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Simple Markers for Systemic Inflammation in Pediatric Atopic Dermatitis Patients

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Abstract

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Background:

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Atopic dermatitis is a dermatological disease characterized by chronic inflammation. In recent years, systemic inflammation is also mentioned along with local inflammation for its pathogenesis. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) are nonspecific indicators of systemic inflammation, and they were shown to be associated with the disease and its prognosis in allergic or nonallergic diseases.

Aims and Objectives:

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The aim of this study was to evaluate the values of NLR, PLR, and MPV in atopic dermatitis patients and also to investigate the associations of them with the atopic dermatitis disease severity and duration.

Materials and Methods:

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Two hundred and fifty-two atopic dermatitis patients and 75 control group individuals were included in the study. Mean/median values of NLR, PLR, and MPV were compared among patients and controls, severity groups classified according to SCORing Atopic Dermatitis (SCORAD) and intrinsic and extrinsic groups. Correlation of disease duration and SCORAD with NLR, PLR, and MPV values were examined. Disease duration and its association with NLR were evaluated by correlation and linear regression analysis.

Results:

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Mean NLR and median PLR values of atopic dermatitis patients were higher than those of controls (0.97 ± 0.69 and $80.86 [59.86-108.23]$, respectively). NLR and PLR values were found to be positively correlated with disease duration and NLR was positively associated with disease duration after adjustment. NLR value was also higher in the extrinsic group than the intrinsic group.

Conclusion:

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Presence of systemic inflammation in the pathogenesis of atopic dermatitis was considered to be associated with increased NLR and PLR values. These parameters were also associated with disease duration and might vary between subtypes of atopic dermatitis. NLR and PLR were cheaper and easily accessible alternatives to the systemic inflammation biomarkers that were expensive and not accessible for all laboratories, particularly in economically disadvantaged countries.

KEY WORDS: *Atopic dermatitis, lymphocyte, mean platelet volume, neutrophil, pediatrics*

What was known?

- Studies in the literature have reported the presence of systemic inflammation in atopic dermatitis along with local inflammation.
- Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) are indicators of subclinical and clinical systemic inflammation.

Introduction

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Atopic dermatitis is a dermatological disease characterized by chronic inflammation. Its prevalence in children is quite high. This prevalence is reported to be increasing in recent years. Acute, subacute or chronic, itchy eczematous skin lesions that may occur through triggers and dry skin are the main characteristics of atopic dermatitis.[1,2]

Local inflammation observed on the skin, which occurs as a result of a complex interaction between the barrier defect in the skin, abnormal immune response, and triggers, has a key role in the pathogenesis of atopic dermatitis.[3]

Although Th2 type immune response is dominant in atopic dermatitis, studies showed the presence of an inflammation where Th1, Th17/23, Th22, and innate lymphoid cells were also factors in its pathogenesis.[4]

In recent years, studies in the literature have reported the presence of systemic inflammation in atopic dermatitis alongside local inflammation. It has been reported that the skin barrier defect in atopic dermatitis may cause a more heterogeneous allergic profile as well as the known atopic march. This condition, starting with the barrier defect and progressing with inflammation in the airways, may be an evidence for the systemic inflammation in atopic dermatitis.[5] Although this cause and effect relationship is disputable, comorbidities such as cardiovascular and neuropsychiatric disorders that are reported to accompany atopic dermatitis have been suggested to be the evidence of presence of systemic inflammation in atopic dermatitis along with local inflammation.[6,7] In addition, it was reported that the skin barrier defects in nonlesional skin might be secondary to systemic inflammation.[8]

Atopic dermatitis is classified as extrinsic in the presence of increased total immunoglobulin E (IgE), specific IgE, and familial atopy, and if these are not present, then it is classified as intrinsic atopic dermatitis.[9] Among these two atopic dermatitis subtypes, it has been shown that there is discrepancy between inflammatory cells and cytokines. Th2 type inflammatory response was dominant in both extrinsic and intrinsic atopic dermatitis groups. However, a strong activation of Th17 and 22 was observed only in the intrinsic group.[4]

Inflammation is a biological process protecting the body, and both cells in the blood circulation, such as neutrophils, monocytes, lymphocytes and platelets, and endothelial and epithelial cells within the tissues act collaboratively. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) are indicators of subclinical and clinical systemic inflammation. In comparison with other blood parameters, NLR and PLR are more stable as they are less affected by dehydration, overhydration, and laboratory techniques.[10] Inflammation is also present in the pathogenesis of some diseases identified as noninflammatory. There are studies reporting the relationship between increased NLR, PLR and MPV values in these diseases and their prognoses (e.g. various cancer types; neurological diseases such as multiple sclerosis and Parkinson's disease; cardiologic diseases such as atherosclerosis, acute coronary syndrome, and myocardial infarction; allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis; and diabetes mellitus).[11,12,13]

Some studies conducted on children reported that NLR, PLR, and MPV values were higher in children with asthma, allergic rhinitis, and atopic dermatitis than in normal children. It was highlighted that this

might point towards the presence of the systemic inflammation in these diseases and their association with disease severity.[14,15,16]

The aim of this study was to evaluate NLR, PLR, and MPV values in patients with atopic dermatitis, to present the association of these values with disease severity and disease duration, and to assess if there was a significant difference between intrinsic/extrinsic atopic dermatitis groups in terms of these values. This might shed light on the presence of systemic inflammation, and contributed to the understanding of atopic dermatitis pathogenesis by a method that could be easily applied, and which was accessible to everyone.

Materials and Methods

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Two hundred and fifty-two patients (1 month-17 year of age), who presented to the pediatric allergy department of Tokat State Hospital between January 2015 and June 2015, and were diagnosed with atopic dermatitis and followed up, were included in the study as the patient group and 75 children, who presented to the same department, and were not diagnosed with allergic diseases, were included as the control group. The study was approved by the local ethics committee.

Patients with other acute and chronic infectious and inflammatory diseases and patients with atopic dermatitis accompanied with other allergic diseases such as asthma and allergic rhinitis were excluded from the study. Atopic dermatitis was diagnosed in accordance with UK Working Party's Diagnostic Criteria.[17]

The health records of the patient and the control groups were retrospectively examined. Routine blood tests of the patients, requested at first admittance, were analyzed. These tests were complete blood count (CBC), food-specific IgE (fx5), inhalant allergen-specific IgE (ph diotop), and total IgE. In our clinic, CBC is routinely analyzed with The Mindray BC-6800 hematology analyzer (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China).

NLR was calculated by dividing the absolute values of neutrophils to lymphocytes and PLR was calculated by dividing the absolute values of platelets to lymphocytes in CBC analysis. MPV was also recorded from CBC results.

Disease duration was specified as the time between the first complaint of the disease and the time when the patient was included in the study and tested.

Skin prick test results of all patients were recovered and viewed from their health records. Skin prick test was applied with the same technique to all patients admitted to our clinic. Skin prick test was applied to the forearm or back of the patient, depending on their age. Histamine (10 mg/ml) and physiological saline were used as positive and negative references. Reactions were evaluated 15 min after the application. Positive reaction of 3 mm or larger than the negative control was considered to be the positive test. Common aeroallergens were used in skin prick test (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grasses mix, cereals mix, trees mix, weed mix, cockroaches, cat dander, and dog dander) (ALK-Abello skin prick test kit) and applied by a lancet (Heinz Herenz, Hamburg).

Atopic dermatitis patients were grouped according to their SCORAD. Patients who had <25 points were grouped as mild, 25–50 points were grouped as moderate, and >50 points were grouped as severe atopic dermatitis.

Atopic dermatitis patients were also grouped as intrinsic and extrinsic. The patients with high total IgE and/or positive food or inhalant specific IgE and/or familial atopy were considered as extrinsic atopic dermatitis. The patients with low total IgE and negative food and inhalant specific IgE and no familial atopy were considered as intrinsic atopic dermatitis groups.

Statistical analyses Results were given as either mean $\pm$ standard deviation or as median $\pm$ interquartile range according to the distribution. Student's *t*-test was used for the comparison of normally distributed variables. Mann–Whitney U test was used for nonnormally distributed variables. Pearson's and Spearman's correlations were used. $P < 0.05$ was considered as statistically significant.

Results

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The mean age of the patient group was 49.10 ± 46.56 months, and the mean age of the control group was 60.01 ± 46.45 months. A total of 119 (47%) of atopic dermatitis patients and 32 (43%) of control group individuals were girls. There were no differences between the patient and the control groups in terms of age and sex.

The mean NLR value for atopic dermatitis patients was 0.97 ± 0.69 , and 0.76 ± 0.33 for the control group individuals. The mean value of NLR in atopic dermatitis patients was significantly higher than those of the control group individuals ($P=0.012$) [[Table 1](#)].

The median PLR value for atopic dermatitis patients was 80.86 (59.86–108.23) and 66.34 (48.26–87.84) for the control group individuals. The median PLR value of atopic dermatitis patients was significantly higher than the median PLR value of the control group ($P < 0.001$) [[Table 1](#)].

The median MPV value was 9.00 fL (8.40–9.60) in atopic dermatitis patients and 8.80 (8.10–9.40) fL in the control group individuals. There was no significant difference among the groups for the MPV value ($P=0.095$) [[Table 1](#)].

SCORAD of only 244 patients could be recovered. According to SCORAD, 120 (49.2%) patients were classified to mild, 78 (32%) patients to moderate, and 46 (18.8%) patients to severe atopic dermatitis group. There were no significant differences between the mean/median NLR, PLR, and MPV values among these groups [[Table 2](#)]. When the correlation of SCORAD with NLR, PLR, and MPV values were analyzed, no statistically significant correlations were found ($P=0.615$; $P=0.313$; $P=0.350$, respectively) [[Table 3](#)].

When the correlation of disease duration with NLR, PLR, and MPV were analyzed, NLR and PLR values were found to be positively correlated with disease duration ($r=0.846$, $P < 0.001$; $r=0.700$, $P < 0.001$, respectively). Disease duration and MPV were not correlated ($r=0.02$, $P=0.728$) [[Table 4](#)]. When patients were grouped as under 1-year-old (53 patients) and over 1-year-old (199 patients), NLR and disease duration were positively correlated for both groups ($r=0.71$, $P < 0.001$; $r=0.86$, $P < 0.001$) and PLR and disease duration were positively correlated for the group over 1 year ($r=0.68$, $P < 0.001$). There was no statistically significant correlation between PLR and diseases duration in the under 1-year-old group ($P=0.154$). MPV was not found to be correlated with the disease duration in under 1-year-old and above 1-year-old groups ($P=0.445$).

A total of 107 (42.5%) of atopic dermatitis patients were in the intrinsic atopic dermatitis group and 145 (57.5%) of them were in the extrinsic atopic dermatitis group. Mean/median NLR, PLR, and MPV values were compared between intrinsic and extrinsic atopic dermatitis groups. The mean NLR value was 0.85 ± 0.55 in the intrinsic group and the mean NLR value was 1.05 ± 0.76 in the extrinsic group. The mean NLR value was significantly higher in the extrinsic atopic dermatitis group ($P=0.023$). There was no significant difference between intrinsic and extrinsic atopic groups for the median PLR and MPV values [[Table 5](#)].

Discussion

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Atopic dermatitis is a chronic inflammatory skin disease. In recent years, the presence of systemic inflammation is being mentioned along with local inflammation in atopic dermatitis pathogenesis. In this study, NLR and PLR values were found to be high in the patients with atopic dermatitis, and these values increased with the disease duration. NLR value was also higher in the extrinsic atopic dermatitis group than the intrinsic group.

NLR is an indication of systemic inflammation. In the literature, increased NLR value was shown to be associated with disease presence and prognosis in some nonallergic diseases. NLR was higher in asthmatics than the control group, and it was associated with hospitalization.[[14](#),[18](#)] In another study, NLR values were found to be higher in allergic rhinitis patients in comparison with the control group, and it was reported that NLR value increased with the disease severity.[[15](#)] In the literature, only one study reported the relation between NLR and atopic dermatitis; NLR values in pediatric patients with atopic dermatitis were higher than the control group, and NLR values determined to be associated with atopic dermatitis severity.[[16](#)] The present study aimed to obtain more accurate data by including more patients, and the mean NLR values of atopic dermatitis patients were found to be higher than that of the control group, which was in line with other studies in the literature. However, to the contrary to the other studies, NLR

was not correlated with disease severity and no significant difference was found for the mean NLR values between the severity groups. This might suggest that systemic inflammation was present in disease pathogenesis of atopic dermatitis independently of disease severity, or it might be explained by the fewer number of patients in the severe atopic dermatitis group compared to the other groups.

The role of the platelets in inflammation was reported by other studies in the literature. Some platelets were activated during inflammation. Platelet production rate was increased. Platelets generated chemotaxis signals by interacting with endothelia and stimulated the secretion of adhesion molecules. They contributed to the inflammation by increasing pro-inflammatory mediator release.[19,20] The PLR and MPV values were also systemic inflammation indicators. They were shown to be related with disease presence and prognosis like NLR in nonallergic diseases.[11,21,22] Studies in the literature reported that PLR values in adult asthmatic patients were higher than in the control group.[23] There was only one known study evaluating the PLR and MPV values in atopic dermatitis patients. In this study, MPV and PLR values of pediatric patients with atopic dermatitis were not different from the control group; however, PLR values varied among disease severity groups of atopic dermatitis patients and values were higher in the severe atopic dermatitis group. Information about increased PLR value in systemic inflammation was clear, whereas MPV information was more contradictory. There were studies showing that cytokines affected megakaryopoiesis during inflammation and suppressed platelet sizes, thereby, causing smaller platelets to be released in the blood circulation and making decreased MPV an inflammation indicator. There were also other studies suggesting that larger platelets, caused by the increased turnover due to platelet activation, were released to the blood circulation making increased MPV an inflammation indicator.[24,25,26] In this study, the median PLR value was higher in the atopic dermatitis patients than the control group; therefore, this might be an indicator of systemic inflammation mentioned in the atopic dermatitis pathogenesis. However, there was no significant difference in the median MPV value between the atopic dermatitis group and the control group, and it was not associated with disease severity. As there were contradictory reports stating MPV might either be increased or decreased in systemic inflammation, the role of MPV in indicating the systemic inflammation had yet to be clarified. Therefore, MPV values might not have been associated with atopic dermatitis in any of the analyses performed.

In the present study, we aimed to examine the association of systemic inflammation with the disease duration in atopic dermatitis patients by evaluating the relationship between disease duration and the NLR/PLR/MPV values. We concluded that systemic inflammation was gradually accumulating to the disease pathogenesis, as disease duration showed positive correlation with NLR and PLR values in atopic dermatitis, and it was also found to be related to NLR even after adjusting for age and sex. As NLR and PLR values varied depending on the age, we analyzed patients under and over 1-year old separately, for better evaluation of the association of disease duration with NLR and PLR values. Disease duration in both groups was found to be associated with NLR and PLR. Association with disease duration was not evaluated in other studies that assess the NLR, PLR, MPV relationship with allergic diseases in the literature.[14,15,16]

In recent years, the importance of phenotypes is presented for the personalization of atopic dermatitis therapy. Phenotype-specific treatment approaches are sought to be developed by identifying various phenotypes based on the age of onset, ethnic origin, presence or absence of atopic sensitization, cytokine or genetic biomarkers.[27] In this study, when patients were divided into groups according to the presence of atopic sensitization, NLR values of the extrinsic group patients were found to be higher. In line with this result, it might be speculated that there was more severe systemic inflammation in the patients of this group, and it might be considered that these patients might respond better to systemic treatments.

Limitations of our study

1. Having fewer patients in the severe atopic dermatitis group might have affected our results
2. Although some analyses of patients under 1-year old were examined separately, neutrophil and lymphocyte values in children were influenced by the age interval, and this might have affected our results.

Conclusion

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In atopic dermatitis patients, although the major pathomechanism is the inflammation due to the abnormal immunologic response to the antigens and the abnormal epidermal barrier function in the skin, the

presence of systemic inflammation and its association with disease duration should not be overlooked. Although there are many complex biochemical assays to detect the systemic inflammatory response in atopic dermatitis, for underresourced and economically disadvantaged clinical settings, a practical and routine blood test including NLR and PLR may also reflect this systemic inflammation, so these may be alternative tests. Yet, further studies are needed in this field.

Financial support and sponsorship Nil.

Conflicts of interest There are no conflicts of interest.

What is new?

- Disease duration is associated with NLR and PLR values in atopic dermatitis patients.
- NLR values are higher in extrinsic atopic dermatitis patients than in the intrinsic atopic dermatitis patients.

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Figures and Tables

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Table 1

The comparison of the mean/median values of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and mean platelet volume between the atopic dermatitis and the control groups

	Atopic dermatitis patients (n=252)		Control (n=75)		P
	Mean/median	SD/25%-75%	Mean/median	SD/25%-75%	
NLR	0.97	±0.69	0.76	±0.33	0.012
PLR	80.86	59.86-108.23	66.34	48.26-87.84	<0.001
MPV (fL)	9.00	8.40-9.60	8.80	8.10-9.40	0.095

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MPV: Mean platelet volume, SD: Standard deviation

Table 2

The comparison of the mean/median values of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and mean platelet volume between atopic dermatitis severity groups according to the SCORAD Index

	Mild (n=120)		Moderate (n=78)		Severe (n=46)		P
	Mean/median	SD/25%-75%	Mean/median	SD/25%-75%	Mean/median	SD/25%-75%	
NLR	0.94	±0.73	0.97	±0.53	1.08	±0.81	0.478
PLR	80.14	60.46-106.89	85.54	57.70-113.53	79.38	56.98-106.59	0.822
MPV (fL)	9.05	8.50-9.68	8.80	8.20-9.50	9.00	8.50-9.73	0.159

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MPV: Mean platelet volume, SD: Standard deviation

Table 3

The correlations of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and mean platelet volume with SCORAD of atopic dermatitis patients

	<i>r</i>	<i>P</i>
NLR	0.03	0.615
PLR	-0.07	0.313
MPV	-0.06	0.350

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio,
MPV: Mean platelet volume

Table 4

The correlations of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and mean platelet volume with disease duration

	<i>r</i>	<i>P</i>
NLR	0.87	<0.001
PLR	0.70	<0.001
MPV	0.02	0.728

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio,
MPV: Mean platelet volume

Table 5

The comparison of the mean/median values of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and mean platelet volume between intrinsic and the extrinsic atopic dermatitis groups

	Intrinsic atopic dermatitis (n=107)		Extrinsic atopic dermatitis (n=145)		P
	Mean/median	SD/25%-75%	Mean/median	SD/25%-75%	
NLR	0.85	±0.55	1.05	±0.76	0.023
PLR	78.13	56.36-104.93	81.64	62.35-114.05	0.121
MPV (fL)	9.00	8.30-9.60	9.00	8.40-9.60	0.834

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MPV: Mean platelet volume, SD: Standard deviation

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