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Research Article

Relationship Between Platelet-to-Lymphocyte Ratio and Rheumatic Heart Disease

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Abstract

Objectives: Rheumatic heart disease is a significant cause of morbidity and mortality in developed and undeveloped countries. Rheumatic valve disease is the most long-term sequel in rheumatic heart disease, and the platelet to lymphocyte ratio is a novel biomarker which is associated with poor clinical outcomes in various cardiovascular disorders. We evaluated the relationship between the platelet-to-lymphocyte ratio and chronic rheumatic heart disease.

Methods: We analyzed 54 patients with rheumatic heart disease and 49 healthy subjects. All patients were evaluated using transthoracic echocardiography. In addition to echocardiographic and biochemical parameters, the platelet-to-lymphocyte ratio was compared between the groups.

Results: There was no significant difference between the groups regarding ejection fraction, left atrium, left ventricular end diastolic diameter and left ventricle end systolic diameter in the echocardiographic assessment. Biochemical parameters were similar between the groups regarding glucose, creatine, total cholesterol triglyceride, and low-density lipoprotein. The lymphocyte count was significantly lower in the rheumatic heart disease group than the control group (2.46±0.70 vs. 2.64±0.53, p=0.01). The platelet-to-lymphocyte ratio was significantly higher in the rheumatic heart disease group (110.86±46.67 vs. 90.07±21.56, p=0.01).

Conclusion: The platelet-to-lymphocyte ratio was high, and the lymphocyte count was low in the rheumatic heart disease group than the control group.

Keywords: Inflammation; platelet-to-lymphocyte ratio; rheumatic heart disease.

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Rheumatic heart disease (RHD), chronic acquired disorder, is an important cause of morbidity and mortality in developing and undeveloped countries.[1] RHD is an inflamatory and autoimmune pathology that occurs as a complication of untreated group A β-hemolytic streptococcal pharyngitis.[2] The inflammatory reaction can lead to the progression of valvular damage.[3] Lymphocyte accumulation and complement deposition were demonstrated in the heart tissues in patients with RHD.[4] In addition, an immunologic cross-reactivity was demonstrated between streptococcal antigens and glycoproteins of the cardiac valves.[5] Although, the manifestations of RHD include carditis, pericarditis, and valvulitis, it primarily affects the endocardium and causes chronic inflammation in the valvular apparatus which is characterized by progressive and permanent valve disorder. Imaging modality for the diagnosis of rheumatic valve disease is an echocardiographic examination.[6]

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Inflammation and platelet activation plays a central role in the initiation and progression of atherosclerosis process. [7] Lymphocyte count is inversely correlated with inflammation and a low blood lymphocyte count was related to worse cardiovascular outcomes in patients with coronary artery disease.[8] The platelet to lymphocyte ratio (PLR) was introduced as a potential marker for excess thrombotic activity.[9] Also, The platelet-to-lymphocyte ratio (PLR), an inflammatory marker, is associated with various cardiovascular diseases.[10] The association between PLR and RHD is unknown. The study aimed to evaluate the relationship between PLR and the presence of the RHD.

Methods

From September 2018 to March 2019, 54 patients with RHD and 49 healthy, age and sex matched control subjects were included in the study. All patients underwent detailed medical history, physical examination, laboratory evaluation, ECG and echocardiography.The RHD group consisted of patients who were previously diagnosed and followed up at the Department of Cardiology, Adıyaman Training and Research Hospital. The inclusion criteria was having mild mitral regurgitation and/or mitral stenosis. Patients with moderate or sever mitral regurgitation and/or mitral stenosis, hyperthyroidism, left ventricular hypertrophy, coronary artery disease, significant renal disease, respiratory disease, cardiomyopathy, diabetes mellitus, hypertension, acute corticosteroids use, acute infection, chronic hepatic disease and hematological disease were excluded from the study. Hyperlipidemia was reported for total cholesterol ≥200 mg/dL, low-density lipoprotein (LDL) level ≥190 mg/dL, or use of cholesterol-lowering medication. A 12-lead electrocardiography (ECG) was recorded.

Transthoracic echocardiography study was performed with a 3.5-MHz transducer to all patients (Vivid 3; GE Medical System, Horten, Norway). All measurements were made according to the guidelines of the American Society of Echocardiography.[11] Rheumatic valvular disease was diagnosed based on echocardiographic detection of typical B-mode features such as thickening of the valve leaflets and chordal apparatus, restricted leaflet separation, diastolic doming of the anterior mitral leaflet, and upward movement of the posterior mitral leaflet in early diastole.[12] The mean pressure gradient across the mitral valve was determined using the simplified Bernoulli equation. Mitral valve area was measured by planimetry and pressure half-time methods. [13] The assessment of the mitral stenosis was based on the mean gradient, systolic pulmonary artery pressure, and valve area according to the ACC/AHA guidelines for the management of patients with valvular heart disease.[11] Mild stenosis is associated with a mean trans-valvular gradient of <5 mmHg, PASP pressures <30 mmHg, and a valve area <1.5 cm^2. Pulmonary artery pressure was estimated measuring the velocity of the tricuspid regurgitant jet. Doppler methods including assessment of regurgitant jet characteristics were used in the assessment of the severity of valvular regurgitation.[12] The left ventricle end-diastolic diameter and end-systolic diameter and left atrial diameter were measured from the 2-D guided parasternal long-axis window in M-mode echocardiographic tracing. The left ventricular ejection fraction (LVEF) was measured according to the Simpson's method.

Blood samples are collected from the antecubital vein by an atraumatic puncture and are sent to the laboratory for analysis after an echocardiographic examination. Common blood counting parameters stored in citrate based anti-coagulated tubes were measured by Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc, Mervue, Galway, Ireland) within five minutes of sampling. Routine complete blood count and biochemical parameters including total cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL) and high-density lipoprotein-cholesterol (HDL), blood glucose and creatinine were determined by the hospital biochemistry laboratory. PLR was calculated as the ratio of the platelet count to the lymphocyte count. The study protocol was approved by the local ethics committee of the Adıyaman University Training and Research Hospital, and each patient provided written, informed consent.

Statistical Analysis

Data were analyzed with SPSS software version 20.0 for Windows (SPSS Inc, Chicago, Illinois). The Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed. Normally distributed variables were expressed as mean±standard deviation (SD).The categorical variables are presented as percentages. Differences between two groups were evaluated with Student's unpaired t test with a normal distribution. The frequencies of nominal variables were compared using the Fisher's exact test or chi-square test. The Spearman test was used for correlation analysis. A Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cutoff level for the PLR values that best predicted RHD. Statistical significance was defined as $p<0.05$.

Results

The demographic and clinical data of the study population is presented in Table 1. No difference was found in the demographic characteristics between the groups regarding age and gender. In the electrocardiographic analyze the heart rate was similar between the groups. There was no significant difference between the groups regarding ejec-

Table 1. The demograhic, blood and echocardiographic charecteristics of the patients

	RHD (n=54) Mean±SD	Control (n=49) Mean±SD	p
Age, years	24.28±4.12	26.80± 5.51	0.09
Male, n (%)	26 (55)	21 (44)	0.59
Heart Rate, bpm	77.35±12.87	72.86±13.03	0.63
Ejection fraction, %	57.74±1.64	55.53±2.45	0.43
Left atrium, cm	3.75±0.22	3.65±0.24	0.31
LVEDD, cm	4.70±0.27	4.70±0.31	0.16
LVESD, cm	3.02±0.13	3.04±0.15	0.18
MVA, cm^2	1.96±0.09	2.03±0.10	0.58
MG, mmHg	3.07±0.61	2.67±0.47	0.68
PG, mmHg	6.81±1.20	6.29±1.00	0.29
PASP, mmHg	31.76±2.43	30.57±2.19	0.34
Glucose, mg/dL	92.44±14.84	93.43±12.26	0.37
Creatine, mg/dL	0.78±0.11	0.69±0.11	0.93
Total cholesterol mg/dL	179.13±37.25	176.63±31.98	0.25
Triglyceride, mg/dL	151.41±69.33	167.16±64.60	0.62
LDL, mg/dL	108.11±24.83	99.20±24.37	0.72
HDL, mg/dL	43.83±6.78	43.35±8.98	0.01
WBC count, $x10^3/mm^3$	8.24±2.47	7.37±2.17	0.34
Hemoglobin, g/dL	14.38±1.80	13.55±1.83	0.54
Hematocrit, %	43.14±5.39	42.67±5.19	0.93
RDW, %	11.00±1.16	11.73±1.45	0.14
MPV(fl)	8.25±1.68	7.80±1.52	0.79
Neutrophil count, $x10^3/mm^3$	4.63±1.50	3.98±1.68	0.27
Platelet, count, $x10^3/mm^3$	247.30±47.54	231.14±46.49	0.63
Lymphocyte, count, $x10^3/mm^3$	2.46±0.70	2.64±0.53	0.01
PLR, n	110.86±46.67	90.07±21.56	0.01

RHD: rheumatic heart disease; LVEDD: left ventricule end diastolic diameter; LVESD: left ventriclue end systolic diameter; MVA: mitral valve area; MG: mean gradient; PG: peak gradient; PASP: pulmonary artery systolic pressure; LDL: low density lipoprotein; HDL: high density lipoprotein; WBC: white blood cell; RDW: red cell distribution width; MPV: mean platelet volume; PLR: platelet-to- lymphocyte ratio.

tion fraction, left atrium, left ventricular end diastolic diameter and left ventricle end systolic diameter in the echocardiographic assessment. There was no significant difference between the groups in the mitral valve area and gradients. The pulmonary artery pressure measurements were similar between the groups. Biochemical parameters were similar between the groups regarding glucose, creatine, total cholesterol triglyceride and low density lipoprotein, whereas the high density lipoprotein was significantly higher in the RHD group (p=0.01). In the hematological analyze, no difference was found between the groups regarding white blood cell count, hemoglobin, hematocrit, platelet, red cell distribution width, mean platelet volume and neutrophil count. The lymphocyte count was significantly lower in the RHD group than the control group (p=0.01). Against the platelet count was similar, the PLR was significantly higher because of lower lymphocyte count in the RHD group than the control group (p=0.01). Figure 1 presents the difference between PLR in

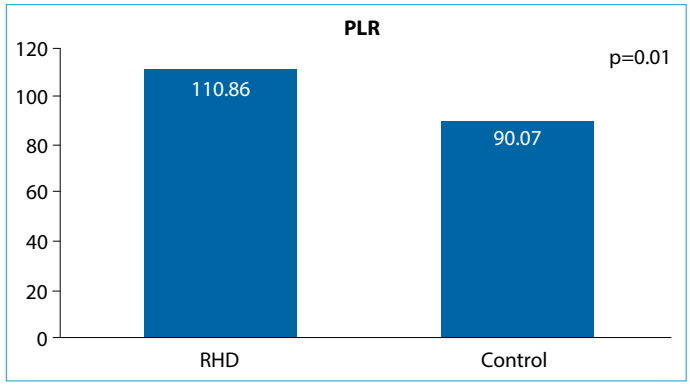

Figure 1. The PLR (Platelet-to-lymphocyte ratio) was increased in the RHD (rheumatic heart disease) patients when compared to control group.

the groups. Table 2 shows the correlation between the RHD and platelet, lymphocyte and PLR. There was a positively but insignificant correlation between the RHD and platelet count. The lymphocyte count was negatively and insignifi-

cantly correlated with RHD. The correlation between the PLR and RHD was positive and significant (r=0.231, p=0.019). In ROC curve analyses, an PLR value of 94.33 was determined as an effective cut-off point in RHD with a sensitivity of 57% and a specificity of 56% (area under the curve=0.63 p=0.02; 95% confidence interval 0.52-0.74) (Fig. 2).

Discussion

This study demonstrated one major finding in patients with RHD. The PLR was significantly higher and correlate in RHD patients.

Chronic RHD develops in around 30% of patients with rheumatic fever.[14] Genetic and environmental factors are considered to have a role in the development of the RHD. RHD has an autoimmune and inflammatory pathophysiological features. Cytokines produced by activated lymphocytes plays a role in the pathogenesis of acute rheumatic fever. Inflammation plays a key role in RHD, and it continues sub-clinically in the chronic form of the disease.[3] RHD is the serious form of rheumatic fever, and rheumatic valve disease is the devastating complication. The process of rheumatic carditis results in varying degree of valve damage, and rheumatic valve disease is a common manifestation of the RHD. In the previous study demonstrated the levels of chronic inflammatory markers were higher in patients with RHD than control groups.[15] In one study demonstrated increased high-sensitivity CRP (hs-CRP) levels in RHD patients, who were in the chronic period, as compared with a control group.[3] Chiu-Braga et al.[16] showed that increased oxidative stress products in patients with chronic RHD when compared with healthy subjects.

Table 2. The correlation between the RHD and platelet, lymphocyte and PLR

	r	p
Platelet	0.163	0.099
Lymphocyte	-0.119	0.232
PLR	0.231	0.019

RHD: rheumatic heart disease; PLR: platelet-to- lymphocyte ratio.

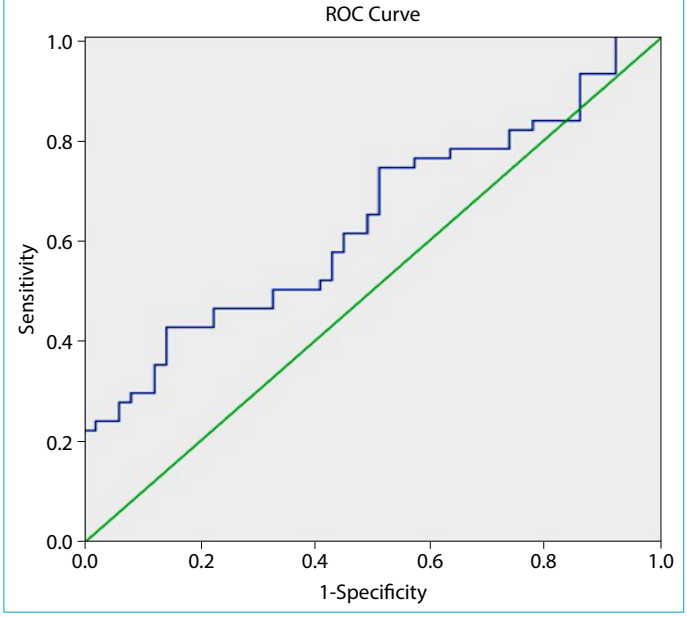

Figure 2. In ROC curve analyses, a Platelet-to-lymphocyte ratio value of 94.33 was determined as an effective cut-off point in rheumatic heart disease with a sensitivity of 57% and a specificity of 56% (AUC=0.63 p=0.02; 95% CI (0.52-0.74).

Platelets increase in number with stimulus such as inflammation and chronic systemic infection, and lead to overproduction of inflammatory cytokines.[17] The cause of lymphopenia is the increased lymphocyte apoptosis secondary to increased inflammatory status in patients with rheumatic mitral valve stenosis.[18] The PLR is calculated from white blood cell count, and it is a biomarker which reflects inflammatory activity. The PLR, which is a hematological biomarker indicating the pro-thrombotic and inflammatory state, was associated with poor prognosis in patients with cardiovascular diseases. Gary et al.[19] demonstrated the PLR established a significant correlation with inflammatory indices such as C-reactive protein and fibrinogen in patients with limb ischemia. In another study showed a positive correlation between PLR and hs-CRP in patients who had an non-ST segment elevation myocardial infarction and poor collateral circulation.[20] In a previous study demonstrated the relationship between PLR and left atrial thrombus in patients with rheumatic mitral stenosis.[21] The PLR and C-reactive protein levels were significantly higher in patients with left atrial thrombus. In addition, the PLR was independently associated with the presence of LA thrombus in the same study. Higher platelet count and lower lymphocyte count were detected in the group with LA thrombus. Similarly, in this study, we found the higher PLR and lower lymphocyte count in the RHD group. The main cause of increased PLR was probably the increased apoptosis of lymphocytes triggered by the increased inflammatory status in RHD. In other study showed the CRP levels were correlated with the severity of rheumatic valvular heart diseases.[22] We found the higher PLR and concluded that the PLR could be a sign of chronic ongoing inflammation in patients with RHD.

The neutrophil-to-lymphocyte ratio (NLR), which is a biomarker of inflammation, was higher in patients with rheumatic mitral valve stenosis when compared with the control group.[23] Baysal et al.[24] demonstrated the NLR was associated with the RHD. The NLR, MPV and Pulmonary artery

systolic pressure were higher in the severe rheumatic mitral stenosis (RMS). In addition, they found that an increased NLR was independently associated with the degree of RMS. In a recent study, it was shown that high NLR predicted presence and severity of MS in patients with rheumatic mitral valve disease.[25] Yavuz et al.[26] showed the MPV levels was a sign of an increased risk of thromboembolic events in patients with RMS. They found that MPV was higher in patients with RMS when compared to healthy control subjects. In our study, there was no difference in the MPV levels between groups.

Limitations

This present study has some limitations. This was a single-center study and based on a relatively small group of patients. The study was lack of other established inflammatory markers, such as C-reactive protein, interleukin-6, tumor necrosis factor-α, and oxidative stress markers, which is another limitation of the study. The multi-center prospective and randomized studies are needed to confirm our findings.

Conclusion

We demonstrated that PLR was higher and lymphocyte count was lower in the RHD group than the control group. PLR is a new inflammatory biomarker which can be related with chronic RHD. The PLR is a simple and readily available in the clinical settings. Thus, PLR can be used as a practical, inexpensive, and important tool for evaluating the RHD. PLR may also enable risk stratification and selection of a treatment strategy in patients with RHD.We suggest the need for further evaluation of PLR as a predictor of RHD in prospective studies.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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