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Original Article

An Evaluation of Platelet Parameters and Neutrophil/Lymphocyte Ratios in Children with Acute Rheumatic Fever

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ABSTRACT

Aim: Acute rheumatic fever (ARF) is an inflammatory disease developing as a response to group A streptococcal infection. Platelet parameters and neutrophil/lymphocyte ratios (NLRs) have been used as markers of inflammation severity in various inflammatory diseases in recent years. The purpose of this study was to evaluate platelet parameters and NLRs of patients with a diagnosis of ARF under monitoring by our clinic, and to compare these with a healthy control group.

Materials and Methods: Fifty patients diagnosed with ARF (37 with carditis and 13 without carditis) and 50 age- and sex-matched healthy children were included in the study. The subjects' demographic characteristics, complete blood count values, acute phase reactants, and transthoracic echocardiography findings were recorded.

Results: NLR, leukocyte, neutrophil, and platelet numbers were statistically significantly higher in the ARF group than in the control group ($p<0.001$), while hemoglobin, lymphocyte, and mean platelet volume (MPV) values were significantly lower ($p<0.001$). No statistically significant difference in MPV, plateletcrit (PCT) or NLR values was observed between the ARF subgroups with or without carditis. Platelet distribution width (PDW) was significantly higher in those ARF patients with carditis ($p=0.003$). Correlation analysis revealed that platelet count was positively correlated with leukocyte and neutrophil numbers, MPV was negatively correlated with leukocyte numbers, and PCT was significantly positively correlated with leukocyte and neutrophil numbers. PDW exhibited negative correlation with lymphocyte count and positive correlation with NLR.

Conclusion: MPV values were significantly lower and NLR values significantly higher in patients with ARF. Thus, it is thought that these parameters can be used as markers in patients diagnosed with ARF.

Keywords: Acute rheumatic fever, neutrophil/lymphocyte ratio, mean platelet volume, platelet distribution width, platelet

Introduction

Acute rheumatic fever (ARF) is an inflammatory disease resulting from an autoimmune response to group A beta haemolytic streptococcal infection in sensitive individuals. It is particularly important due to being capable of leading to rheumatic heart disease associated with high morbidity and mortality (1-4). Cytokines produced by lymphocytes and macrophages that are differentiated following an antigenic stimulus play an important role in the triggering of immunological and inflammatory reactions and therefore in the pathogenesis of ARF (5-7).

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New findings have shown that platelets are not only involved in haemostasis, but also constitute an important component of the inflammatory response (8,9). Chemokines, cytokines and other inflammatory mediators are released by activated platelets (10). Mean platelet volume (MPV) indicates platelet size and the rate of platelet production in bone marrow, and can be used as a marker of severity of inflammation and platelet activation (6,8,11-13). Platelet distribution width (PDW), another marker of platelet activation, indicates variation in platelet dimensions (14,15). Plateletcrit (PCT) provides more comprehensive information about the total thrombocyte mass (16). It is similar to the red cell haematocrit and indicates the percentage of the blood produced by the platelets (17,18). The neutrophil/lymphocyte ratio (NLR), which is easily calculated from blood count parameters, has also become increasingly important as an inflammation marker in recent years (19-24). Although C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), widespread and classic markers of inflammation for many years, continue to be valuable, modern studies suggest that MPV and NLR are also promising as novel acute phase reactants (21,23).

Some studies have examined MPV and NLR together in various disease groups with an inflammatory pathogenesis, including Familial Mediterranean Fever (19), Behçet's disease (20), Henoch-Schönlein purpura (24), rheumatoid arthritis (RA) (25), and systemic lupus erythematosus (26), but there have been no studies on the subject involving ARF, another inflammatory disease. The purpose of this study was to evaluate platelet indices and NLR in children diagnosed with ARF and to reveal the relation between these parameters and the disease.

Materials and Methods

Patients

Fifty patients, 26 boys and 24 girls, with a mean age of 10.7±2.4 years with patient files opened following inpatient treatment for ARF between 2010 and 2014 were retrospectively included in the study. Fifty healthy children, 27 boys and 23 girls, with a mean age of 10.8±2.8 years presenting to our outpatient clinic for routine monitoring were enrolled as the control group. This study was approved by the University of Health Sciences, Haseki Training and Research Hospital Ethics Committee (approval number: 137, date: 20.08.2014). All of the parents gave their informed consent prior to their inclusion in the study.

ARF was diagnosed on the basis of modified Jones criteria (27). Patients with chronic kidney disease, abnormal liver function, acute or chronic infection, haematological disease, chronic systemic inflammatory or autoimmune disease, malignity, or with a history of anti-inflammatory drug use within the previous one month were excluded from the study. These exclusion criteria were also applied to the control group.

Patient group files were scanned and acute phase reactant, and complete blood count (leukocyte, neutrophil, lymphocyte, NLR, hemoglobin, haematocrit, platelet, MPV, PDW, and PCT) values were recorded. Complete blood count (neutrophil, lymphocyte, NLR, hemoglobin, haematocrit, platelet, MPV, PDW, and PCT) values were also recorded for the control group.

The ARF group was also divided into two subgroups with or without carditis. Diagnosis of carditis was based on physical examination, auscultation and echocardiography (ECHO) findings.

Laboratory Analysis

Blood samples were collected (without stasis after morning fasting) from all participants and placed into tubes with gel, and tubes containing K2 EDTA (Becton Dickinson, UK) on the first day of admission. Complete blood counts were performed using an ABX Pentra DX 120 (Horiba Medical, Montpellier, France) haematology analyser. The NLR was calculated as a simple ratio between absolute neutrophil and absolute lymphocyte counts. Serum CRP levels were measured using an immune turbidimetric method with an AU-2700 autoanalyzer [(Beckman Coulter, United States of America (USA)]. An ESR automated analyser 120 device was used for ESR.

Transthoracic Echocardiography

Cardiac dimensions were measured by M-mode and two-dimensional ECHO. They were acquired on a General Electric (GE) Vivid S5 (GE Medical Systems, USA) ultrasound platform using an S3 curved-array transducer. Echo images were acquired from the third or fourth intercostal space according to the patient's age, and with the subject in the supine or left lateral decubitus position.

Statistical Analysis

Statistical analysis was performed on SPSS 15.0 for Windows software. Descriptive statistics were expressed as number and percentage for categorical variables, and as mean and standard deviation for numerical variables. Student's t-test was used to compare two independent groups if normal distribution was established, and the Mann-Whitney U test was used if normal distribution was not established. Comparisons between more than two independent groups were performed using ANOVA when normal distribution was established and with the Kruskal-Wallis test in the absence of normal distribution. Subgroup analyses were performed with the parametric Tukey test

and the non-parametric Mann-Whitney U test, and were interpreted with Bonferroni correction. Proportions of categorical variables between groups were tested using chi-square analysis. Relations between numerical variables were examined using Spearman correlation analysis since parametric test conditions were not established. Statistical alpha significance was set at $p<0.05$.

Results

There was no statistically significant difference between the groups in terms of sex or age (p=0.757, p=0.841, respectively). Leukocyte and neutrophil counts, NLR, and platelet count were significantly higher in the ARF group, while lymphocyte count and hemoglobin and MPV values were significantly lower (p=0.005 for lymphocytes, p<0.001 for the others). No significant difference was determined between the groups' mean PCT and PDW values (p=0.063, and p=0.133, respectively) (Table I).

Carditis was present in 37 (74%) of the children with ARF. PDW was significantly lower in the ARF patients with carditis than in the subjects without carditis (p=0.003). No statistically significant difference was determined in

Table I. A comparison of the demographic features and laboratory results of the acute rheumatic fever and control groups

Parameters	**ARF (n=50), n (%)**			**Controls (n=50), n (%)**			**p value**
Gender							
Male	26 (52.0)			27 (54.0)			0.841
Female	24 (48.0)			23 (46.0)			-
	Mean ± SD	**Minimum**	**Maximum**	**Mean ± SD**	**Minimum**	**Maximum**	**p value**
Age (years)	10.7±2.4	5	15	10.8±2.8	5	15	0.757
Leu (10^3/mm^3)	11.8±4.2	5.3	25	7.7±1.7	5.0	12.0	**<0.001**
Neu (10^3/mm^3)	8.2±3.7	2.5	20.3	4.2±1.5	1.9	9.0	**<0.001**
Lym (10^3/mm^3)	2.4±0.9	0.76	5.2	2.7±0.7	1.12	4.48	**0.005**
NLR	3.7±2.0	1.1	10.3	1.7±1.0	0.58	5.3	**<0.001**
Hgb (g/dL)	10.5±1.4	6.3	13.8	12.9±1.1	11.1	16.6	**<0.001**
Plt (10^3/mm^3)	419.2±123.0	218	775	333.9±86.5	132	523	**<0.001**
MPV (fL)	8.1±1.1	6.3	11.7	9.1±1.1	6.9	11.8	**<0.001**
PCT	0.33±0.08	0.16	0.59	0.30±0.07	0.14	0.49	0.063
PDW (fL)	14.9±4.4	0.1	38.6	15.7±0.3	15	16.6	0.133

ARF: Acute rheumatic fever, Leu: Leucocyte, Neu: Neutrophil, Lym: Lymphocyte, NLR: Neutrophil to lymphocyte ratio, Hgb: Hemoglobin, Plt: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width; fL: Femtoliters, SD% Standard deviation

Table II. A comparison of cases of carditic and non-carditic acute rheumatic fever

	ARF without carditis, (n=37)	**ARF with carditis, (n=13)**	**p value**
	Mean ± SD	**Mean ± SD**	
Leucocyte (10^3/mm^3)	13.0±4.4	11.3±4.1	0.138
Neutr (10^3/mm^3)	8.8±3.5	8.0±3.8	0.419
Lymph (10^3/mm^3)	2.9±1.0	2.2±0.8	0.020
NLR	3.2±1.2	3.9±2.2	0.347
Hemoglobin (gr/dL)	10.9±1.3	10.4±1.4	0.335
Platelet (10^3/mm^3)	460.9±98.5	404.5±128.6	0.052
MPV (fL)	8.0±1.2	8.2±1.1	0.329
PCT	0.36±0.07	0.32±0.09	0.224
PDW (fL)	13.3±1.9	15.5±4.9	**0.003**

ARF: Acute rheumatic fever, SD: Standard deviation, Neutr: Neutrophil, Lymph: Lymphocyte, NLR: Neutrophil-lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, fL: Femtoliters

terms of the other parameters, with the exception of PDW, between the subgroups with and without carditis (Table II).

A significant inverse correlation was determined in the ARF patients between MPV and platelet and leukocyte counts (rho=-0.469, p=0.001; rho=-0.306, p=0.031, respectively). PCT was significantly positively correlated with platelet, leukocyte and neutrophil counts (rho=0.793, p<0.001; rho=0.383, p=0.006; and rho=0.352, p=0.012, respectively) (Table III). PDW was significantly inversely correlated with lymphocyte count (rho=-0.344, p=0.014) (Table III) and significantly positively correlated with NLR (rho=0.389, p=0.005) (Table IV).

Discussion

Neutrophils, lymphocytes, and platelets occupy an important place in the control of inflammation. Ours is the first study to examine platelet indices and NLR together in children with ARF. Significantly lower MPV and higher NLR values in patients with ARF compared to the control group were determined.

Platelet indices are simple and practical parameters that can be easily investigated at routine complete blood count (8). When platelet numbers fall, platelet production in bone marrow increases, and the resulting new platelets are larger and more reactive, and MPV values are therefore higher (6).

MPV has been used as a simple marker of severity of inflammation in various studies, but the results have been inconsistent. Yazici et al. (28) reported an increase in MPV values in an active RA group compared to a control group. In contrast, Kisacik et al. (29) determined significantly lower MPV values in patients with active RA compared to patients with osteoarthritis and healthy controls. Kim and Kim (30)

Table III. Correlation between platelet indices and neutrophil-lymphocyte ratio, and with other parameters, in the acute rheumatic fever and control groups

	Platelet		MPV		PCT		PDW	
ARF	**rho**	**p value**	**rho**	**p value**	**rho**	**p value**	**rho**	**p value**
Leukocyte	0.508	**<0.001****	-0.306	0.031*	0.060	**0.006****	0.060	0.679
Neutrophil	0.454	**0.001***	-0.247	0.084	0.214	**0.012***	0.214	0.136
Lymphocyte	0.266	0.062	-0.292	0.039*	0.344	0.251	-0.344	**0.014***
Hemoglobin	-0.118	0.416	-0.020	0.131	0.893	0.192	0.131	0.364
ESR	0.164	0.255	-0.079	-0.007	0.115	0.426	-0.007	0.959
CRP	0.052	0.721	0.189	-0.129	0.155	0.283	-0.129	0.372

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed). MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, ARF: Acute rheumatic fever, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table IV. Correlation between neutrophil to lymphocyte rate and platelet indices, and with other parameters, in the acute rheumatic fever group

Neutrophil to lymphocyte rate n=50		
ARF group Parameters	**rho**	**p value**
Leucocyte	0.517	**<0.001****
Neutrophil	0.739	**0.001****
Lymphocyte	-0.583	**0.001****
Hemoglobin	0.019	0.895
Platelet	0.147	0.309
MPV	0.020	0.890
PCT	0.174	0.228
PDW	0.389	**0.005****
ESR	0.149	0.302
CRP	0.117	0.417

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed). ARF: Acute rheumatic fever, MPV: Mean platelet volume, PDW: Platelet distribution width, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

also reported lower MPV in their active RA group compared to the control group, and showed that MPV increased after treatment compared to pre-treatment values. Studies have also determined that MPV increases in low-grade inflammatory conditions such as myocardial infarction, atherothrombotic diseases and arteriovenous thrombosis (10,31), and that it decreases in high-grade inflammatory conditions (6,29).

Very few studies have investigated platelet parameters in patients with ARF, an inflammatory disease. Sert et al. (13) investigated 40 children with ARF (32 with carditis) and 40 healthy children. MPV values were lower in the acute period in those children with ARF compared to the healthy control group, and also MPV values were inversely correlated with WBC, ESR, and platelet count before ARF treatment. In contrast, another study of 53 patients diagnosed with acute rheumatic carditis and 53 control subjects determined no significant variation in MPV and PDW values between the patient and control groups (6). In addition, no significant difference was observed with the comparison of MPV and PDW values before and after treatment in the patient group with acute carditis (6). Another study determined high MPV values in children with rheumatic heart disease (1). However, that study was not performed in the acute phase.

In agreement with Sert et al. (13), MPV values in our study were significantly lower in the ARF group than in the control group ($p<0.001$). However, although PDW values were lower than in the control group, the difference was not statistically significant. Comparison of the ARF groups with and without carditis revealed no significant difference in terms of MPV values, while PDW was significantly lower in the ARF patients without carditis than in the ARF group with carditis.

Various mechanisms may be responsible for the low MPV values in our ARF patients. Blood mononuclear cell cultures from rheumatic children have been reported to produce more tumor necrosis factor-α (TNF-α) than those from a control group (32). Together with Interleukin (IL)-6 and IL-8, TNF-α is thought to play a pathogenic role in rheumatic fever (33). In addition, significant elevation of IL-1 levels has been determined in patients with ARF and rheumatic heart (34). Another study described IL-1α as a minor criterion for the diagnosis of carditis and IL-6 for arthritis (35). Decreased MPV values in conditions in which inflammatory markers increase, such as the active stage of ARF, can indicate the severity of the inflammatory process. Overproduction of cytokines such as IL-6 and acute phase reactants can suppress the size of platelets released from bone marrow by affecting megakaryopoiesis (6,9). Previous studies have shown that IL-6 causes a decrease in MPV values in addition to an increase in platelet numbers (36,37). Serum IL-6 levels have been shown to increase significantly during ARF attacks (5). Low MPV values during ARF attacks can be attributed to IL-6 due to its effect on platelets. This is important in terms of low MPV stimulating ARF activation.

Another explanation of low MPV in ARF may be associated with intensive consumption of large platelets in the area of inflammation. Large platelets are more active than small platelets in the release of various pro-inflammatory and thrombotic agents, and consumption of these increases during the acute phase of inflammation (13).

MPV was inversely correlated with leukocyte and platelet counts in our ARF patient group. These results suggest that MPV exhibits negative acute phase reactant characteristics.

PCT, which is another platelet parameter, did not differ between the groups. In the correlation analysis, PCT and platelet had a positive correlation with leucocyte and neutrophil. There is a limited number of studies about PCT. Ozturk et al. (17) showed that PCT values and platelet increased in infectious conditions accompanied by leukocytosis. As far as we are aware, there is no study examining PCT in children with ARF.

NLR is a novel inflammatory marker frequently used in clinical practice and it can easily be calculated from blood count parameters. Its associations with various diseases, particularly cancer and cardiovascular diseases, have begun to be investigated in recent years (18,19,20,38). The number of studies investigating the relation between rheumatic diseases and NLR is limited. One meta-analysis published in 2017 examined a total of 17 studies on the subject (six involving patients with ankylosing spondylitis, three involving RA, four involving Behçet's disease, and four involving SLE), and NLR increases were determined in patients with ankylosing spondylitis, RA and Behçet's disease. However, no association was observed between SLE and NLR (39). Several studies of patients with rheumatic mitral valve stenosis have reported NLR elevation (22,23). These studies have involved adult patients and the chronic phase of the disease. No previous studies have investigated NLR in children with ARF. NLR elevation in inflammatory diseases has been linked to neutrophilia and relative lymphopenia caused by increased cortisol (23). We also determined significantly high neutrophil and low lymphocyte counts in our ARF cases compared to the control group.

The principal limitations of our study are its retrospective nature and the fact that measurements were not repeated after treatment, meaning that the effectiveness of treatment could not be assessed. However, our study is nevertheless

important in being one of the rare investigations of the subject in children with ARF and in eliciting significant findings.

Conclusion

MPV values were significantly low and NLR were significantly high in patients with ARF. Therefore, it is thought that these parameters can be used as markers in the early evaluation of patients with suspected ARF. Further, wide-scale, prospective studies are now needed for a definitive conclusion to be drawn.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences, Haseki Training and Research Hospital Ethics Committee (approval number: 137-20/14).

Informed Consent: All of the parents gave their informed consent prior to their inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.S.D., Design: N.S.D., Data Collection or Processing: A.A., M.E., Analysis or Interpretation: N.S.D., Literature Search: A.A., N.S.D., Writing: N.S.D.

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