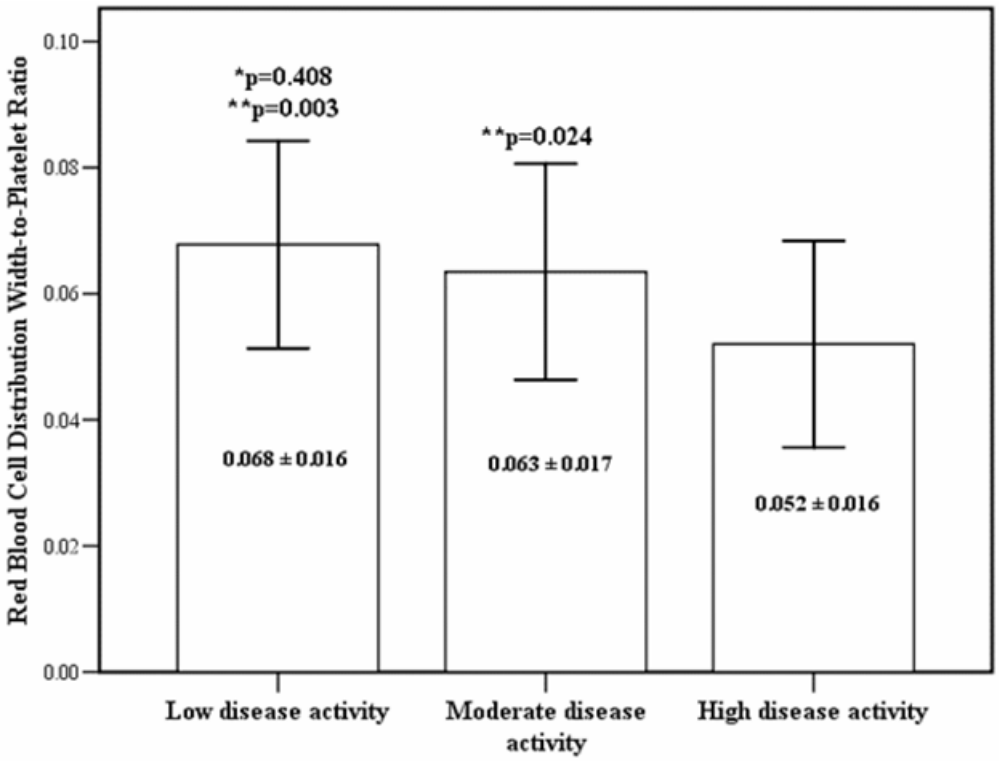
Table 1

Demographic data, clinical and biochemical parameters of the study population

Variables	Control group (n = 34)	RA group (n = 67)	p-value
Female (n/%)	29 (85.3)	63 (94.0)	0.145
Male (n/%)	5 (14.7)	4 (6.0)	
Age (years)	51.1 ± 7.4	54.7 ± 11.9	0.067
CRP (mg/L)	0.85 (0.48 – 1.53)	5.6 (1.4 – 22.9)	< 0.0005
ESR (mm/h)	10.5 (7.0 – 18.5)	5.6 (1.4 – 22.9)	< 0.0005
Fibrinogen (g/L)	3.9 ± 0.6	4.4 ± 1.1	0.011
PLT (x 10^9)	244.5 (214.0 – 290.5)	265.0 (213.0 – 337.0)	< 0.0005
RBC (x 10^{12})	4.5 ± 0.4	4.3 ± 0.3	0.04
RDW (%)	14.4 ± 0.8	15.7 ± 1.7	< 0.0005
RPR	0.061 ± 0.012	0.060 ± 0.018	0.767

Results are presented as: mean ± SD, or median with interquartile range (25–75 percentile), percentages (%); n = number of subjects; RA – Rheumatoid arthritis; VAS – Visual Analogue Scale; CRP – C reactive protein; ESR – Erythrocyte Sedimentation Rate; PLT – Platelet count; RBC – Red Blood Cells count; RDW – Red Blood Cell Distribution Width; RPR – Red Blood Cell Distribution Width-to-Platelet Ratio; p value – probability.

Statistically significant difference (p = 0.006) was observed between RPR of RA patients in terms of DAS28-ESR score. The RPR values in patients with low disease activity were higher, but not significantly (p = 0.408) than those in patients with moderate disease activity, and significantly (p = 0.003) higher than those in, patients with high disease activity. Significant difference (p = 0.024) in RPR values was observed between patients with moderate and high DAS28-ESR scores (Figure 1).



Each bar shows upper and lower quartile, while the square and its central bar indicate interquartile range and median. p – probability; NS – not significant; *in comparison with Moderate disease activity; ** in comparison High disease activity

Figure 1. Box-and-whisker plots of the Red Blood Cell Distribution Width-to-Platelet Ratio values in RA patients with different stages of disease activity.

There were statistically significant negative correlations between RPR and parameters of disease activity: ESR (rho = –0.309; p = 0.012), CRP (rho = –0.421; p = 0.001), swollen joint count (rho = –0.368; p = 0.002), tender joint count (rho = –0.355; p = 0.003), DAS28-ESR (rho = –0.409; p = 0.001), DAS28-CRP (rho = –0.422; p < 0.0005) and VAS (rho = –0.260; p = 0.033) in patients with rheumatoid arthritis (Table 2).

Table 2

Spearman's correlation coefficient between Red Blood Cell Distribution Width-to-Platelet Ratio and clinical and biochemical indicators of disease activity status in patients with rheumatoid arthritis

Variables	Red Blood Cell Distribution Width-to-Platelet Ratio	
	rho	p-value
ESR (mm/h)	–0.309	0.012
CRP (mg/L)	–0.421	0.001
Fibrinogen (g/L)	0.008	0.956
RBC (x 10^{12})	–0.024	0.844
Swollen joint count	–0.368	0.002
Tender joint count	–0.355	0.003
DAS28-ESR	–0.409	0.001
DAS28-CRP	–0.422	< 0.0005
VAS (mm)	–0.260	0.033

ESR – Erythrocyte Sedimentation Rate; CRP – C reactive protein; RBC – Red Blood Cells count; DAS28-ESR – Disease Activity Score 28-ESR; DAS28-CRP – Disease Activity Score 28-CRP; VAS – Visual Analogue Scale; rho – Spearman's correlation coefficient; p value – probability.

DISCUSSION

To the best of our knowledge, the present study is the first research which evaluated the RPR value and explore its clinical significance in Bosnian RA patients. Moreover, the association between RPR and inflammatory and disease activity parameters in RA patients.

C-reactive protein and ESR are the most extensively studied acute-phase biomarkers, important in monitoring of disease activity and providing prognostic information in RA [12]. In the present study median values of CRP concentrations and ESR in the RA patients were statistically significantly higher ($p < 0.0005$) compare to those observed in the control group.

These results are in accordance with results of the study by Klimenta *et al.* which compared inflammation biomarkers values, the ESR and CRP, between patients with RA and a healthy control group of females of the Public Institution Health Centre of Sarajevo Canton (Bosnia and Herzegovina). Mentioned study showed that the values of the ESR ($p < 0.0001$) and CRP ($p < 0.0001$) were significantly increased in RA patients compared to those in the control group and were extensively above the normal maximum value. They concluded that ESR and CRP were the most sensitive indicators of disease in patients with RA [13].

Yildirim *et al.* have also noticed that ESR and CRP levels were higher in 47 patients with RA, compared with 50 healthy controls. These authors also reported that of the numerous acute phase reactant tests investigated, CRP was in strongest correlation with DAS28 score in their sample of patients with RA [14].

An elevated ESR is considered to be one of the nonspecific biological markers of inflammatory process in RA [15]. Fibrinogen assessment is an alternative option to ESR because of its strong impact on ESR during inflammatory reaction [12].

Our study shows that the concentrations of fibrinogen were also significantly ($p = 0.011$) higher among RA patients than among participants in the control group.

Various hematologic abnormalities have a significant role in the development of autoimmune rheumatic diseases (ARDs) including RA. Anemia and thrombocytosis are the most frequent hematological findings in RA patients[16].

It has been previously demonstrated that platelets play a crucial role in thrombogenesis and are also involved in inflammation, endothelial dysfunction, and atherogenesis [17]. Many different soluble mediators secreted as a response of the systemic inflammation have important role in platelet function and they can increase the number of platelets [18]. Studies have already found that a positive association exists between the levels of erosion in joints and platelet and RBC counts in RA patients [19]. The results of our study have shown significantly higher values ($p < 0.0005$) of platelet count and significantly lower values ($p = 0.04$) of erythrocyte blood count in the peripheral blood of RA patients compared to the control group.

The inflammatory environment in RA affects RBCs. Several studies have shown that proinflammatory cytokines downregulate erythropoietin receptor expression, suppress erythropoietin gene expression, inhibit proliferation of erythroid progenitor cells, and decrease erythrocyte lifespan [20]. In the present study, the RDW values were significantly higher in patients with RA compared with healthy controls. Cakir *et al.* [21] have also reported that the patients with RA have significantly higher RDW values compared to age-sex matched healthy subjects. Increased values of RDW can be the outcome of a nutritional deficiency, chronic inflammation, or bone marrow depression in RA patients [22, 23]. According to the study conducted by Lee *et al.* [24], patients with RA had increased RDW when compared with osteoarthritis patients. Mentioned study also showed that RDW was positively correlated with CRP in RA patients, regardless of anemia. Rodríguez-Carrio *et al.* reported that RDW is positively correlated with DAS-28, which indicates that RDW is a potential index in estimating the disease activity in RA patients. In this regard, mention study reported that elevated RDW might be a useful marker of inflammatory stress and impaired iron mobilization in RA patients [25]. Possible explanation is that inflammation may contribute to increased RDW values by inhibiting responses to erythropoietin or suppressing the production of erythropoietin and shortening red blood cell survival.

According to our findings, RPR was decreased, but not significantly in RA patients when compared with healthy controls ($p = 0.767$). The possible reason for the lack of statistically significant difference between RPR values in patients with RA and healthy controls may be that our study included only active RA patients and in the same percent patients with different disease activity score. However, statistically significant difference ($p = 0.006$) was observed between RPR of RA patients in terms of DAS28.

The RPR values in patients with low disease activity were higher, but not significantly (p = 0.408), than those in patients with moderate disease activity, and significantly (p = 0.003) higher than those in patients with high disease activity. Significant difference (p = 0.024) in RPR values was observed between patients with moderate and high disease activity scores.

In addition, we noted a statistically significant negative correlations between RPR and parameters of disease activity: swollen joint count (rho = –0.368; p = 0.002), tender joint count (rho = –0.355; p = 0.003), DAS28-ESR (rho = –0.409; p = 0.001) DAS28-CRP (rho = –0.422; p < 0.0005) and VAS (rho = –0.260; p = 0.033) in RA patients. In this study we showed that in patients with RA, RPR values inversely correlated with the inflammatory status of the patients as assessed by the inflammatory markers ESR (rho = –0.309; p = 0.012) and CRP (rho = –0.421; p = 0.001).

To the best of our knowledge, association between serum RPR with parameters of disease activity and inflammatory markers in RA patients has not been investigated so far, so we could not compare our results with results of other authors. The mechanisms underlying this inverse relationship are still unclear, but it is probably that some drugs can have effect on RPR values in RA patients; therefore, further studies should analyze and take into consideration the type of drugs taken by the patients.

There were some limitations to this study. First, the cross-sectional study design and a relatively small number of the patients due to RA low incidence might undervalue or overvalue the relationship between RPR and clinical and biochemical indicators of disease activity in RA. Another study limitation might be that this study is a single-center based study thus results may not be fully representative for all cases of the disease in the patient population.

CONCLUSIONS

Despite previously mentioned limitations, inverse, significant association between RPR and ESR, CRP, DAS28-ESR and DAS28-CRP scores, SJC and TJC in patients with RA supports a link between RPR and inflammation and suggests that lower RPR values are associated with the disease activity indicators in RA patients. Further prospective studies on a larger sample size should be conducted for an interpretation and explanation of exact mechanisms underlying observed associations between RPR and parameters of disease activity in RA patients.

Introducere. *Studiul şi-a propus să verifice parametrul RPR (red blood cell distribution width-to-platelet ratio) la pacienţii cu AR (artrită reumatoidă) şi să examineze corelaţia cu indicatori clinici şi paraclinici.*

Metode. *A fost realizat un studiu transversal în care au fost selectaţi 67 de pacienţi cu RA şi 34 de martori sănătoşi. Pacienţilor cu AR le-a fost evaluată severitatea bolii (DAS28-ESR) şi au fost împărţiţi în 2 grupuri – cu boală moderată (20 pacienţi) şi severă (25 pacienţi). Au fost evaluaţi paramerii inflamatori. S-a utilizat softul SPSS versiunea 13 pentru analiza statistică cu un prag de 0,05 pentru semnificaţia statistică.*

Rezultate. *Pacienţii cu severitate mai mică aveau niveluri semnificative mai mari ale RPR (p = 0,006). RPR s-a corelat cu VSH (rho – 0,309; p = 0,012), CRP (rho = –0,421; p = 0,001), cu swollen joint count – SJC (rho = –0,368; p = 0,002) şi cu tender joint count – TJC (rho = –0.355; p = 0,003), cu DAS28-ESR (rho = –0,409; p = 0,001), cu DAS28-CRP (rho = –0,422; p < 0,0005) şi cu durerea pe scală vizuală analogă – VAS (rho = –0,260; p = 0,033).*

Concluzii. *Studiul a demonstrat niveluri mai mici ale RPR la pacienţii cu severitate mai mare a RA.*

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