

# The neutrophil-to-lymphocyte ratio and mean platelet volume can be associated with severity of valvular involvement in patients with acute rheumatic carditis

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## Abstract

**Objectives:** The aim of the study was to investigate the association between the severity of acute rheumatic carditis (ARC) and the neutrophil-lymphocyte ratio (NLR) and mean platelet volume (MPV).

**Methods:** Paediatric patients diagnosed with ARC between 2010 and 2016 and age- and gender-matched controls were retrospectively analysed. At the time of diagnosis, we reviewed the demographic features obtained: echocardiographic data, complete blood count reports, acute-phase reactants, including C-reactive protein, and erythrocyte sedimentation rate values. The patient group was further divided into two subgroups according to the degree of valvular regurgitation, which included those with severe and those with mild-to-moderate valvular regurgitation.

**Results:** The number of cases with ARC and age- and gender-matched controls were 120 and 50, respectively. The mean age of the patients was  $12.25 \pm 2.89$  (range: 7–18) years. NLR, MPV, anti-streptolysin-O, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), haemoglobin level, and white blood cell (WBC) and neutrophil count were significantly higher in patients with acute carditis compared with the controls ( $p < 0.001$ ). NLR was found to have a significantly positive correlation with CRP ( $r = 0.177$ ,  $p = 0.001$ ), ESR ( $r = 0.81$ ,  $p = 0.03$ ) and WBC count ( $r = 0.47$ ,  $p = 0.001$ ). Moreover, we found a positive correlation between NLR and severity of valvular regurgitation ( $r = 0.34$ ,  $p < 0.001$ ), and a negative correlation between MPV and severity of valvular regurgitation ( $r = -0.38$ ,  $p < 0.05$ ) in our patients. In multiple linear regression analysis, severe valvular regurgitation was associated with NLR (0.51; 95% CI: 0.32–0.68;  $p = 0.006$ ) and MPV (–0.78; 95% CI: –0.72 to –0.98;  $p = 0.008$ ).

**Conclusion:** NLR and MPV are novel inflammatory markers and simple, rapid and easily accessible prognostic parameters that can be associated with severity of valvular involvement in patients with ARC.

**Keywords:** neutrophil-to-lymphocyte ratio, mean platelet volume, acute rheumatic carditis

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Acute rheumatic fever (ARF) results from the body's auto-immune response to a throat infection caused by *Streptococcus pyogenes*, also known as group A Streptococcus bacteria. The most serious manifestation is carditis (> 50% of patients) because it can lead to chronic rheumatic heart disease, whereas all other clinical features resolve fully, often within weeks. The most commonly affected valves in rheumatic heart disease are the mitral and aortic valves.<sup>1</sup>

The pathogenic mechanisms of ARF are not completely understood.<sup>2</sup> Activation of the innate immune system begins with a pharyngeal infection that leads to the presentation of *S pyogenes* antigens to the T and B cells. CD4+ T cells are activated and results in the production of specific IgG and IgM antibodies by the B cells.<sup>3</sup> Tissue injury ensues through an immune-mediated mechanism that is initiated via molecular mimicry.<sup>4</sup> Structural similarity between the infectious agent and human proteins leads to cross-activation of antibodies and/or T cells directed against the human proteins.<sup>3</sup>

Leukocytes are the main mediators of inflammation, and changes in their populations reflect the response of the immune system to systemic inflammation.<sup>5</sup> In general, neutrophils are considered a marker of ongoing non-specific inflammation, while lymphocytes are a marker of the immune regulatory response.<sup>6</sup> The neutrophil-to-lymphocyte ratio (NLR) therefore represents the balance between inflammation and immune regulation. It has been shown to predict mortality and major adverse cardiac events in acute coronary syndromes,<sup>7</sup> degenerative aortic stenosis,<sup>8</sup> acute rejection after heart transplantation,<sup>9</sup> and acute myocardial infarction.

Also, platelet activation has a very important role in inflammation; it has been observed to secrete mediators such as chemokines and cytokines.<sup>10</sup> Mean platelet volume (MPV) is a marker of platelet activation that is associated with serious inflammation.<sup>11</sup> In previously reported studies, MPV values were shown to be significantly lower in rheumatoid arthritis and inflammatory bowel disease patients with active disease, compared to controls.<sup>12,13</sup> Furthermore, lower MPV values have been shown in patients with acute rheumatic carditis (ARC).<sup>14</sup> However, there is no study evaluating the correlation between valve involvement and MPV, NLR and other full blood count parameters during the ARC period.

The aims of this study were to compare full blood count parameters in children with ARC with healthy children, and to

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evaluate these parameters in terms of heart valve involvement during the acute phase.

## Methods

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the institutional committee of Erciyes University. Detailed consent forms were signed by the parents of all subjects before participating in the study.

In this matched case-control study, 120 consecutive patients diagnosed with ARC at the Department of Paediatric Cardiology between February 2010 and March 2016, were enrolled in the study. As the Jones criteria for the diagnosis of ARF were modified in 2015,<sup>15</sup> older criteria had been used for the diagnosis of earlier patients. A diagnosis of ARF was established when the last Jones criteria were fulfilled for acute cases.

All patients underwent echocardiographic examination before starting anti-inflammatory treatment. The Vivid 7 Pro Ultrasound System (GE Medical Systems, NE) was used for two-dimensional, M-mode and colour-flow Doppler imaging. A paediatric cardiologist experienced in rheumatic heart disease performed all echocardiographic examinations following the guidelines of the American Society of Echocardiography and European Society of Cardiology.<sup>16</sup> The severity of mitral and aortic regurgitation detected by colour Doppler was defined as mild, moderate and severe when the length of the jet was > 1.5, 1.5–2.9 and > 3 cm, respectively.<sup>17</sup> The patient group was further divided into two subgroups according to the degree of regurgitation, which included those with severe and those with mild-to-moderate regurgitation.

Patients who had taken non-steroidal anti-inflammatory drugs within the last four weeks before blood sampling, and those with abnormal renal function or liver tests and malignancies were excluded.

Arthritis and mild-to-moderate carditis were treated with salicylate, whereas patients with severe carditis were treated with oral prednisolone. Also, oral steroid therapy was started in patients without discriminating between moderate and severe carditis. Initially prednisolone (2 mg/kg/d) was given for two weeks, which was then tapered off, and aspirin was started at 75–100 mg/kg/d (maximum dose 3.5 g/d) to prevent rebound.

Fifty age- and gender-matched healthy children were recruited from the local population. They were referred to our hospital because of cardiac murmur and underwent electrocardiography. They had a negative medical history and no signs or symptoms of acute or chronic disease. All participants in the control group were examined by the same paediatrician and the results of the physical examination were normal.

Full blood count parameters, anti-streptolysin-O (ASO), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) titres and echocardiographic examinations of all subjects were recorded from the same computerised database. Blood samples were drawn from the peripheral veins and collected in plastic tubes (Vacutainer-Becton, Dickinson and Co, USA), containing dipotassium ethylene diamine tetra-acetic acid (EDTA-K2).

The full blood count analysis was done by flow cytometry using the Abxpentra model 120 DX analyser in the laboratory

of our institution. NLR was calculated using the absolute count method. ESR was determined with the Westergren method. ASO (Rapitex ASL) and CRP titres were determined using standard reagents on the Beckman-Coulter DXC 800 systems analyser in the same laboratory.

## Statistical analysis

Data are reported as mean  $\pm$  standard deviation. If not normally distributed, parameters are presented as median (range). The distribution pattern of data was assessed with the Shapiro-Wilks test. Differences between quantitative groups with normal distribution were evaluated with the Student's *t*-test. The Mann-Whitney *U*-test was used for abnormally distributed data. The associations between parameters were assessed using Pearson's or Spearman's correlation tests. Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical calculations. Beta- and *p*-values were assessed for each independent factor in multiple linear regression analysis; *p*-values < 0.05 were considered to be statistically significant.

## Results

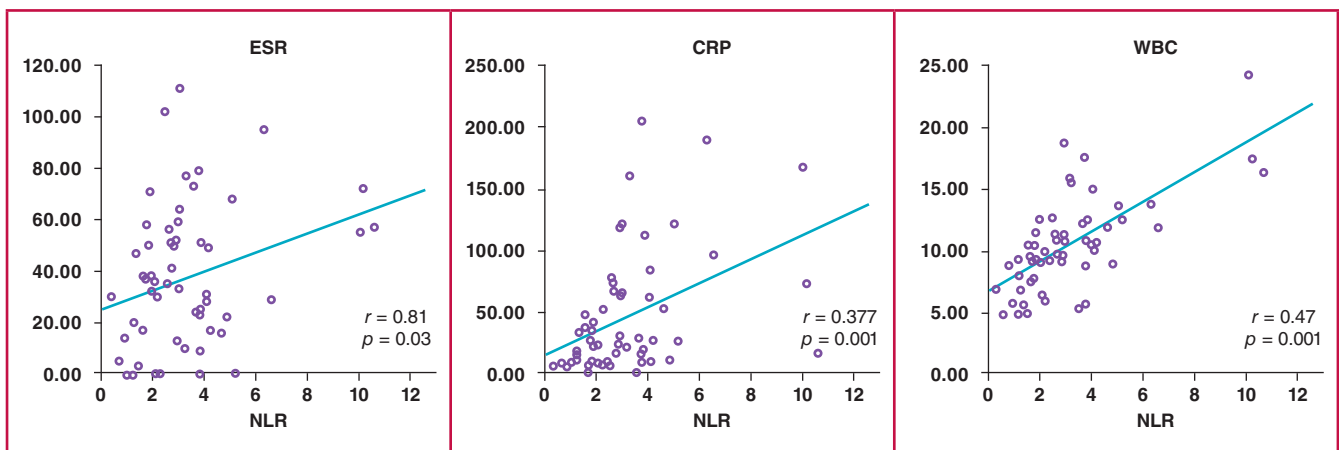
One hundred and twenty patients (72 female), who were diagnosed with ARC, and 50 age- and gender-matched healthy children were included in this study. The mean age of the patients was  $12.25 \pm 2.89$  (range: 7–18) years. Baseline clinical and laboratory characteristics of patients and control subjects are shown in Table 1.

Compared with the controls, ASO, CRP, ESR, haemoglobin, white blood cell count (WBC), neutrophil count, MPV and NLR values were significantly higher in patients with acute carditis compared with the controls ( $p < 0.001$ ) (Table 1). Also, platelet counts ( $p = 0.002$ ) and MPV ( $p = 0.049$ ) values were significantly higher in the patients. NLR was found to have a significantly positive correlation with CRP ( $r = 0.177$ ,  $p = 0.001$ ), ESR ( $r =$

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

Characteristics	Control (n = 50)	ARF (n = 120)	p-value
Age (years)	12.96 $\pm$ 2.55	12.25 $\pm$ 2.89	0.48
Males, n (%)	12	48	0.86
WBC count ( $\times 10^3$ cells/mm <sup>3</sup> )	7.02 $\pm$ 1.86	10.58 $\pm$ 3.76	< <b>0.01</b>
Haemoglobin (g/dl)	13.60 $\pm$ 1.09	12.35 $\pm$ 1.03	< <b>0.01</b>
ESR (mm/hour)	3.83 $\pm$ 2.57	37.12 $\pm$ 27.63	< <b>0.001</b>
CRP (mg/l)	3.34 $\pm$ 0.54	46.37 $\pm$ 48.78	< <b>0.001</b>
ASO (U/ml)	244.91 $\pm$ 239.62	995.24 $\pm$ 1023.69	< <b>0.001</b>
Platelet count ( $\times 10^3$ cells/mm <sup>3</sup> )	291.30 $\pm$ 67.80	355.22 $\pm$ 103.3	<b>0.002</b>
MPV (fl)	10.21 $\pm$ 1.25	9.01 $\pm$ 1.35	< <b>0.003</b>
RDW (%)	13.65 $\pm$ 1.30	12.88 $\pm$ 0.89	0.26
Neutrophil count ( $\times 10^3$ cells/mm <sup>3</sup> )	3.64 $\pm$ 1.20	7.21 $\pm$ 3.56	< <b>0.001</b>
Lymphocyte count ( $\times 10^3$ cells/mm <sup>3</sup> )	2.64 $\pm$ 0.84	2.55 $\pm$ 0.84	0.67
NLR <sup>a</sup>	1.35 (1.02–1.94)	3.73 (2.02–4.07)	< <b>0.001</b>
MCV (fl)	82.95 $\pm$ 5.04	80.15 $\pm$ 6.01	0.06

ARF: acute rheumatic fever, ASO: anti-streptolysin-O, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MPV: mean platelet volume, WBC: white blood cell, RDW: red blood cell distribution width, NLR: neutrophil-to-lymphocyte ratio, MCV: mean corpuscular volume (fl). Parametric values are expressed as means with standard deviation. Significance is determined by  $p < 0.05$  and shown in bold. <sup>a</sup>If not normally distributed, values are presented as median and range in parentheses.



**Fig. 1.** The relationship between neutrophil-to-lymphocyte ratios (NLR) and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count. The same numerical values are shown once on the figures.

0.81,  $p = 0.03$ ) and WBC count ( $r = 0.47$ ,  $p = 0.001$ ) (Fig. 1). However, there was no significant difference in lymphocyte count and red blood cell distribution width between the groups ( $p > 0.05$ ).

Mitral regurgitation (MR) existed in 68 patients, aortic regurgitation (AR) in 16, and combined valve involvement in 36 patients. There were 38 patients with severe valve regurgitation. Twenty-eight patients had severe MR, six had severe AR, and four had severe combined valve regurgitation. We found a positive correlation between NLR and the severity of valvular regurgitation ( $r = 0.34$ ,  $p < 0.001$ ), and a negative correlation between MPV and the severity of valvular regurgitation ( $r = -0.38$ ,  $p < 0.05$ ). The MPV and NLR values according to valve involvement in the groups are shown in Fig. 2.

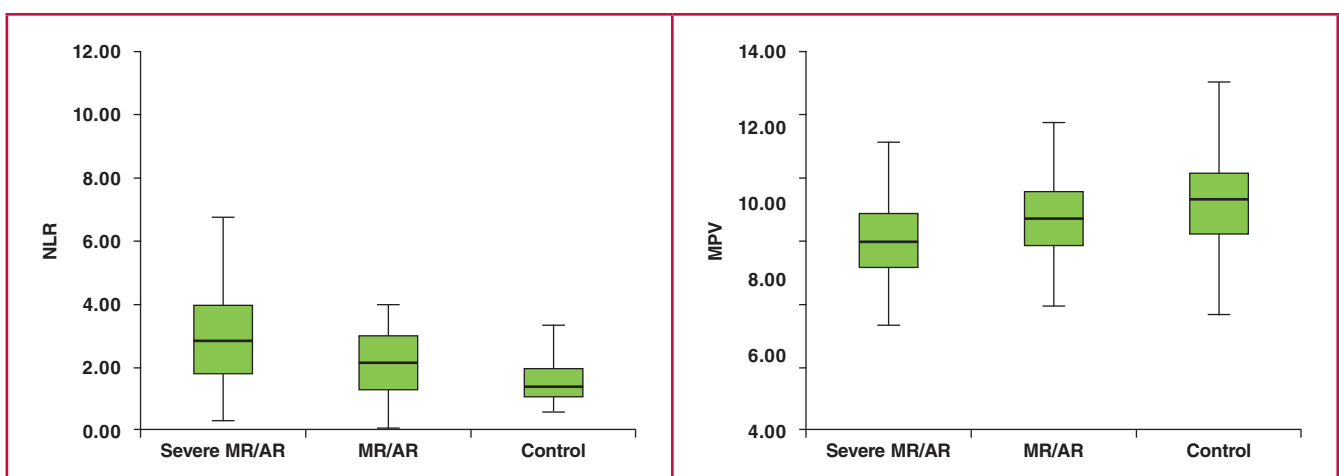
Clinical and echocardiographic variables, which were correlated with NLR and MPV values in the Student's *t*-test (severe valvular regurgitation), were included in multiple linear regression analysis to detect the determinants of possible platelet volume decrease and NLR increase in the patient group. In regression analysis, NLR (OR = 0.51, 95% CI: 0.32–0.68,  $p = 0.006$ ) and MPV (OR = -0.78, 95% CI: -0.72–0.98,  $p = 0.008$ )

were found to be independent predictors for the presence of severe valvular regurgitation (Table 2).

## Discussion

To the best of our knowledge, this study showed for the first time that increased NLR and decreased MPV levels can be associated with severity of valvular involvement in patients with ARC. Furthermore, NLR values were correlated with WBC count, ESR and CRP during ARF.

In the case of ARF, several inflammatory cells such as neutrophils, macrophages, and T and B lymphocytes infiltrate both the myocardium and the valves. Activated lymphocytes and macrophages secrete tumour necrosis factor cytokines, and interleukins play an important role in the pathogenesis of ARC. The healing process of rheumatic carditis results in varying degrees of fibrosis and valve damage. Kumar *et al.* reported that macrophages and neutrophils, which infiltrate the myocardium, may through the generation of oxygen free radicals, play a role in the pathogenesis of cardiac damage seen in patients with rheumatic heart disease. Also, they showed that the enzymatic



**Fig. 2.** Box plot showing neutrophil-to-lymphocyte ratios (NLR) and mean platelet volume (MPV) in the controls and in acute rheumatic carditis patients (the severity of mitral and aortic regurgitation was defined as mild and moderate or severe). MR: mitral regurgitation, AR: aortic regurgitation.

**Table 2. Independent predictors of severity of valve regurgitation**

Independent variables	Univariate logistic regression		Multiple logistic regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
WBC count (× 10 <sup>3</sup> cells/mm <sup>3</sup> )	0.79 (0.53–2.86)	0.034		
Haemoglobin (g/dl)	1.53 (1.26–1.87)	0.042		
ESR (mm/h)	0.38 (0.21–0.76)	0.50		
CRP (mg/l)	0.92 (0.88–0.97)	0.22		
Platelet count (× 10 <sup>3</sup> cells/mm <sup>3</sup> )	0.26 (0.18–0.52)	0.035		
MPV (fl)	0.44 (0.24–0.94)	< 0.001	0.78 (0.72–0.98)	0.008
Neutrophil count (× 10 <sup>3</sup> cells/mm <sup>3</sup> )	0.85 (0.54–1.89)	0.042		
NLR	0.42 (0.27–0.66)	< 0.001	0.51 (0.32–0.68)	0.006
MCV	0.36 (0.26–0.64)	0.024		

Dependent variable: severe valve regurgitation cases with or without two-valve regurgitation (n = 38).  
 OR: odds ratio, CI: confidence interval, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, NLR: neutrophil-to-lymphocyte ratio, MCV: mean corpuscular volume (fl).

response of neutrophils and monocytes was similar although the magnitude of NADPH oxidase activity was significantly higher in neutrophils than in monocytes of patients with ARF.<sup>18</sup>

In recent years, there has been a focus on WBC subtypes, such as neutrophils, lymphocytes, and NLR as predictors of cardiovascular risk. Many studies have shown that high ratios are associated with increased inflammation in various cardiovascular diseases. Öztürk *et al.* reported that higher NLR was associated with spontaneous echocardiographic contrast in rheumatic mitral valve stenosis.<sup>19</sup> Increased neutrophil count was found to be associated with infarct size and adverse angiographic outcomes in patients with myocardial infarction,<sup>6</sup> while low lymphocyte count was related to adverse outcomes in patients with myocardial infarction and chronic heart failure.<sup>20</sup>

Akboga *et al.* evaluated adult patients with rheumatic mitral valve stenosis (RMS) and found median NLRs to be significantly higher in patients with RMS compared with the control group. Moreover, they also showed NLRs to increase with the severity of mitral stenosis.<sup>21</sup> Baysal *et al.* revealed that high levels of NLR were an independent predictor of severe RMS.<sup>22</sup> In a recent study, it was reported that patients with severe RMS had significantly higher NLRs than those with mild-to-moderate RMS.<sup>23</sup> In addition, higher NLRs were associated with an increased risk of long-term mortality in patients admitted with acute decompensated heart failure.<sup>24</sup>

In our study, we found that there was a significant positive correlation between CRP, ESR and NLR in ARC, indicating that NLR was associated with inflammation in this group of patients. Kucuk *et al.* demonstrated a strong association of CRP and ESR levels in children with ARC.<sup>17</sup> Similarly, Ozdemir *et al.* showed higher CRP and ESR levels in ARF.<sup>25</sup>

The NLR may be the more preferable marker owing to three factors. First, although some conditions such as exercise and dehydration may increase the absolute number of neutrophils and lymphocytes, NLR is less commonly affected.<sup>26</sup> Second, NLR is calculated from the counts of products of two different but complementary immune pathways.<sup>6</sup> Third, the reason for the increased NLR was probably increased apoptosis of the lymphocytes, associated with the increased inflammatory status in ARF.

We also discovered increasing platelet counts and decreasing MPV values in patients with ARC, which reflect the inverse relationship between changes in platelet count and size. The mechanism of increase in platelet volume is thought to be that inflammatory cytokines stimulate the production of large, reactive platelets, which have a shorter life span.<sup>27</sup>

Sert *et al.* showed lower MPV levels in ARF patients.<sup>14</sup> They speculated that lower MPV values during ARF may be related to the effect of interleukin 6 (IL-6). In a previously reported study, administration of IL-6 was shown to cause an increase in platelet number as well as a decrease in MPV values.<sup>28</sup> Previous studies showed that serum IL-6 levels were significantly elevated during attacks of ARF.<sup>29</sup> Regarding the effect of IL-6 on thrombocytes, low MPV values during ARF may be related to the effect of IL-6. Similarly, in a prospective study, MPV values significantly decreased together with CRP and IL-6 values and platelet counts in response to two-year anti-rheumatic treatment, questioning the inverse correlation between MPV and thrombocytosis.<sup>30</sup>

Since 2015, there have been changes in the diagnosis of ARF due to the revised Jones criteria. Changing the criteria may have led to an increase in our patient numbers. However, at least one extra major criterion or at least two minor criteria were definitely identified besides clinical carditis in the patient group prior to 2015. Therefore none of the ARC patients were excluded from the study.

Although conducted with a relatively large ARC patient cohort, the retrospective design represents this study's main limitation. Also we could not find follow-up full blood count values for the majority of patients due to their lack of adherence. Therefore the study was conducted using pre-treatment blood values.

## Conclusion

NLR and MPV are simple, rapid and easily accessible inflammatory markers that could be prognostic parameters associated with the severity of valvular involvement in ARC. However, prospective studies with larger numbers of patients are needed to evaluate the role of NLR and MPV values in ARC.

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