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The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio acute rheumatic fever in children with cardiac involvement

A new index in acute rheumatic fever?

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Abstract
Aim: Acute rheumatic fever is the most common cause of heart disease in many parts of the world, especially in children in developing countries and young adults. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in peripheral blood indicate systemic inflammatory response (SIR). NLR is of late importance in the identification of certain pathologies characterized by a systemic or local inflammatory response such as coronary artery disease, ulcerative colitis, and inflammatory arthritis. In the current literature, there is no study evaluating the relationship between ARF cardiac involvement and NLR and PLR indices in children. In this study, we aimed to contribute to a better understanding of ARF pathophysiology by taking advantage of the NLR and PLR indices, which are considered as SIR markers and to evaluate whether these parameters are related to the carditis degree. Material and Method: Patients who applied to the pediatric cardiology clinic between 2013 and 2016 and were provided with our service were included in the study. Patient's laboratory and clinical data were obtained retrospectively from hospital records. Twenty-seven newly diagnosed patients were included in the study. Leukocyte, neutrophil, lymphocyte and thrombocyte counts, sedimentation, CRP, NLR, and PLR indices were compared before and after treatment. It was also evaluated whether these parameters were affected by the carditis degree. Results: There was no statistical significance in the change of NLR, PLR, and NLR, PLR after treatment with cardiac involvement at the time of diagnosis. In addition, there was no statistical significance in NLR, PLR index and CRP, sedimentation values before and after treatment between normal and mild insufficiency, 1st-degree insufficiency, 2nd and 3rd-degree insufficiency in echocardiography findings. Positive correlation between NLR and PLR before treatment (p = 0,002, r = 0,567) was strong. After treatment, there was a moderate positive correlation between NLO and PLO (p = 0,088, r = 0,335). Discussion: The significance of rheumatic fever is almost solely due to its cardiac sequel. Cardiac involvement leads to rheumatic heart disease. People who have had acute rheumatic fever previously are at higher risk of subsequent episodes associated with further cardiac valve damage. RHD is the most common form of pediatric heart disease in the world and is the leading cause of cardiac death in the first five decades of life. There are noteworthy studies that have been conducted recently and have evaluated SIRS markers in peripheral blood such as NLR, PLR that can be easily measured through hemogram test. The studies conducted show that high NLR and PLR values indicate increased inflammation, and are reported to be associated with increased cardiovascular risk, related to poor prognosis. Previous reports have shown convincing evidence that there is ongoing inflammation in RHD. Intralesional mononuclear cells that are secreting inflammatory cytokines have been identified in the chronic phase of RKD. In our study, there was no statistically significant difference in NLR, PLR between those with heart involvement and those without heart involvement. Our study had several limitations. First, this study is retrospective and includes a small number of patients. Second limitation of this study is that in the current literature, there is no study evaluating the relationship between ARF cardiac involvement and NLR and PLR indices in children. In patients with ARF cardiac involvement was not associated with CRP, sedimentation, and NLR and PLR index. It should be considered that there may be other underlying causes that aggravate endothelial injury. Larger and prospective studies are needed to clarify this situation. In patients with ARF cardiac involvement was not associated with CRP, sedimentation increasing and NLR and PLR index. It should be considered that there may be other underlying causes that aggravate endothelial injury. Larger and prospective studies are needed to clarify this situation.

Keywords
Acute Rheumatic Fever; Neutrophil-Lymphocyte Ratio; Platelet-Lymphocyte Ratio; Child

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Introduction

Acute rheumatic fever (ARF) is a nonsuppurative sequela that occurs two to four weeks following group A Streptococcus pharyngitis and may consist of arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Damage to cardiac valves may be chronic and progressive, resulting in cardiac decompensation [1]. Acute rheumatic fever is the most common cause of acquired heart disease in children and young adults in many areas of the world and especially in developing countries. There are at least 15.6 million patients with rheumatic heart disease worldwide [2]. Each year 500 000 new ARF cases are seen. About 280 000 of these acquire rheumatic heart disease and 233 000 individuals are lost due to ARF or rheumatic heart disease yearly [3]. The pathogenic mechanisms that lead to the development of ARF remain incompletely understood. Streptococcal pharyngeal infection is clearly required, and genetic susceptibility may be present. On the other hand, the evidence that toxins produced by Streptococcus are important is sparse. Within this framework, molecular mimicry is thought to play an important role in the initiation of the tissue injury [4].

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in peripheral blood are the markers of simple systemic inflammatory response (SIR). They are evaluated through blood parameters. NLR is highly important for the diagnosis of certain pathologies that are characterized by systemic or local inflammatory response such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis [5]. The proportion of these two cell types helps to detect inflammation [6].

In the current literature, there have not been any studies evaluating the relationship between ARF and NLR and PLR. Therefore, we aimed to investigate the correlations between ARF and NLR and PLR.

Material and Method

This study was carried out in the pediatric cardiology outpatient clinic and pediatric service of our hospital between January 2013 and December 2016. The study population consisted of 30 patients newly diagnosed. We diagnosed ARF by using the modified Jones criteria [3]. The patients were compared before and after treatment. All patients were treated by the same pediatrician Echocardiography.

Patients with congenital heart disease or systemic diseases such as diabetes mellitus, hypertension, acute coronary artery disease, active connective tissue disorder, vasculitis, inflammatory bowel disease, chronic renal failure, and chronic liver failure were excluded.

Hematological parameters were analyzed using a hematology analyzer within 30 minutes after the blood was collected. Leucocyte (103/μL), neutrophil (103/μL), lymphocyte (103/μL) and platelet (103/ μL) counts were recorded. The results were expressed in 103/μL. NLR and PLR were calculated using the results of these parameters. Hemoglobin values were expressed in g/dL. Sedimentation and CRP values of patients were recorded. Leukocyte, neutrophil, lymphocyte and platelet counts, NLR and PLR were compared between patients with ARF before and after the treatment. Also, it was determined whether these parameters were affected by the carditis degree.

Statistical Analysis

Version 15.0 of SPSS Windows program was used, for statistical analysis of the data. Number, percentage, mean, standard deviation and standard error were used in the evaluation of the data. The Mann-Whitney U test was used to compare the measurements of a particular variable in two separate groups, and the Kruskal Wallis test was used to compare the measurements of more than one group. The coefficient of correlation (r) between 0,000-0,249 regarded as weak; between 0.250-0.499 as medium; from 0,500 to 0,749 as strong. The relationship between 0,750-1,000 was evaluated as a very strong. The level of significance was $p < 0.05$.

Results

The data of 30 patients were analyzed. The mean age of the analyzed group was 11.7 ± 3.1(SD), and 30% of the patients were male. There was no statistically significant difference in the ratio of diagnosis neutrophil/lymphocyte, platelet/lymphocyte, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio. In addition, there was no statistical significance between neutrophil/lymphocyte ratio, platelet/lymphocyte, neutrophil, lymphocyte, sediment, CRP and blood pressure between the patients with and without heart involvement. In addition, there was no statistically significant difference in neutrophil/lymphocyte ratio, platelet/lymphocyte ratio changes before and after treatment between normal and mild insufficiency, first-degree insufficiency, second and third-degree insufficiency in echo findings. Spearman's correlation analysis showed a strong positive correlation between systolic ($p = 0,000$, $r = 0,706$) and diastolic ($p = 0,002$, $r = 0,578$) and systolic ($p = 0.004$, $r = 0.535$) positive correlation was found between blood pressure and strength. Positive correlation was found between neutrophil/lymphocyte ratio and platelet / lymphocyte ratio ($p = 0.002$, $r = 0.567$) before treatment. After treatment, there was a moderate positive correlation between neutrophil/lymphocyte ratio and platelet/lymphocyte ratio ($p = 0,088$, $r = 0,335$). There was a moderate negative correlation between CRP and neutrophil ($p = 0,050$, $r = -0,381$), CRP and neutrophil/lymphocyte ($p = 0,018$, $r = -0,452$)

Table 1. Demographic characteristics of patients

	Minimum	Maximum	Median	Standart deviation
Age	6	17	11,7	3,17
Neutrophil count-1	2670	16500	8077	4207
Lymphocyte count-1	1000	19500	2934	3398
Platelet count-1	185000	722000	392000	136500
Sedimentation-1	3	120	47	27
CRP-1	3	160	57	50
Neutrophil count-2	2100	165000	6100	3700
Lymphocyte count -2	1000	5100	2565	940
Platelet count-2	140000	502000	313000	84670
Sedimentation -2	1	24	10	7,6
CRP-2	3	15	4	2,3
NLO-1	0,2	16,5	4	3,2
PLO-1	24	341	176	80
NLO-2	0,6	16	3	3,2
PLO-2	73	257	133	49

Table 2. Echocardiographic findings of patients

echocardiographic findings	n	%
Normal-mild insufficiency	9	33
1.Degree failure	11	40
2.-3.Degree failure	7	27

after treatment. Moderate positive correlation between sediment CRP before treatment (p = 0,012, r = 0,477) and moderate positive correlation between sediment CRP (p = 0,059, r = 0,368) after treatment were found. There was a weak negative correlation between pre- and post-treatment CRP.

Discussion

In this study, we aimed at contributing to the better understanding of the pathophysiology of ARF by evaluating the NLR, PLR, sedimentation, CRP that are considered as SIRS markers and to evaluate whether these parameters are related to the carditis degree.

The potential complications of group A Streptococcus (GAS) pharyngeal infection include both suppurative and inflammatory, nonsuppurative conditions. The disease presents with various manifestations that may include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum [1]. The pathogenic mechanisms that lead to the development of ARF remain incompletely understood. Streptococcal pharyngeal infection is clearly required, and genetic susceptibility may be present. On the other hand, the evidence that toxins produced by Streptococcus are important is sparse. Within this framework, molecular mimicry is thought to play an important role in the initiation of the tissue injury. However, the factors responsible for the perpetuation of the process remain unclear [4]. The significance of rheumatic fever is almost solely due to its cardiac sequel. Cardiac involvement leads to Rheumatic Heart Disease (RHD) [7]. People who have had ARF previously are at higher risk of subsequent episodes associated with further cardiac valve damage. RHD is the most common form of pediatric heart disease in the world and is the leading cause of cardiac death in the first five decades of life [8].

There are noteworthy studies that have been conducted recently and have evaluated SIRS markers in peripheral blood such as NLR, PLR that can be easily measured through hemogram test. Neutrophils are related to the hypercoagulability and viscosity of blood and responsible for the microvascular damage on endothelial surface [9]. Lymphocytopenia induced by the systemic inflammatory response reveals depression of innate cellular immunity indicated by a marked decrease in T4 helper lymphocytes and an increase in T8 suppressor lymphocytes [10]. Platelets can increase in number in response to various stimuli such as systemic infection, inflammatory conditions, bleeding, and tumors as acute phase reactants, which can result in the overproduction of pro-inflammatory cytokines that stimulate megakaryocytic proliferation and produce a relative thrombocytosis [11]. Higher platelet counts may reflect underlying inflammation and lower lymphocyte counts may represent an uncontrolled inflammatory pathway. Thus, a higher PLR may be a useful inflammatory marker [12]. The studies conducted show that high NLR and PLR values indicate increased inflammation, and are reported to be associated with increased cardiovascular risk, related to poor prognosis [13].

Turak et al. [14] showed that admission NLR was an independent predictor of poor prognosis in patients with infective endocarditis. According to these data, we thought that there might be a relationship between NLR and cardiac involvement [14]. Unfortunately, in our study, there was no statistically significant difference in NLR, between those with heart involvement and those without heart involvement. In addition to parameters used for risk stratification in various cardiovascular diseases, a recent review has shown the NLR to be a simple, easily obtainable marker of inflammation [15].

Previous reports have shown convincing evidence that there is ongoing inflammation in RHD. Intralesional mononuclear cells that are secreting inflammatory cytokines have been identified in the chronic phase of RKD [16]. In our study, there was no statistically significant difference in NLR, PLR between those with heart involvement and those without heart involvement. In addition, there was no statistically significant difference in NLR, PLR changes before and after treatment between normal and mild insufficiency, first-degree insufficiency, second and third-degree insufficiency in echo findings. We showed that the NLR was severe positively correlated with the PLR before treatment, and also there was a moderate positive correlation between NRL and PLR. In a study by Polat et al. [17], the NLR was significantly higher in patients with rheumatic mitral valve stenosis (RMVS) compared to those with RHD without stenosis and control patients. In another study by Akboğa et al. [18], the NLR was significantly higher in patients with RHD.

In a study by Davutoglu et al. [19], patients with RMVD had increased levels of chronic inflammatory markers (plasma levels of interleukin [IL]-6, IL-8, IL-2 receptor, tumor necrosis factor a, and hs-CRP) as indicators of ongoing inflammation compared with the control group. The CRP is a well-known inflammation marker. In a study by Golbasi et al., levels of high-sensitivity C-reactive protein (hsCRP) were higher in patients with chronic rheumatic valvular disease than in healthy participants and patients with valve replacement [20]. Similarly, in a study conducted on patients with RMS, hs-CRP levels were significantly higher in patients with RMS than in the control group, and hs-CRP values correlated with the Wilkins valve score and its components [21]. Unlike our study, there was no statistical significance between the cardiac involvement degree and CRP value. Kaya et al. [22], detected a significant positive correlation between the hs-CRP and the NLR in patients with RMS. In this study, only patients with RMS were included, and patients with and without spontaneous echo contrast were compared in terms of NLR [22]. In our study, there was a moderate negative correlation between after treatment CRP levels and neutrophil counts, and a moderate negative correlation between after treatment CRP level and NLR.

Our study had several limitations. First, this study is retrospective and includes a small number of patients. Second limitation of this study is that in the current literature, there is no study evaluating the relationship between ARF cardiac involvement and NLR and PLR indices in children. The third limitation is that there is no control group in the study.

Conclusion

In patient with ARF, cardiac involvement was not associated with CRP, sedimentation, and NLR and PLR indices. It should be considered that there may be other underlying causes that aggravate endothelial injury. Larger and prospective studies are needed to clarify this situation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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