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Original Article

Can whole-blood parameters be used in follow-up of children with rheumatic valvular heart disease?

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Abstract *Objectives:* The aim of the present study was to investigate the relationships between red blood cell distribution width, platelet distribution width, and mean platelet volume and the presence and severity of valvular involvement in patients with rheumatic heart disease. *Methods:* Between April, 2012 and December, 2015, 151 patients who were admitted to the Pediatric Cardiology Unit with diagnosis of rheumatic heart disease and 148 healthy children were included to our study. Transthoracic echocardiography for all children was performed, and the values of red blood cell distribution width, platelet distribution width, and mean platelet volume, besides other blood count parameters, erythrocyte sedimentation rate, and C-reactive protein levels were recorded. *Results:* Red blood cell distribution width, platelet distribution width, mean platelet volume, and C-reactive protein levels were significantly higher in patients with rheumatic heart disease when compared with healthy controls ($p < 0.01$). Red blood cell distribution width was positively correlated with both C-reactive protein ($r = 0.271$, $p = 0.035$) and erythrocyte sedimentation rate ($r = 0.308$, $p = 0.006$). When single valve involvement was compared with both aortic valve and mitral valve involvement in the study group, red blood cell distribution width and platelet distribution width were higher in patients with double valve involvement; however, this was not statistically significant ($p > 0.05$). *Conclusion:* This is the first study in children with rheumatic heart disease that demonstrated significantly increased red blood cell distribution width, platelet distribution width, and mean platelet volume levels, as well as evaluated all three parameters together. Furthermore, red blood cell distribution width values in the chronical period of acute rheumatic fever, due to the positive correlation with the other chronic inflammatory markers, may help make the diagnosis in children.

Keywords: Red blood cell distribution width; mean platelet volume; platelet distribution width; rheumatic heart disease

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ACUTE RHEUMATIC FEVER IS AN INFLAMMATORY disease that develops as a result of immunological response against infection of group A β haemolytic streptococcus. Although the incidence of rheumatic heart disease has been declining in developed countries, it is still one of the most important causes of acquired heart disease in young children and adults in developing countries.[1] Involvement of the heart valves is the most important long-term effect of acute rheumatic fever, closely associated with morbidity and mortality.[2] Heart valve involvement has been observed in 60% of patients with acute rheumatic fever, and the most commonly affected valves are the mitral and aortic valves.[2] Although the mechanism of valvular damage is not clear, the role of inflammatory cytokines in the pathophysiology of acute rheumatic fever is well known. Furthermore, activation of complements, accumulation of lymphocytes, and excess release of adhesion molecules are present in the heart tissue.[3,4]

Red blood cell distribution width is associated with inflammatory markers in chronic inflammation.[5,6]

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It has been found that this parameter causes the progression of diseases characterised by chronic inflammation and even increases in many cardiovascular diseases such as heart failure, acute myocardial infarction, and coronary artery disease.[6–9] In addition, because of platelet activation, which has a very important role in inflammation, it has been observed to secrete mediators such as chemokines and cytokines.[10] Mean platelet volume and platelet distribution width are platelet activation markers, which are associated with serious inflammation.[11,12]

The aims of the present study were to compare red blood cell distribution width, mean platelet volume, and platelet distribution width values in children with rheumatic heart disease with healthy children and to demonstrate the evaluation of these three parameters in combination in clinical follow-up of patients at long term.

Materials and methods

Patients who were admitted to the Pediatric Cardiology Unit between April, 2012 and December, 2015 diagnosed with rheumatic heart disease by transthoracic echocardiography were retrospectively recorded. A total of 151 patients who were diagnosed with rheumatic carditis according to the pathological valvular insufficiency criteria via transthoracic echocardiography or had been diagnosed with acute carditis and treated properly for 6 months were included. All the patients had secondary prophylaxis with antibiotics. Transthoracic echocardiography was performed on all patients by an experienced paediatric cardiologist. The demographic characteristics of the patients were obtained from patient information system. In addition, a control group was included consisting of 148, healthy, age- and sex-matched children with normal transthoracic echocardiographic findings.

Complete blood count including white blood cell count, platelet count, red blood cell distribution width, mean platelet volume, and platelet distribution width, erythrocyte sedimentation rate, and C-reactive protein levels of all patients and control subjects were recorded. Transthoracic echocardiography was performed via Vivid S5 Pro Ultrasound System (GE Medical Systems, Horten, Norway), using 3 and 6 MHz transducers in two-dimensional, M-mode, and colored Doppler visualising modes. Cardiac valves were evaluated for annular and chordal pathologies and regurgitation, prolapses, and presence of vegetation. Mitral and aortic valve regurgitations were assessed by colored Doppler echocardiography in the apical and parasternal long-axis windows. Pathological valve insufficiency was considered for the mitral valve as continuation of regurgitation during systole and for the aortic valve as continuation of regurgitation during diastole at least in two windows as a jet of mosaic colour 1 cm in length with a peak velocity of 2.5 m/second.[13]

Exclusion criteria for both patient and control groups included the following: having any infectious or inflammatory diseases or using anti-inflammatory or anticoagulant drugs in the last 1 month, having anaemia, thrombocytopaenia, or haematological problems. Local Ethics Committee approval was obtained for the study protocol.

Statistical analysis

Data are summarised as means and their standard deviations, medians, and minimum and maximum values.

Control of numerical data was performed using the "Shapiro–Wilk Normality Test". The "Mann–Whitney U-Test" was used for red blood cell distribution width, and the "Independent t-test" was used for the other parameters. "Spearman's Correlation Analysis" was used to determine the relationships between parameters.

After evaluation of red blood cell distribution width, platelet distribution width, mean platelet volume, and C-reactive protein levels one by one (univariate) between subgroups of patients and the control group to evaluate the effects of them together, analyses of multiple variants were performed (multivariate); $p < 0.05$ was considered statistically significant.

Results

In this study, 151 patients (80 male and 71 female) who were diagnosed with rheumatic heart disease and 148 age- and sex-matched healthy children were included. The mean age of the patients was 14.04 ± 2.5 (with a range from 7 to 18) years. Mitral regurgitation existed in 52 patients and aortic regurgitation in 33 of them, and both were present in 66 patients. Demographic and laboratory characteristics of the patient and control groups are shown in Table 1. Red blood cell distribution width, platelet distribution width, mean platelet volume, and C-reactive protein levels of the patient group were significantly higher when compared with the control group ($p < 0.01$); however, there were no significant differences in values of haemoglobin, haematocrit, platelet count, and white blood cell count between the groups ($p > 0.05$).

The red blood cell distribution width levels according to valve involvement between the groups are shown in Figure 1. The difference of red blood cell distribution width level was statistically significant between the two valve involvement groups and the

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Table 1. Demographic and laboratory characteristics of the patient and control groups.

	Patient	Control	p Value
Age	14.04 ± 2.5	13.5 ± 2.5	0.435
Sex (F/M)	80/71	67/81	
Haemoglobin	13.01 ± 3.2	13.06 ± 1.4	0.207
Haematocrit	37.6 ± 3.5	37.3 ± 3.5	0.910
Platelet	306.000 ± 92	300.000 ± 70	0.059
WBC	8.934 ± 4.15	9.170 ± 3.1	0.323
RDW	13.81 ± 1.5	13.12 ± 0.9	<0.01
MPV	9.99 ± 1.11	9.84 ± 0.78	<0.01
PDW	12.41 ± 2.3	11.58 ± 1.73	<0.01
CRP	5.95 ± 8.01	1.95 ± 2.92	<0.01
ESR	10.1 ± 8.9	–	

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; F = female; M = male; MPV = mean platelet volume; PDW = platelet distribution width; RDW = red blood cell distribution width; WBC = white blood cell count

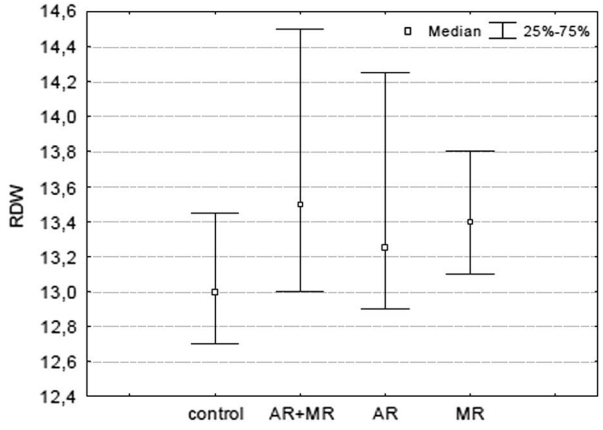

Figure 1.
Red blood cell distribution width (RDW) levels according to rheumatic valvular involvement. AR = aorta regurgitation; MR = mitral regurgitation.

control group (p = 0.002). When C-reactive protein and platelet distribution width were added to the evaluation of red blood cell distribution width, the value of statistical model was increased (p = 0.001). The red blood cell distribution width alone had no impact on the difference between the patients with aortic regurgitation and the controls (p = 0.334), but when added C-reactive protein, platelet distribution width and mean platelet volume to the model, it was found to be statistically significant (p = 0.001).

It was also observed that red blood cell distribution width differed between patients with mitral regurgitation and controls (p = 0.007). Moreover, red blood cell distribution width was still significant when evaluated together with the effects of the haemogram parameters, platelet distribution width, and mean platelet volume (p = 0.049), but when C-reactive protein was added to the model significance was lost (p = 0.108) (Table 2).

Red blood cell distribution width was found to have a significantly positive correlation with both C-reactive protein (r = 0.271, p = 0.035) and sedimentation (r = 0.308, p = 0.006). The red blood cell distribution width and platelet distribution width values were higher in patients with involvement of both valves, but this increase was not statistically significant (p > 0.05).

Discussion

This is the first study in children with chronic rheumatic valvular heart disease to evaluate the combination of red blood cell distribution width, platelet distribution width, and mean platelet volume parameters, and all of them were significantly increased. Our study also identified that there is a positive correlation between inflammatory markers and red blood cell distribution width in patients with chronic rheumatic carditis.

Rheumatic fever is an autoimmune disease that develops after group A streptococcus infection due to abnormal cellular and hormonal responses in susceptible individuals. Although major histocompatibility antigens, tissue-specific antigens, and antibody formation have been considered significant risk factors in the pathogenesis of this disease, the exact developing mechanism of the acute rheumatic fever is still undefined. The clinical severity of the disease is shaped not only by abnormal immune response but also by genetic predisposition of the host, virulence of the organism that infects, and environmental conditions. Rheumatic valvular disease is the most serious complication of acute rheumatic fever and is in turn one of the most common causes of acquired heart disease in developing countries.[1] Cytokines secreted by activated lymphocytes and macrophages, tumour necrosis factor, and interleukins play an important role in the pathogenesis of rheumatic heart disease. M protein and anti-carbohydrate antibodies of group A streptococcus cause damage to the valvular endothelium in susceptible individuals, resulting in increased release of vascular cell adhesion molecule 1 and other adhesion molecules. Subsequently, the interaction between VCAM-1 and activated lymphocytes stimulates cluster of differentiation 4 and cluster of differentiation 8 T cells. The inflammatory reaction that is triggered by the activation of the complement system as a consequence of T cell infiltration and autoreactivity causes a progressive and permanent damage to the valves.[13,14]

Mean platelet volume and platelet distribution width levels that demonstrate the variability in size of

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Table 2. Comparison of subgroups by valvular involvement with the control group when red blood cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), and C-reactive protein (CRP) are included.

	MR – control		AR – control		AR + MR – control	
Variables	p value	Wilk's λ	p value	Wilk's λ	p value	Wilk's λ
RDW	0.049	0.969	0.006	0.936	<0.001	0.922
MPV	0.294		0.098		0.882	
RDW	0.118	0.958	0.001	0.756	0.001	0.823
CRP	0.098		<0.001		<0.001	
RDW	0.070	0.938	0.006	0.947	<0.001	0.892
PDW	0.007		0.503		0.005	
RDW	0.049	0.922	0.006	0.934	<0.001	0.896
MPV	0.294		0.503		0.882	
PDW	0.004		0.098		0.004	
RDW	0.108	0.929	0.001	0.737	0.002	0.831
MPV	0.073		0.245		0.949	
CRP	0.096		<0.001		<0.001	
RDW	0.108	0.875	0.001	0.740	0.001	0.783
CRP	0.096		<0.001		<0.001	
PDW	0.001		0.695		0.004	
RDW	0.108	0.874	0.001	0.737	0.002	0.807
CRP	0.096		<0.001		<0.001	
PDW	0.001		0.695		0.003	
MPV	0.073		0.245		0.949	

AR = aorta regurgitation; MR = mitral regurgitation

platelets can be used as markers of platelet activation. Moreover, it has been shown that these two markers reflect the severity of inflammation and also increase in myocardial infarction and chronic pulmonary diseases.[10,15,16] The mechanism of increase in mean platelet volume and platelet distribution width is not understood exactly until now. It has been emphasised that inflammatory cytokines induce the production of large and reactive platelets and these circulating platelets have a shorter life span.[15]

Ozdemir et al[17] compared the levels of mean platelet volume and platelet distribution width in patients with acute rheumatic fever before and after the treatment in a study and they found no significant differences. Mean platelet volume levels in patients with acute rheumatic fever and controls were also compared in a study by Sert et al[18]; the result showed lower levels in patients. The results of these two studies are conflicting in terms of mean platelet volume and platelet distribution width levels. In our study, on the other hand, mean platelet volume and platelet distribution width levels were significantly higher in patients with chronic rheumatic heart disease compared with the control group. Ozdemir et al did not detect any changes in these parameters before and after treatment, which can be explained as continuation of the inflammation process after the treatment. In another study, on the contrary, the level of mean platelet volume was found to be lower in acute rheumatic fever and in chronic inflammatory diseases, whereas in myocardial infarction and pulmonary diseases the marker was found to be increased.[10,15,16] In our study, high C-reactive protein levels have been accepted as an indicator of chronic inflammation in patients, and simultaneous elevation in the value of mean platelet volume and platelet distribution width has been concerned due to the chronic inflammation as well.

Red blood cell distribution width, reflecting the variability in size of red blood cells in circulation, increases in some heart diseases regardless of the haemoglobin level and is considered as a new marker for predicting mortality.[5,6–8,19] Oxidative stress and chronic inflammation shorten the life span of erythrocytes and increase the number of immature and different-sized erythrocytes in circulation.[20] Therefore, in this study, increased red blood cell distribution width in patients when compared with the control group suggests that red blood cell distribution width is a marker of the underlying chronic inflammation, which increases the risk of cardiovascular disease. Similarly, C-reactive protein is one of the well-known inflammatory markers. C-reactive protein level was found to be higher in patients with chronic rheumatic heart disease compared with the control group, and this increase was accepted as an indicator of the continuing inflammation.[21,22] Some studies show a strong correlation between red blood cell distribution width and C-reactive protein levels, and some suggest that red blood cell distribution

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width can be used in determining the risk of mortality.[23] In addition, some studies in patients with coronary artery disease underline the elevation in red blood cell distribution width level as associated with C-reactive protein level, which may be an independent predictor of mortality.[24,25] Furthermore, Tonelli et al[9] found an independent relationship between red blood cell distribution width and death and/or the risk of cardiovascular events in patients with asymptomatic heart failure who had myocardial infarction previously. Akboğa et al[26] in a study including patients with rheumatic mitral valvular stenosis found that the red blood cell distribution width levels were significantly increased in parallel with the severity of valvular stenosis, which was also correlated with C-reactive protein levels. In our study, similarly, the red blood cell distribution width level in patients with chronic rheumatic heart disease was significantly higher compared with the control group. Furthermore, there was a positive correlation between C-reactive protein and red blood cell distribution width levels as in the literature.

On the basis of the data, it is assumed that evaluating the red blood cell distribution width and platelet markers together would be more effective in follow up patients with acute rheumatic fever having valvular involvement. Meanwhile, the red blood cell distribution width levels in patients with mitral regurgitation and both mitral and aortic regurgitation were significantly higher compared with the control group, and this significance increased with the addition of platelet distribution width and mean platelet volume to the comparison. Even when red blood cell distribution width level alone was not different in patients with aortic regurgitation compared with the control group, the results were found to be statistically significant when red blood cell distribution width together with platelet distribution width, mean platelet volume, and C-reactive protein were interpreted. Thus, as noted in many other studies previously, our results support the role of chronic inflammation in the pathophysiology of chronic rheumatic heart disease and the association of red blood cell distribution width, platelet distribution width, and mean platelet volume with this inflammation.[15,23,24,26]

Consequently, we have been assuming that parameters such as red blood cell distribution width, platelet distribution width, and mean platelet volume that can be determined by complete blood count can be used to predict valvular involvement in the follow-up of patients with chronic rheumatic carditis. Furthermore, red blood cell distribution width can be used as a risk-determining marker in children with rheumatic heart disease, as it has a positive correlation with C-reactive protein, which is a chronic inflammatory marker. Nevertheless, distinguishing congenital mitral regurgitation and patients with quiet carditis may sometimes be a bit difficult. Owing to this fact, it has been assumed that the use of markers such as red blood cell distribution width, mean platelet volume, and platelet distribution width, which demonstrate the process of chronic inflammation and can be easily examined anywhere, will help in overcoming this distinction in near future; however, in order to evaluate the relationship, more comprehensive prospective studies are required.

The retrospective design of the study is a major limitation. Besides inflammation, parameters known to affect red blood cell distribution width such as erythropoietin, iron, folic acid, and fibrinogen levels were not taken into consideration; however, patients with anaemia or any haematological problems were not included in the study.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of Mersin University.

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