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Neutrophil-Lymphocyte Ratio and the Platelet Parameters as Biomarkers of Atopic Dermatitis Severity in Children

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease with a specific immune and inflammatory mechanism. This study investigates inflammatory biomarkers and their correlation with disease severity.
Objectives: The aim of this study is to determine the relationship between platelet parameters [(mean platelet volume (MPV), platelet distribution width (PDW)], the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and AD severity in children.
Methods: In this retrospective study, we reviewed patients diagnosed with AD and a healthy control group at the department of pediatrics at Health Sciences in a university-affiliated hospital in Istanbul, Turkey, between January 2015 and December 2016. The study included 79 children with AD and 75 healthy controls. AD severity was graded using the Scoring Atopic Dermatitis (SCORAD) index. Complete blood count was measured, and NLR and PLR were calculated. NLR, PLR, MPV, PDW were compared between AD patients and healthy controls, and the correlations between these indexes and clinical characteristics were analyzed.
Results: No significant difference was observed between patients and controls for MPV, NLR, and PLR ($P = 0.708$, $P = 0.340$, $P = 0.179$, respectively). In the AD group, PDW was lower than controls (17.39 ± 1.45, 18.04 ± 1.65, $P = 0.006$). In the severe AD group, MPV was higher (7.62 ± 1.81, 6.64 ± 1.16, $P = 0.035$) and PDW was lower than in the mild AD group (16.52 ± 1.49, 17.93 ± 1.44, $P = 0.0001$).
Conclusions: Mean MPV and PDW levels are correlated with atopic dermatitis severity in children.

Keywords: Atopic, Biomarkers, Child, Dermatitis, Eczema, Lymphocytes, Neutrophils, Platelet, Turkey

1. Background

Atopic dermatitis (AD) is a skin disease with eczematous and pruritic lesions (1). AD affects 10% -20% of children in developed countries (2).

The pathophysiology of AD is not well understood. Like other allergic diseases, AD is caused by interactions between genetic and environmental factors (3). Correlations have been reported between AD severity in children and biomarkers such as serum thymus, activation-regulated chemokine, and serum interleukin 10, 17, and 23 (4). However, these markers cannot be routinely examined.

When a platelet is activated, its volume increases. Platelets with increased volume contain denser granules and have a greater capacity to induce inflammation. Mean platelet volume (MPV) is a measure of thrombocyte volume, and increases in MPV are correlated with increases in platelet function and activity. Hence it can be used as an inflammatory indicator (5-7). Platelet distribution width (PDW) reflects an alteration in platelet size, similar to other platelet indexes (8). Recently, MPV and PDW have been highlighted as useful markers of several inflammatory diseases (9).

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are inexpensive indicators to evaluate, which can quickly and easily detect inflammatory reactions (10). It has been reported that there is a correlation between PLR and the severity of rheumatoid arthritis and systemic lupus erythematosus (11). NLR has been associated with chronic inflammation in such conditions as psoriasis and rheumatoid arthritis (12, 13). In children, some studies have reported that NLR, PLR, and MPV were higher in patients with atopic dermatitis, allergic rhinitis, and asthma. These studies emphasized that this might indicate the presence of inflammation in allergic diseases and be associated with disease severity (14-16).

A few studies conducted on children have shown a cor-

relation between AD and platelet parameters, NLR, and PLR (16-18). In our study, we investigated the correlation between platelet parameters, NLR, PLR, and AD severity in children, as assessed with the Scoring Atopic Dermatitis (SCORAD) index.

2. Objectives

This study aimed to identify useful and easily calculated indicators of systemic inflammation in AD; evaluated potential correlations between inflammatory markers and disease severity.

3. Methods

3.1. Patients

We retrospectively reviewed all patients diagnosed with AD and a healthy control group at the department of pediatrics at Health Sciences University, Bagcilar Training and Research Hospital, which is a general tertiary referral governmental hospital, in Istanbul, Turkey, between January 2015 and December 2016. We collected demographic data, AD signs and symptoms, and initial laboratory data from patient medical records. The inclusion criteria were: an AD diagnosis and an age in the range of 1 - 60 months. The study excluded children who were diagnosed with sepsis, obesity, hyperlipidemia, diabetes mellitus, hypertension, chronic renal disease, nephrotic syndrome, inflammatory bowel disease, or chronic inflammatory disease as well as those who had received systemic steroid treatment before blood count analysis. Patients with immunologic disorders were also excluded. The control group was made up of healthy volunteers from the same age group. Healthy subjects were children who went to the hospital for routine check-ups. Children with any sign of infection, systemic illness, or inflammation were excluded from the control group. After applying these criteria to 250 potential participants, the study included 154 children: 79 children with AD and 75 healthy children. AD was diagnosed following Hanifin and Rajka (19) and severity was graded using SCORAD: < 25 was classified as mild, 25 - 50 was classified as moderate, and > 50 was classified as severe (20). The local ethics committee of the same institute approved our study (2016/494). The study was conducted according to the Declaration of Helsinki. We obtained written informed consent from the parents.

3.2. Laboratory Analysis

Complete blood count was measured within approximately 60 minutes after blood sampling with a Coulter LH 780 Analyzer and a Coulter Hmx Hematology Analyzer (Beckman Coulter, Inc., CA, USA) using the original method and reagents. Based on data from the complete count analysis, NLR was calculated by dividing the percentage of neutrophils by the percentage of lymphocytes. PLR was calculated by dividing the percentage of platelets by the percentage of lymphocytes.

3.3. Statistical Analyses

Data were analyzed with IBM SPSS Statistics for Windows, version 24.0 (IBM, Armonk, NY, USA). Descriptive statistics are presented as means, standard deviations, median, and IQR values for continues data and frequencies and percentages for categorical data. Kolmogorov-Smirnov tests showed the data were not normally distributed, so Mann-Whitney U tests were used to compare the variables of two independent groups. The chi-square tests and, where applicable, Fisher's exact test were conducted to assess differences between categorical variables. Since the variables were not normally distributed, Kruskal-Wallis tests were used to compare more than two groups. Mann-Whitney U tests were used to test the significance of pairwise differences with the Bonferroni correction, to adjust for multiple comparisons. For multivariate analysis, possible factors identified with univariate analysis were further used in logistic regressions to determine independent predictors of AD outcome. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit. The difference was regarded as significant if $P < 0.05$.

4. Results

The patient group comprised 49 (62.1%) male and 30 (37.9%) female children with a mean age of 15.04 ± 11.90 months. The control group comprised 39 (52%) male and 36 (48%) female children with a mean age of 14.03 ± 13.17 months. There was no difference between the age or gender groups ($P > 0.05$). The patient group had significantly higher eosinophil counts, percentages of eosinophils, and lower PDW counts than the control group. There were no significant differences between the MPV, NLR, or PLR of the patients and the controls (Table 1). To determine the factors most affected by AD, logistic regression analysis was performed using percentages of eosinophil and PDW levels as variables. This showed that percentages of eosinophil ($P = 0.069$) and PDW ($P = 0.006$) were the factors most affected by AD (Table 2).

Based on the SCORAD index, AD patients were divided as mild (Group I: SCORAD < 25), moderate (Group II: SCORAD 25 - 50), and severe (Group III: SCORAD > 50). No significant differences were found between groups in terms of age, eosinophil counts, or eosinophils percentage. However, the mean MPV and PDW differed significantly among

Table 1. Comparison of Socio-Demographic Data and Laboratory Results for Patients and Control Groups[a,b]

	AD Group (N = 79)		Control Group (N = 75)		P Value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Age, mo	15.04 ± 11.90	12 (9)	14.03 ± 13.17	9 (7)	0.380[a]
Gender, No. (%)					0.293[b]
Female	30 (37.9)		36 (48)		
Male	49 (62.1)		39 (52)		
Eosinophil count, /mm^3	579 ± 598.99	400 (480)	417 ± 331	320 (352)	0.069[a]
Eosinophil, %	5.76 ± 4.84	4.9 (3.4)	4.07 ± 2.66	3.4 (3.09)	0.011[a]
Neutrophil/Lymphocyte ratio	0.58 ± 0.38	0.42 (0.41)	0.9 ± 1.29	0.51 (0047)	0.340[a]
Platelet count, 10^3/μL	361.29 ± 94.93	361 (130)	344.20 ± 107.68	336 (132)	0.251[a]
PLR	64.04 ± 54.25	58.12 (41.05)	71.97 ± 47.25	64.32 (38.23)	0.179[a]
MPV, fL	6.97 ± 1.29	6.8 (2.10)	6.92 ± 1.20	6.75 (1.57)	0.708[a]
PDW%	17.39 ± 1.45	17.5 (2.38)	18.04 ± 1.65	18.5 (3.10)	0.006[a]

Abbreviations: AD, atopic dermatitis, PLR, platelet-lymphocyte ratio, MPV, mean platelet volume, PDW, platelet distribution width.
[a]Result from the Mann-Whitney U test.
[b]Result from the chi-square test.

Table 2. Logistic Regression Analysis of Factors Associated with AD[a]

Parameters	B	Standard Error	Wald	P Value	Odds Ratio	95% CI for exp(B)	
						Lower	Upper
Percentages of eosinophils	0.137	0.056	5.909	0.015	1.147	1.027	1.281
PDW	-0.283	0.110	6.571	0.010	0.754	0.607	0.936
Constant	4.407	1.955	5.082	0.024	82.061		

Abbreviations: AD, atopic dermatitis, platelet distribution width.
[a]Used together, the constant, percentages of eosinophil, and PDW can predict AD with statistically significance (P < 0.05). Lower PDW reduces the risk of AD with a ratio of 0.755 at a 95% CI (0.607 - 0.936; P = 0.010). A higher percentage of eosinophil increases the risk of AD with a ratio of 1.147 at a 95% CI (1.027 - 1.281; P = 0.015).

groups. Mean MPV was higher (P = 0.035), and PDW was lower (P = 0.0001) in the severe AD group (Table 3). To determine the factors that most affected by SCORAD scores, logistic regression analysis was performed with MPV and PDW. This showed that the PDW level was the factor that most affected SCORAD in AD patients (Table 4).

5. Discussion

In our study, MPV levels were significantly higher, and PDW levels were significantly lower in children with AD and tracked AD severity. Although AD is an inflammatory disease and NLR and PLR reflect inflammation values, these variables showed no significant differences between groups.

MPV and PDW are frequently used as measures of platelet sizes and as inflammatory markers in various diseases (21). Cytokines released during inflammation cause increases in megakaryocyte ploidy and volume as well as the production of large quantities of platelets (22). These platelets are large with variable sizes (23, 24). MPV is an easy test that reflects platelet function or activity (25). The correlation between the MPV and disease activity has been reported in chronic spontaneous urticaria, juvenile idiopathic arthritis, systemic lupus erythematosus, and rheumatoid arthritis (26-29). The relationship between AD and MPV has been investigated in a few recent studies (16, 17). While MPV was found to be higher among AD children (17) in one study, no relationship was found between AD severity and MPV. The same conclusion was reached by Jiang and Ma (16). However, our data do show a relation between atopic dermatitis severity and MPV.

PDW, an index of platelet size heterogeneity, increases during platelet activation (30). Isik et al. (31) found that PDW was an adverse acute-phase reaction in patients with active rheumatoid arthritis. An inverse relationship between ulcerative colitis activity and PDW was identified by Ozturk et.al (32). Topal et al. (17) reported that PDW was lower in AD, but it was not associated with disease severity. Our study also found that PDW was low in AD children,

Table 3. Comparison of Socio-Demographic Data and Laboratory Findings of Patients with Mild (Group I), Moderate (Group II), and Severe Atopic Dermatitis (Group III)

	Group I (N = 46)		Group II (N = 25)		Group III (N = 8)		P Value
	Maen ± SD	Median (IQR)	Maen ± SD	Median (IQR)	Maen ± SD	Median (IQR)	
Age, mo	14.03 ± 9.86	11.82 (8)	19.02 ± 15.25	14.25 (29)	8.44 ± 6.68	7.25 (4.25)	0.079
Eosinophil count, /mm^3	527 ± 614	398 (360)	613 ± 579	400 (550)	767 ± 596	750 (910)	0.496
Eosinophil, %	4.98 ± 3.48	4.22 (3.30)	6.83 ± 6.74	5.20 (4.53)	6.88 ± 4.34	5.2 (4.25)	0.561
Neutrophil/Lymphocyte ratio	0.54 ± 0.33	0.43 (0.38)	0.69 ± 0.48	4.46 (0.67)	0.46 ± 0.35	0.33 (0.42)	0.207
Platelet count, 10^3/μL	352.14 ± 98.24	334.3 (116.05)	374.12 ± 81	381 (95)	373.88 ± 120.66	357.50 (176.25)	0.359
PLR	53.93 ± 38.40	56.35 (53.92)	70.15 ± 41.43	62.22 (47.02)	103.12 ± 122.01	65.65 (48.78)	0.240
MPV, fL	6.64 ± 1.16	6.4 (1.95)	7.38 ± 1.22	7.67 (2.19)	7.62 ± 1.81	7.85 (2.70)	0.035[a]
PDW%	17.93 ± 1.44	18.02 (1.71)	16.70 ± 1.00	16.4 (1.76)	16.52 ± 1.49	16.65 (1.38)	0.000[a]

Abbreviations: PLR, platelet-lymphocyte ratio, MPV, mean platelet volume, PDW, platelet distribution width.
[a]Statistical significance was defined at P < 0.05.

Table 4. Logistic Regression Analysis of Factors Associated with the SCORAD Index in AD Patients[a]

SCORAD Score	B	Standard Error	Wald	P Value	Odds ratio	95% Confidence Interval for exp(B)	
						Lower	Upper
Group II							
Intercept	10.274	5.701	3.247	0.072			
MPV	0.118	0.244	0.233	0.629	1.125	0.697	1.816
PDW	-0.677	0.268	6.396	0.011	0.508	0.301	0.859
Group III							
Intercept	9.065	8.214	1.218	0.270			
MPV	0.248	0.371	0.449	0.503	1.282	0.620	2.651
PDW	-0.732	0.388	3.555	0.059	0.481	0.225	1.029

Abbreviations: AD, atopic dermatitis, MPV, mean platelet volume, PDW, platelet distribution width; SCORAD, severity was graded using the scoring atopic dermatitis.
[a]When the reference category is mild, only PDW is a statistically significant factor for predicting SCORAD group (P < 0.05). Compared to the mild group, the moderate group has lower PDW values, higher SCORAD indices, and an odds ratio of 0.755 with a CI of 95% (0.608 - 0.937; P = 0.011).

and additionally, it correlates with severity.

NLR has been used as an indicator in many inflammatory diseases (12, 13). Neutrophilic inflammation has also been shown to occur with eosinophilic inflammation in AD patients. A positive correlation between potent neutrophil chemoattractant gene set scores and neutrophils of AD patients has been demonstrated (33). Neutrophilic inflammation was detected in lesioned areas but not in perilesional areas. Furthermore, a correlation was found between the number of neutrophils and crust presence. In addition to assessing the extent of lesions in AD, the SCORAD scale is used to assess lesion severity. The crust is also a parameter of density. These results show that neutrophilia is more common in severe AD. When high neutrophil counts are present, NLR is higher. We found no relationship between AD severity and NLR. Comprehensive trails are required to determine their relationship clearly.

PLR has been associated with the severity of many diseases (13, 14, 34-37). The few studies on PLR in AD patients have reported that PLR is correlated with disease severity (16, 18), but our study did not identify this correlation.

One limitation of this study is the small number of participants. The low number of patients was due to the study being conducted at a single center and the study's retrospective design. We did not make groups based on intrinsic and extrinsic atopic dermatitis. Another limiting factor is that there was no threshold value for MPV and PDW, such as CRP. These are the weak points of this study. However, we believe that our study is important because few other studies have evaluated MPV, PDW, NLR, and PLR in AD children and compared them to disease severity. Therefore, our study is important for filling this gap in the literature. As mentioned above, we think that MPV and PDW will be useful for investigating AD severity, as they are for many other inflammatory diseases.

5.1. Conclusions

Our study found no differences in mean MPV, NLR, and PLR values between AD patients and the control group. However, MPV and PDW differed significantly between severe and mild AD patients. MPV and PDW were correlated with AD severity and can be used to track severity. However, more studies are required to examine the relationship between NLR, PLR, and disease severity.

Footnotes

Authors' Contribution: Study concept and design: Ozlem Bostan Gayret and Hikmet Tekin Nacaroğlu; acquisition of data: Hikmet Tekin Nacaroğlu and Ahmet Sener; analysis and interpretation of data: Meltem Erol, Ahmet Sener and Ozlem Bostan Gayret; drafting of the manuscript: Ozlem Bostan Gayret; critical revision: Meltem Erol; technical and material support: Ahmet Sener, Meltem Erol, and Hikmet Tekin Nacaroğlu; supervision: Hikmet Tekin Nacaroğlu.

Conflict of Interests: The authors declare no conflict of interest.

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