Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1364897
J Health Sci Med. 2023;6(6):1313-1321

The diagnostic weight of hemogram parameters in diagnosis, severity, and disease duration of childhood atopic dermatitis: a thorough evidence-focused study

Fatih Çiçek[1], Mehmet Tolga Köle[2], İbrahim Kandemir[3]

[1]Department of Pediatric Allergy and Immunology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey
[2]Department of Pediatrics, Kartal Dr· Lütfi Kırdar City Hospital, İstanbul, Türkiye
[3]Department of Pediatrics, Faculty of Medicine, Biruni University, İstanbul, Turkey

Cite this article as: Çiçek F, Köle MT, Kandemir İ. The diagnostic weight of hemogram parameters in diagnosis, severity, and disease duration of childhood atopic dermatitis: a thorough evidence-focused study. *J Health Sci Med.* 2023;6(6):1313-1321.

Received: 22.09.2023 ◆ **Accepted**: 13.10.2023 ◆ **Published**: 29.10.2023

ABSTRACT

Aims: We aimed to assess the association of hemogram parameters with atopic dermatitis (AD), severity of AD, and disease duration.

Methods: We included the hemogram parameters of patients under follow-up in our pediatric allergy outpatient clinic and healthy group. The blood samples were drawn when they had no complaints or after at least 30 days of infection or a drug-free period. We built H1 and H0 (null) hypotheses, subjected data to Bayesian statistics, and assessed which hemogram parameters have potential and which shall not be used, with presenting evidence levels. We split the transactions into two groups (<49 and ≥49 months old) as there is a lymphocyte predominancy before four years of age and built another model with all individuals.

Results: We included 197 AD-diagnosed patients and 150 controls in the study. Eosinophil was the significant confounder for AD, and White Blood Cell Count, Absolute Neutrophil Count, Platelet Count, and Red Cell Distribution Width (RDW)/Platelet Ratio were independent of AD. Eosinophil/Lymphocyte Ratio (ELR) was correlated with SCORAD index (anecdotal evidence) under four years old, ELR and total IgE in older four years old, and ELR and Eosinophil/Neutrophil Ratio in all age groups. None of the hemogram parameters were correlated with disease duration in our under-4-year-old patient group. However, there was anecdotal evidence for RDW correlation with disease duration in the older four years group. Age, Neutrophil/Lymphocyte Ratio, and Platelet/Lymphocyte Ratio had a strong association with disease duration.

Conclusion: We presented which hemogram parameter could be used and should not be used in children for AD diagnosis and AD follow-up. Multicenter studies are needed for the final conclusion.

Keywords: Atopic dermatitis, hemogram, parameters, children

INTRODUCTION

Atopic dermatitis (AD) is a chronic and recurrent skin condition commonly linked to a combination of genetic susceptibility, immune system response, and environmental factors.[1,2] While studies have shown that it can affect all age groups, it has been emphasized that it is more common in childhood.[3] One of the scales used to assess the severity of the disease is the Scoring Atopic Dermatitis (SCORAD) index. According to this scale, patients with a score below 25 have a mild, those between 25 and 50 have a moderate, and those above 50 have a severe form of the disease.[4]

While the barrier dysfunction in the skin and abnormal immune response resulting in local inflammation play a significant role in AD development, recent studies have emphasized the importance of systemic inflammation.[5-7] Previous studies emphasized that various cells and cytokines play a role in AD pathogenesis.[8,9] Also, some studies draw attention to the relationship between the severity of the disease and various substances such as serum thymus and activation-regulated chemokines and serum interleukin (IL)- 10, IL-17, and IL-23 levels.[9,10] Neutrophils, lymphocytes, and platelets are prominent parameters involved in inflammation and can be easily measured through hemogram tests. Biomarkers created from complete blood count values not only form the basis for allergy research but also underpin many studies in various other disciplines.[11-13] Studies conducted in pediatric patients with AD have also drawn attention to the relationship between serum total IgE, eosinophil, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and eosinophil/lymphocyte ratio (ELR) levels and AD.[14-16] It has been demonstrated that neutrophilic inflammation is linked to

Corresponding Author: Fatih Çiçek, drfatihcck@gmail.com

eosinophilic inflammation in patients with AD.[15] In this study involving 91 AD patients, the authors determined that there was a relationship between the severity of AD and the neutrophil count, where the lymphocyte count had a negative correlation with the disease severity.[15] This study aimed to assess which complete blood count parameters are significant and which are independent factors on diagnosis, disease severity, and disease duration in pediatric patients with AD.

METHODS

The study was carried out with the permission of Dr. Lutfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023/514/246/23). All procedures in the study were performed in accordance with ethical rules and the principles of the Declaration of Helsinki.

We conducted this case-control study retrospectively between December 2022 and March 2023, including a total of 196 patients who were followed-up with AD in the pediatric allergy clinic and 150 healthy controls, without any chronic or allergic diseases who presented to the pediatric clinic for routine follow-up without active complaints or infections. We recorded the patients' clinical assessments, SCORAD index data, disease duration, serum total IgE and complete blood count parameters (White Blood Cell Count (WBC), Mean Corpuscular Volume (MCV), Absolute Neutrophil Count (NC), Absolute Lymphocyte Count (LC), Absolute Eosinophil Count (EC), percentage of eosinophils (E%), Red Cell Distribution Width (RDW %), Absolute Platelet Count (PC), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), NLR, PLR, ELR, Eosinophil/Neutrophil Ratio (ENR), Platelet/Neutrophil Ratio (PNR), Red Cell Distribution Width/Platelet Ratio (RDW/P)) from hospital records. The patient group was diagnosed with AD by a pediatric allergy specialist based on the Hanifin and Rajka criteria. The clinical severity of AD was scored using the SCORAD index. Based on this index, AD was categorized as mild (0-24.9), moderate (25-50), and severe (>50).[17] Because lymphocyte dominance is present in children under the age of four, patients were divided into two groups: Those under four years old (<49 months) and those four years and older (≥49 months). Patients with concomitant chronic inflammatory skin infections during their application, those with systemic infection symptoms receiving antibiotic treatment, those with anemia or receiving treatment due to anemia, and those receiving topical or systemic glucocorticoid therapy and multivitamin supplements within the last month were excluded from the study. In our country, iron and vitamin D prophylaxis is given to children under 1. Considering the possible effects of these drugs on hemogram parameters, we kept the control group large and paid attention to randomization. The parameters WBC, MCV, NC, LC, EC, E%, RDW, PC, PDW, and MPV were recorded from the individuals' complete blood count results. The Neutrophil/Lymphocyte Ratio (NLR) was obtained by dividing NC by LC; the PLR by dividing PC by LC; the ELR by dividing EC by LC; the ENR by dividing EC by NC; the PNR by dividing PC by NC; and the RDW/P by dividing RDW by PC. The measurements of hemogram parameters were performed using the Coulter Hmx Hematology Analysis Device. Serum total IgE was measured by nephelometric method with Siemens Healthcare Diagnostics Products, Marburg, Germany.

Statistical Analysis

Data is interpreted as mean+/-sd, median (Interquartile range), and n(%) regarding the distribution and data type. We used the Kolmogorov-Smirnov test, skewness, kurtosis, and Q-Q plot to conclude normal distribution.

We used Bayesian Kendall's tau and Bayesian Pearson tests to calculate H1 (difference) and H0 (null) hypotheses and interpreted BF_{10} evidence as anecdotal ($BF_{10}>1$), moderate ($BF_{10}>3$), strong ($BF_{10}>10$), very strong ($BF_{10}>30$) and extreme ($BF_{10}>100$) for H1 hypothesis. We interpreted BF_{10} evidence as anecdotal ($BF_{10}<0.9$), moderate ($BF_{10}<0.3$), and strong ($BF_{10}<0.1$) evidence for the H0 hypothesis. The stretched beta prior width was assumed 1 for bayesian correlation calculations. We transformed the data with logarithms, BOXCOX transformation, square root, or exponential.

We used a generalized linear model (GLM) for multivariate calculations to assess confounding factors among potential factors with the "backward elimination" method and interpreted the results with a graphic and an estimated marginal means table. $P<0.05$ were considered for statistical significance.

RESULTS

We included 197 AD-diagnosed patients (median age 28.0 months (11.0-59.0) and 150 control (median age 37 (16.8-68.5)) in the study. The patient and control groups, according to the age of individuals, are provided in Table 1. The mean diagnosis age was 8 months (1-40), and the follow up time 8 months (5-18). The mean SCORAD score was 27.2±11.1 in < 4 years and 26.6±11.9 in ≥ 4 years age group. The two groups were comparable regarding age ($p>0.05$, Mann-Whitney U test). Female ratios were 50.8% and 50.6% in the patient and control groups, respectively ($p>0.05$, chi-square test). We split the transactions into two groups (<49 and ≥49 months old) as there is a lymphocyte predominancy under four years.

Table 1 . The patient and the control groups regarding the individuals' age

	< 49 months	≥ 49 months	Total
Patient	129	68	197
Control	100	50	150

We aimed to present evidence levels with Bayesian statistical calculations in this study. We hypothesized that complete blood count parameters had a correlation between two independent variables (H1), and the null hypothesis (H0) indicated no correlations between the variables. All the transactions focused on assessing the evidence level for both the H1 (correlation) and H0 (null) hypotheses.

Correlation Hypotheses of Hemogram Parameters with Atopic Dermatitis

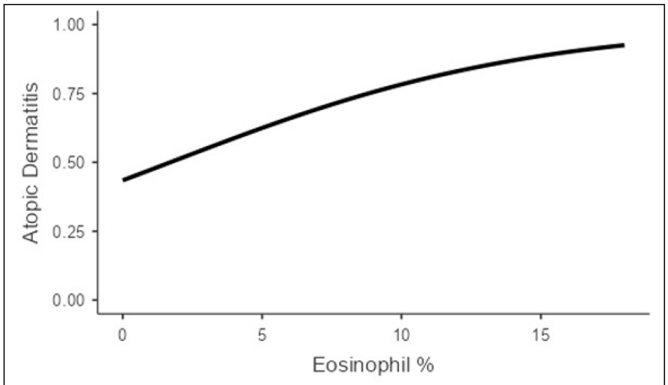
<4 years: H1 hypothesis: There was strong evidence (BF_{10}>10) that E% had correlation with AD, moderate (BF_{10}>3) evidence for EC and ENR, and anecdotal (BF_{10}>1) evidence for ELR. H0 (null) hypothesis: There was strong evidence that WBC, NC, PC, and RDW/P were independent from AD (BF_{10}<0.1), moderate evidence for LC, MPV, NLR, PLR, and PNR (BF_{10}<0.3), and anecdotal evidence for MCV, RDW, and PDW (BF<0.9) (Table 2).

As we subjected the correlated four factors (E%, ENR, EC, and ELR) as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:0.6 X^2:0.3, X^2:0.4, and X^2:0.3, respectively (Loglikelihood ratio test). After eliminating insignificant factors, the E% (Loglikelihood ratio X^2:8.1, p=0.005) remained the most significant confounder (GLM, R^2:0.03). Each 1% increase in E% increased AD odds by 1.17 (95%CI:1.05-1.32). The graphic and the estimated marginal means are presented in Figure 1.

Table 2. Bayesian statistics results of correlation hypotheses of hemogram parameters with atopic dermatitis

	<4 years				>4 years				All patients			
	C	AD	τ	BF_{10}	C	AD	τ	BF_{10}	C	AD	τ	BF_{10}
Age (months)	18 (10-28)	16 (9-27)	-0.043	0.138 N,M	71.5 (60.5-88.8)	67.5 (57.8-91.3)	-0.037	0.143 N,M	28 (13.3-60)	28 (11.0-59.0)	-0.014	0.076 N,*
WBC (*1000/µL)	9.7 (7.8-11.2)	9.5 (7.7-11.7)	0.020	0.096 N,*	8.5 (6.9-10.0)	8.75 (7.2-11.5)	0.087	0.315 N,M	9.3 (7.4-11.0)	9.1 (7.6-11.7)	0.044	0.147 N,M
MCV (fl)	77.3 (74.2-80.8)	78.4 (75.1-80.9)	0.077	0.383 N,A	80.5 (78.2-82.2)	80.4 (78.0-82.9)	0.036	0.142 N,M	78.4 (75.1-81.5)	79.0 (76.6-82.0)	0.061	0.299 N,M
NC (*1000/µL)	2.7 (1.8-4.3)	2.7 (2.1-3.6)	-0.018	0.094 N,*	3.7 (2.8-5.7)	4.2 (2.8-5.5)	0.014	0.123 N,M	3.1 (2.0-4.6)	2.9 (2.2-4.2)	-0.012	0.075 N,*
LC (*1000/µL)	5.3 (4.1-6.4)	5.37 (4.1-7.1)	0.058	0.203 N,M	3.3 (2.5-3.9)	3.4 (2.6-4.1)	0.052	0.169 N,M	4.4 (3.1-5.7)	4.5 (3.3-6.3)	0.040	0.133 N,M
EC (*100/µL)	2.3 (1.4-3.7)	2.8 (1.9-4.7)	0.131	6.640 M	200 (100-323)	245 (158-570)	0.134	1.204 A	210 (120-365)	270 (170-530)	0.134	68.5 **
RDW (%)	13.9 (13.2-14.8)	13.5 (12.9-14.7)	-0.084	0.509 N,A	13.1 (12.6-13.8)	13.3 (12.9-13.7)	0.020	0.127 N,M	13.7 (13.0-14.6)	13.4 (12.9-14.4)	-0.063	0.328 N,M
PC (*1000/ml)	354 (296-427)	348 (306-420)	-0.011	0.089 N,*	330 (280-413)	353 (314-409)	0.064	0.201 N,M	349 (292-422)	348 (308-418)	0.013	0.075 N,*
PDW (%)	10.4 (9.7-11.6)	10.6 (9.7-12.5)	0.082	0.477 N,A	10.4 (9.3-12.0)	10.7 (9.8-11.4)	0.043	0.152 N,M	10.4 (9.5-11.7)	10.7 (9.8-12.0)	0.069	0.431 N,A
MPV (fl)	9.8 (9.5-10.3)	9.8 (9.3-10.8)	0.030	0.108 N,M	9.6 (9.1-10.6)	9.8 (9.3-10.2)	0.050	0.166 N,M	9.8 (9.3-10.3)	9.8 (9.3-10.6)	0.032	0.105 N,M
NLR (*100)	52.9 (33.7-82.7)	49.5 (32.6-76.7)	-0.051	0.167 N,M	109 (85.5-201)	112 (90-179)	-0.015	0.124 N,M	73.6 (42.9-112)	68.5 (38.0-113)	-0.028	0.095 N,*
PLR (*100/1000)	7.5 (5.5-9.5)	7.1 (4.9-9.1)	-0.072	0.323 N,M	10.2 (8.6-14.1)	10.9 (8.5-13.3)	0.030	0.135 N,M	8.2 (6.2-10.5)	8.2 (5.9-10.7)	-0.025	0.089 N,*
ELR (*100)	4.6 (2.8-6.9)	5.3 (3.4-9.1)	0.117	2.781 A	5.5 (3.5-10.7)	7.5 (4.1-17.5)	0.104	0.483 N,A	4.8 (2.9-8.2)	5.7 (3.8-11.1)	0.108	6.371 M
ENR (*100)	7.8 (3.9-15.2)	10.5 (6.0-20.6)	0.120	3.180 M	4.9 (3.0-9.3)	6.7 (3.5-14.2)	0.115	0.648 N,A	6.7 (3.3-13.8)	9.4 (4.8-17.5)	0.118	14.5 *
PNR (*100/1000)	12.7 (8.4-18.7)	13.1 (9.2-17.3)	0.028	0.105 N,M	8.5 (6.2-13.2)	8.7 (6.4-11.4)	0.015	0.124 N,M	11.3 (7.5-17.5)	11.8 (8.1-16.4)	0.019	0.081 N,*
RDW/P (*100)	3.9 (3.3-4.9)	4.0 (3.2-4.8)	-0.014	0.091 N,*	4.0 (3.2-5.0)	3.8 (3.2-4.4)	-0.088	0.325 N,M	3.9 (3.3-5.0)	3.9 (3.2-4.5)	-0.039	0.126 N,M
E% (*100)	2.5 (1.5-3.9)	2.94 (2.0-4.8)	0.138	10.6 *	2.3 (1.4-4.0)	2.7 (1.5-6.7)	0.097	0.403 N,A	2.4 (1.4-3.9)	2.9 (1.9-5.3)	0.127	34.3 *

AD: Atopic dermatitis group, C:Control group. WBC: White Blood Cell Count, MCV: Mean Corpuscular Volume, NC: Neutrophil Count, LC: Lymphocyte Count, EC: Eosinophil Count, RDW: Red Cell Distribution Width (%), PC:Platelet Count*1000, PDW: Platelet Distribution Width (%), MPV: Mean Platelet Volume (fl), NLR: Neutrophil/Lymphocyte Ratio*100, PLR: Platelet/Lymphocyte Ratio (*100), ELR: Eosinophil/Lymphocyte Ratio (*100), ENR: Eosinophil/Neutrophil Ratio (*100), PNR: Platelet/Neutrophil Ratio (*100), RDW/P: Red Cell Distribution Width (%)/Platelet Ratio (*100), E%: Eosinophil Count / White Blood Cell Count(*100).τ: Bayesian Kendall's Rank Correlation Coefficient. The correlation and Bayesian results are rounded for a better presentation. A: Anecdotal evidence for alternative or null hypothesis, M: Moderate evidence for alternative or null hypothesis, *:Strong evidence for alternative hypothesis, **: Very strong evidence for alternative hypothesis, ***: Extreme evidence for alternative hypothesis, N*: Strong evidence for null hypothesis

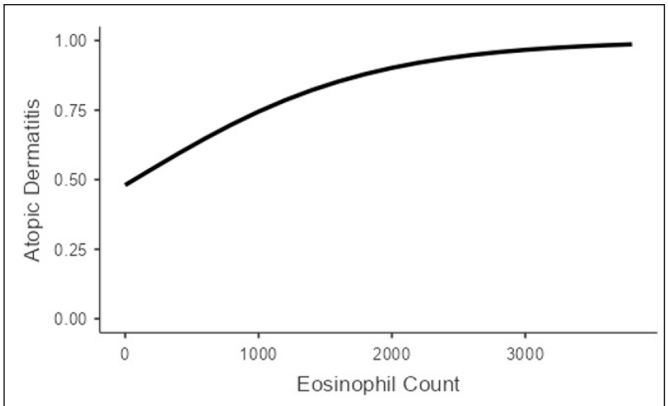


Eosinophil Count / WBC Count (*100)	Mean Atopic Dermatitis Probability (95%CI)
1.7	50.0% (42.1-57.8)
2.7	53.8% (47.0-60.5)
4.4	60.1% (52.8-66.9)

Figure 1. The association between eosinophil count / WBC count and atopic dermatitis probability and the estimated marginal means with 95% confidence intervals (95%CI)

>4 years: H1 hypothesis: There was anecdotal evidence (BF_{10}>1) that EC had correlation with AD. H0 (null) hypothesis: There was moderate evidence that WBC, MCV, NC, LC, EC, RDW, PC, MPV, NLR, PLR, PNR, and RDW/P were independent from AD (BF_{10}<0.3), and anecdotal evidence for ELR, ENR, and E% (BF<0.9) (Table 2).

As we subjected EC as a covariate in a multivariate model (GLM), the loglikelihood ratio test resulted in X^2:4.4 (p=0.035, GLM, R^2:0.03). Each 100 unit increase in EC increased AD odds by 1.12 (95%CI:1.01-1.29). The graphic and the estimated marginal means are presented in Figure 2.

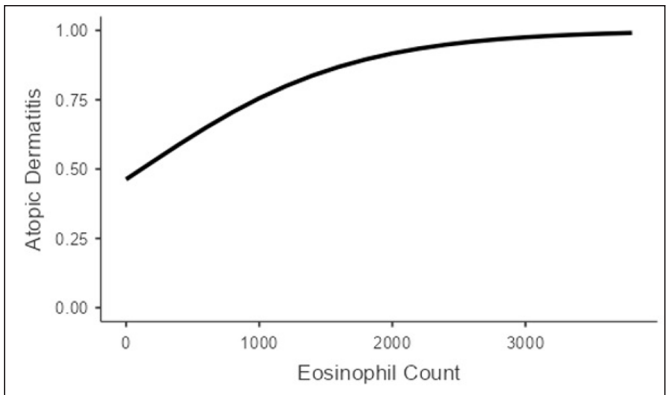


Eosinophil Count	Mean Atopic Dermatitis Probability (95%CI)
1.3	51.8 (41.0-62.4)
2.3	54.6 (45.1-63.9)
4.6	60.9 (50.7-70.3)

Figure 2. The association between eosinophil count and atopic dermatitis probability and the estimated marginal means with 95% confidence intervals (95%CI) in >4 years old group

All age groups: H1 hypothesis: There was strong evidence (BF_{10}>10) that EC, ENR, and E% had correlation with AD had correlation with AD, and moderate evidence (BF_{10}>3) for ELR. H0 (null) hypothesis: There was strong evidence that NC, PC, NLR, PLR, and PNR were independent from AD (BF_{10} 0.1), moderate evidence for WBC, MCV, LC, RDW, MPV, and RDW/P (BF_{10}<0.3), and anecdotal evidence for PDW (BF<0.9) (Table 2).

As we subjected the correlated four factors (E%, EC, ENR, and ELR) as covariates in a multivariate model (GLM), likelihood ratio tests resulted as X^2:0.0, X^2:0.4, X^2:0.1, and X^2:0.2, respectively (Loglikelihood ratio test). After eliminating insignificant factors, EC (Loglikelihood ratio X^2:12.3, p<0.001) remained the most significant confounder (GLM, R^2:0.03). Each 100 unit increase in EC increased AD odds by 1.14 (95%CI: 1.05-1.24). The graphic and the estimated marginal means are presented in Figure 3.



Eosinophil Count	Mean Atopic Dermatitis Probability (95%CI)
1.5	51.1% (44.8-57.3)
2.5	54.3% (48.7-59.7)
4.5	60.3% (54.4-66.0)

Figure 3. The association between eosinophil count and atopic dermatitis probability and the estimated marginal means with 95% confidence intervals (95%CI) in all age groups

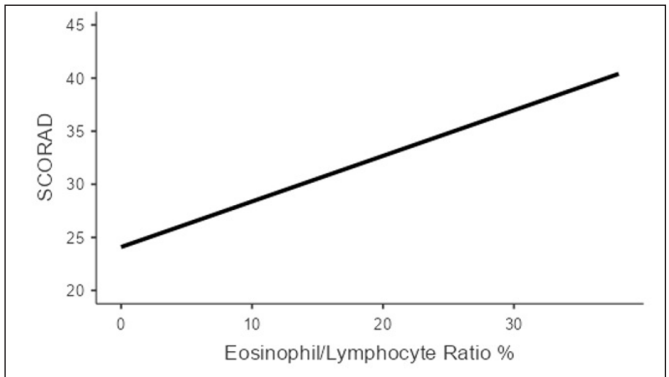
Correlation hypotheses of hemogram parameters with SCORAD index and disease duration: We subjected hemogram parameters to correlation calculations with SCORAD index and disease duration. We hypothesized H1 hypothesis (correlation) and the null (H0) hypothesis (not correlated, independence).

<4 years, SCORAD index: H1 hypothesis: There was anecdotal evidence (BF_{10}>1) that ELR had correlation with SCORAD index. H0 (null) hypothesis: There was moderate evidence (BF_{10}<0.3) that age, WBC, MCV, NC, LC, RDW, PC, PDW, MPV, NLR, ENR, PNR, RDW/P, and IgE (BF_{10}<0.3) were independent from SCORAD index, and anecdotal evidence (BF_{10}<0.9) for disease duration, EC, PLR, and E% (Table 3). Each 1% increase in ELR increased SCORAD index by 0.4 (95%CI:0.3-0.6) points in the multivariate model (loglikelihood ratio test: X^2:27.5, GLM, R^2:0.05). The graphic and the estimated marginal means are presented in Figure 4.

Table 3. Bayesian statistics results of correlation hypotheses of hemogram parameters with SCORAD index and disease duration

	<4 Years Old				>4 Years Old				All			
	SCORAD index		Disease duration		SCORAD index		Disease duration		SCORAD index		Disease duration	
	r	BF_{10}	r	BF_{10}	r	BF_{10}	r	BF_{10}	r	BF_{10}	r	BF_{10}
Disease duration	-0.157	0.52 N,A	—		-0.164	0.36 N,A	—		-0.137	0.56 N,A	—	
Age (months)	-0.073	0.15 N,M	0.427	33009 ***	0.017	0.15 N,M	-0.017	0.15 N,M	-0.060	0.13 N,M	0.455	$4.87x10^6$ ***
WBC (*1000/µL)	-0.005	0.11 N,M	-0.118	0.26 N,M	0.030	0.16 N,M	-0.099	0.21 N,M	0.004	0.09 N*	-0.130	0.47 N,A
MCV (fl)	0.047	0.13 N, M	-0.029	0.12 N, M	0.188	0.48 N,A	0.030	0.16 N,M	0.082	0.17 N,M	0.075	0.15 N,M
NC (*1000/µL)	0.053	0.13 N,M	0.079	0.16 N,M	-0.051	0.17 N,M	-0.064	0.17 N,M	0.005	0.09 N*	0.139	0.59 N,M
LC (*1000/µL)	-0.096	0.20 N,M	-0.159	0.55 N,A	-0.187	0.47 N,A	-0.198	0.55 N,A	-0.102	0.25 N,M	-0.316	2219 ***
EC (*100/µL)	0.151	0.47 N,A	-0.102	0.21 N,M	0.353	10.8 *	-0.089	0.20 N,M	0.230	17.1 *	-0.089	0.19 N,M
RDW (%)	0.010	0.11 N,M	-0.065	0.14 N,M	0.010	0.15 N,M	-0.246	1.12 A	0.012	0.09 N*	-0.157	1.01
PC (*1000/ml)	0.114	0.25 N,M	-0.072	0.15 N,M	-0.101	0.21 N,M	-0.013	0.15 N,M	0.046	0.11 N,M	-0.053	0.12 N,M
PDW (%)	-0.072	0.15 N,M	-0.116	0.26 N,M	-0.019	0.15 N,M	0.068	0.18 N,M	-0.052	0.12 N,M	-0.086	0.18 N,M
MPV (fl)	-0.092	0.19 N,M	-0.161	0.56 N,A	0.020	0.15 N,M	0.017	0.15 N,M	-0.055	0.12 N,M	-0.127	0.43 N,A
NLR (*100)	0.095	0.20 N,M	0.155	0.50 N,A	0.082	0.19 N,M	0.057	0.17 N,M	0.067	0.14 N,M	0.292	477 ***
PLR (*100/1000)	0.149	0.45 N,A	0.103	0.21 N,M	0.152	0.32 N,M	0.193	0.51 N,A	0.121	0.37 N,A	0.278	206 ***
ELR (*100)	0.195	1.24 A	-0.020	0.11 N,M	0.393	32.5 **	-0.037	0.16 N,M	0.250	45.1**	0.041	0.10 N,M
ENR (*100)	0.113	0.25 N,M	-0.133	0.34 N,A	0.337	7.26 M	-0.057	0.17 N,M	0.196	4.0 M	-0.151	0.84 N,A
PNR (*100/1000)	0.027	0.12 N,M	-0.115	0.25 N,M	0.007	0.15 N,M	0.057	0.17 N,M	0.017	0.09 N*	-0.152	0.85 N,A
RDW/P (*100/1000)	-0.116	0.26 N,M	0.033	0.12 N,M	0.104	0.22 N,M	-0.042	0.16 N,M	-0.042	0.11 N,M	-0.010	0.09 N*
E% (*100)	0.167	0.65 N,A	-0.065	0.14 N,M	0.351	10.4 *	-0.059	0.17 N,M	0.241	28.8 *	-0.045	0.11 N,M
IgE (IU/ml)	-0.039	0.12 N, M	0.040	0.12 N,M	0.442	160 ***	-0.049	0.16 N,M	0.097	0.22 N,M	0.162	1.15 A

WBC: White Blood Cell Count, MCV: Mean Corpuscular Volume, NC: Neutrophil Count, LC: Lymphocyte Count, EC: Eosinophil Count, RDW: Red Cell Distribution Width (%), PC:Platelet Count*1000, PDW: Platelet Distribution Width (%), MPV: Mean Platelet Volume (fl), NLR: Neutrophil/Lymphocyte Ratio*100, PLR: Platelet/Lymphocyte Ratio (*100), ELR: Eosinophil/Lymphocyte Ratio (*100), ENR: Eosinophil/Neutrophil Ratio (*100), PNR: Platelet/Neutrophil Ratio (*100), RDW/P: Red Cell Distribution Width (%)/ Platelet Ratio (*100), E%:Eosinophil Count / White Blood Cell Count(*100), IgE:Total Immunoglobulin E. r: Bayesian Pearson's correlation coefficient. A: Anecdotal evidence. M: moderate evidence. *: strong evidence NA: Not applicable (could not be transformed into normal-distributed data with arithmetic calculations). All calculations were performed after transforming into normal distributed data with LN (Logarithm Natural), square-root, or Box Cox calculations in order to use with Bayesian Pearson test. The correlation and Bayesian results are rounded for a better presentation. A: Anecdotal evidence for alternative or null hypothesis, M: Moderate evidence for alternative or null hypothesis, *:Strong evidence for alternative hypothesis, **: Very strong evidence for alternative hypothesis, ***: Extreme evidence for alternative hypothesis, N*: Strong evidence for null hypothesis



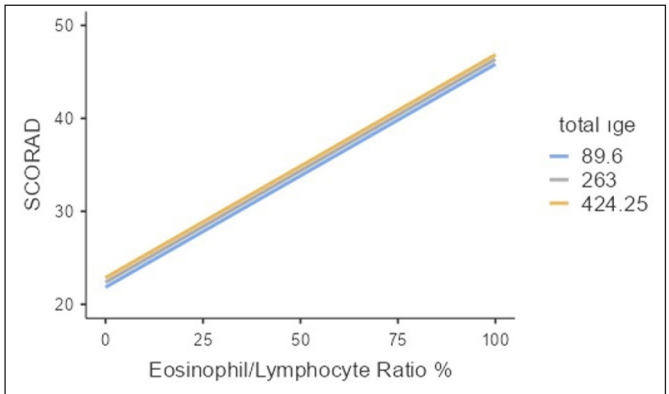
Eosinophil/Lymphocyte Ratio %	Mean SCORAD Index (95%CI)
3.4	25.5 (24.5-26.6)
5.4	26.4 (25.5-27.3)
9.1	28.0 (27.0-29.0)

Figure 4 . The association between eosinophil/ lymphocyte ratio and SCORAD index and the estimated marginal means with 95% confidence intervals (95%CI)

<4 years, disease duration: H1 hypothesis: None for disease duration. H0 (null) hypothesis: There was moderate evidence that WBC, MCV, NC, EC, RDW, PC, PDW, PLR, ELR, PNR, RDW/P, E%, and IgE (BF_{10}<0.3) were independent from disease duration, and anecdotal evidence for LC, MPV, NLR, and ENR (BF<0.9) (Table 3).

>4 years, SCORAD index: H1 hypothesis: There was extreme evidence (BF_{10}>100) that IgE had correlation with SCORAD index, strong for EC, ELR, and E% (BF_{10}>10) and moderate (BF_{10}>3) evidence for ENR. H0 (null) hypothesis: There was moderate evidence that age, WBC, NC, RDW, PC, PDW, MPV, NLR, PLR, PNR, and RDW/P (BF_{10}<0.3) were independent from SCORAD index, and anecdotal evidence for disease duration, MCV, and LC (BF<0.9) (Table 3).

As we subjected EC, ELR, IgE, and E% as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:0.8, X^2:15.0, X^2:7.7, X^2:0.5, respectively (Loglikelihood ratio test). After eliminating insignificant factors with the backward elimination method, ELR (X^2:38.7)and IgE (X^2:8.9) remained as significant confounders (GLM, R^2:0.247). The graphic and the estimated marginal means are presented in Figure 5.



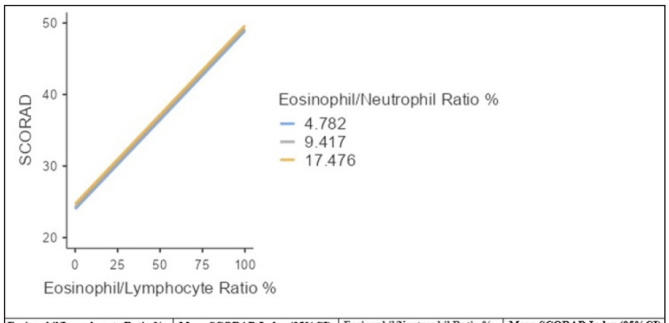
Eosinophil /Lymphocyte Ratio	Mean SCORAD index (95%CI)	Total IgE	Mean SCORAD index (95%CI)
0.041	24.1 (22.4-25.7)	89.6	25.4 (23.9-26.8)
0.075	24.9 (23.6-26.2)	263	25.9 (24.6-27.2)
0.175	27.3 (26.0-28.6)	424.3	26.4 (25.2-27.6)

Figure 5 .The association between eosinophil/ lymphocyte ratio, IgE and SCORAD index and the estimated marginal means with 95% confidence intervals (95%CI)

>4 years, disease duration: H1 hypothesis: There was anecdotal evidence (BF_{10}>1) that RDW resulted in anecdotal evidence for association with Disease duration (BF_{10}<0.9). H0 (null) hypothesis: There was moderate evidence that age, WBC, MCV, NC, EC, PC, PDW, MPV, NLR, ELR, ENR, PNR, RDW/P, E% and IgE (BF_{10}<0.3) were independent from disease duration, and anecdotal evidence for LC and PLR (BF_{10}<0.9) (Table 3).

All age groups, SCORAD index: H1 hypothesis: There was very strong evidence (BF>30) that ELR had correlation with SCORAD index, strong (BF>10) for EC and E%, and moderate (BF_{10}>3) for ENR. H0 (null) hypothesis: There was strong (BF_{10}<0.1) that evidence that WBC, NC, RDW, and PNR were independent from SCORAD index, moderate (BF_{10}<0.3) for age, MCV, LC, PC, PDW, MPV, NLR, RDW/P, and IgE, and aencdotal evidence for disease duration and PLR (BF<0.9) (Table 3).

As we subjected EC, ELR, E%, and ENR as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:0.3, X^2:12.1, X^2:0.6, and X^2:1.9, respectively (Loglikelihood ratio test). After eliminating insignificant factors with the backward elimination method, ELR (X^2:40.8) and ENR (X^2:3.2) remained as significant confounders (GLM, R^2:0.1). The graphic and the estimated marginal means are presented in Figure 6.



Eosinophil/Lymphocyte Ratio %	Mean SCORAD Index (95%CI)	Eosinophil/Neutrophil Ratio %	Mean SCORAD Index (95%CI)
3.8	25.5 (24.6-26.4)	4.78	26.4 (25.5-27.4)
5.7	26.0 (25.2-26.7)	9.42	26.7 (25.9-27.5)
11.1	27.3 (26.6-28.0)	17.48	27.1 (26.4-27.9)

Figure 6. The association between eosinophil/ lymphocyte ratio, eosinophil/neutrophil ratio and SCORAD index and the estimated marginal means with 95% confidence intervals (95%CI)

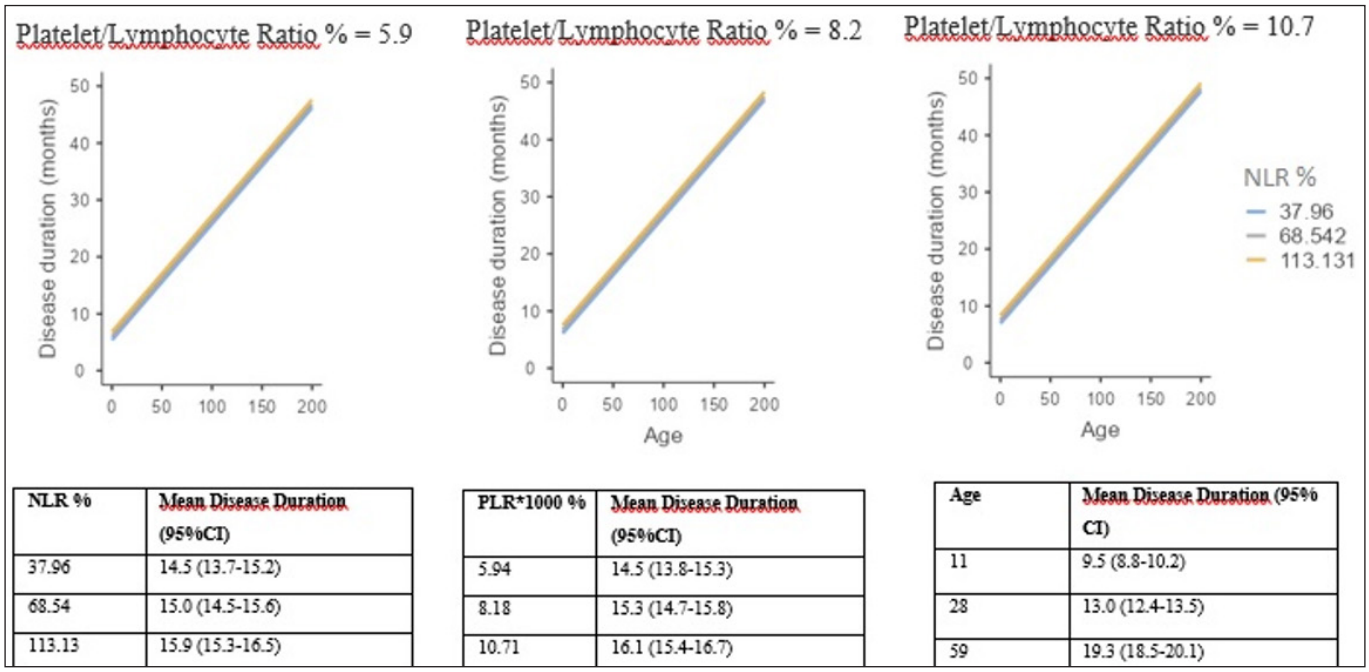
All age groups, disease duration: H1 hypothesis: There was extreme evidence (BF_{10}>100) that age, LC, NLR, and PLR had correlation with disease duration. H0 (null) hypothesis: There was moderate evidence that (BF_{10}<0.3) MCV, NC, EC, PC, PDW, ELR, and E% were independent from disease duration and anecdotal evidence (BF_{10}<0.9) for WBC, MPV, ENR, PNR, and IgE. Also, RDW gave no evidence (BF_{10}:1.01)

As we subjected age, LC, NLR, and PLR as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:301.7, X^2:0.3, X^2:10.4, and X^2:6.5, respectively (Loglikelihood ratio test). After eliminating insignificant factors with the backward elimination method, age (X^2:306.9), NLR (X^2:11.8) and PLR ((X^2:11.8)) remained as significant confounders (GLM, R^2:0.257). Each 1 month increase in age increased SCORAD index by 0.2 points (95%CI:0.18-0.23), 1% unit increase in NLR increased by 0.02 points (0.01-0.03), and 1% unit increase in PLR increased by 0.3 points (0.1-0.5). The graphic and the estimated marginal means are presented in Figure 7.

DISCUSSION

In the under-4-years group, there was strong evidence for E% correlation with AD, moderate evidence for EC and ENR, and anecdotal evidence for ELR, which were affected by eosinophils. In the multivariate analysis, E% was the significant confounder in our study.

In our study group, WBC, NC, PC, and RDW/P values were independent of AD disease. Similar to this result, a study reported that they did not find a correlation with AD regarding WBC, MCV, or RDW values; however, they reported increased MPV and decreased PDW in the AD group.[18] Another study (aged 14.03±13.17 months patient group) did not find significant differences regarding MPV, NLR, or



NLR %	Mean Disease Duration (95%CI)
37.96	14.5 (13.7-15.2)
68.54	15.0 (14.5-15.6)
113.13	15.9 (15.3-16.5)

PLR*1000 %	Mean Disease Duration (95%CI)
5.94	14.5 (13.8-15.3)
8.18	15.3 (14.7-15.8)
10.71	16.1 (15.4-16.7)

Age	Mean Disease Duration (95% CI)
11	9.5 (8.8-10.2)
28	13.0 (12.4-13.5)
59	19.3 (18.5-20.1)

Figure 7. The association between NLR (neutrophil/ lymphocyte ratio), PLR (platelet/ lymphocyte ratio) age and disease duration and the estimated marginal means with 95% confidence intervals (95%CI)

PLR, but they reported decreased PDW in the AD group,[19] and increased E% and decreased PDW were the significant confounder factors.[19] In another study (6.4+/-3.5 months), MPV and PLT were lower in the AD group, where WBC, NC, LC, EC, NLR, PLR, ELR, and RDW were not statistically different.[20]

In the older-4 years group, EC remained the only factor to differentiate AD from the control group with anecdotal evidence, and other parameters had moderate and anecdotal evidence for the independence hypothesis in our study group. In the all-age group, there was strong evidence for EC, ENR, and E% correlation with AD and moderate evidence for ELR, and in the multivariate analysis, the significant confounder was EC. Another considering finding was that NC, PC, NLR, PLR, and PNR were independent of AD, and MCV, RDW, MPV, and RDW/P were likely to be independent of AD (moderate evidence) in our study.

A study (patient group aged between 1 month and 18 years) reported that ELR could be a significant factor in AD diagnosis, similar to our results; however, they also reported higher NLR in the AD group.[21] However, another study (aged 5.6+/-2.8 years) reported no significant difference between the two groups regarding NLR.[22] Another study (60.0±46.5 months-aged patient group) reported increased NLR and PLR in AD but no difference regarding MPV.[6] Also, a study (7.3±3.5 years-aged patient group) reported increased NLR, PLR, EC, WBC, NC, and LC in the AD group, where they did not find any significant difference regarding RDW, MPV, and RPR.[23] Another study (2.8+/-2.8 years-aged patient group) reported increased PC, PNR, LC, and EC and decreased NC in AD, where MPV was not significantly different between the two groups.[24] An adults and adolescents-based study reported that E% and EC were higher in the AD group.[25]

There was strong evidence that NC, PC, NLR, PLR, and PNR were independent of AD and moderate evidence for WBC, MCV, LC, RDW, MPV, and RDW/P in our study. We think that as hemogram parameters are affected by the age of the children and as there is a lymphocyte predominancy in the under-4-years age group,[26] we could expect a wide range of different results regarding the age distribution of the study because of LC and the other parameters that LC affects.

A study (14.0±13.2 months-aged children) reported that MPV was higher in the severe-AD group, and PDW was lower in the mild-AD group.[19] However, another study (mean age 14 months) reported that MPV, PDW, and PLT/MPV did not correlate with AD severit.[18] Another study (mean age 6.4+/-3.5 months) reported a PLT and SCORAD correlation, where age, MPV, and IgE did not significantly alter between mild, moderate, and severe AD.[20] Likewise, another study (mean age 60.01±46.45 months) reported no significant correlation between NLR, PLR, and MPV with SCORAD.[6] Another study (mean age 8.1+/-4.8 months) reported a positive correlation with EC and E%.[27] There was anecdotal evidence that ELR correlated with the SCORAD index in our study, and other hemogram parameters were independent of SCORAD with moderate and anecdotal evidence under the 4-year age group.

In the older-4 years group, there was extreme evidence that serum total IgE, EC, ELR, and E% correlated with the SCORAD index and moderate evidence for ENR. ELR and total IgE remained significant confounders among these parameters. There was moderate evidence that age and other studied parameters were independent of the SCORAD index. In all age groups, we found strong evidence for ELR, EC, and E% and moderate for ENR that these parameters correlated with the SCORAD index. In the multivariate analysis, ELR and ENR were the significant confounders in our study. A study reported a positive correlation between serum total IgE levels, WBC, and EC with the SCORAD index.[28] Another study (Mean age 5.6+/-2.8 years) reported that NLR had a positive correlation with SCORAD, but age ELR, ENR, E%, and serum total IgE levels were not statistically different between 3 groups (mild, moderate, and severe AD).[22] Another study (mean age 2.8+/-2.8 years) reported a correlation between PLT, LC, and EC with SCORAD, where MPV, NLR, PNR, and NC did not correlate.[24]

A study (60.01±46.45 months) reported a correlation between NLR and SCORAD.6 However, we could not find evidence for a hemogram parameter correlating with disease duration in our under-4-year-old patient group. RDW had anecdotal evidence for correlating with disease duration.

In all patient groups, a study did not find any statistical difference between mild, moderate, and severe AD regarding disease duration,[22] which was consistent with our results that we did not find any evidence for the SCORAD index correlation with disease duration. Age, NLR, and PLR were significant confounders regarding disease duration in our study group. We linked this situation to decreasing lymphocytes by age[26] and topical steroids, which might increase neutrophil and platelet levels indirectly affecting the ratios. Also, we should notice that increasing age means increased disease duration.

There are conflicting data regarding hemogram parameters in the diagnosis and follow-up of AD; therefore, we aimed to present our results focusing on the evidence level. In addition, to our knowledge, since there is no data in the literature on which hemogram parameters are independent of AD diagnosis and follow-up, this study has been examining this hypothesis, and we think it will make significant contributions to the literature on this subject. One of the main limitations of our study is the inability to assess factors that could affect disease severity, such as comorbid conditions that can accompany atopic dermatitis.

CONCLUSION

Clinicians should consider that age is an independent factor for LC, which will affect hemogram parameters in AD diagnosis and severity indexes. The E% was the most significant parameter for AD diagnosis in the under-4 years age group, and EC in older-4 years and all age groups. NC, PC, NLR, PLR, and PNR were independent of AD in all age groups.

ELR had an anecdotal correlation with the SCORAD index in the under-4-year-old group. ELR and total IgE were significant confounders for SCORAD index correlation in the old group, whereas ELR and ENR were significant confounders in all age groups.

Disease duration correlated with age, NLR, and PLR, which are related to follow-up time and lymphocyte predominancy under four years old.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Lutfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023/514/246/23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab.* 2015;66 Suppl 1:8-16.
2. Pelc J, Czarnecka-Operacz M, Adamski Z. Structure and function of the epidermal barrier in patients with atopic dermatitis - treatment options. Part one. *Postepy Dermatol Alergol.* 2018;35(1):1-5.
3. Wang SS, Hon KL, Kong AP, Pong HN, Wong GW, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. *Pediatr Allergy Immunol.* 2014;25(1):30-35.
4. Ertam İ, Su Ö, Alper S, et al. The Turkish guideline for the diagnosis and management of atopic dermatitis-2018. Turkderm *Turkish Arch Dermatology Venereol.* 2018;52(1):6-23.
5. Peng W, Novak N. Pathogenesis of atopic dermatitis. *Clin Exp Allergy.* 2015;45(3):566-574.
6. Batmaz SB. Simple markers for systemic inflammation in pediatric atopic dermatitis patients. *Indian J Dermatol.* 2018;63(4):305-310.

7. Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. *J Clin Invest.* 2012;122(2):440-447.
8. Di Bari F. Atopic dermatitis and alpha-chemokines. *Clin Ter.* 2015;166(3):e182-e187.
9. Esaki H, Takeuchi S, Furusyo N, et al. Levels of immunoglobulin E specific to the major food allergen and chemokine (C-C motif) ligand (CCL)17/thymus and activation regulated chemokine and CCL22/macrophage-derived chemokine in infantile atopic dermatitis on Ishigaki Island. *J Dermatol.* 2016;43(11):1278-1282.
10. Leonardi S, Cuppari C, Manti S, et al. Serum interleukin 17, interleukin 23, and interleukin 10 values in children with atopic eczema/dermatitis syndrome (AEDS): association with clinical severity and phenotype. *Allergy Asthma Proc.* 2015;36(1):74-81.
11. Kalelioglu T, Karamustafalioglu N, Emul M, et al. Detecting biomarkers associated with antipsychotic-induced extrapyramidal syndromes by using machine learning techniques. *J Psychiatr Res.* 2023;158:300-304.
12. Ünal Ç, Tunçer G, Çopur B, et al. Clinical and inflammation marker features of cancer patients with COVID-19: data of İstanbul, Turkey multicenter cancer patients (2020-2022). *Curr Med Res Opin.* 2023;39(7):987-996.
13. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther.* 2013;11(1):55-59.
14. Inokuchi-Sakata S, Ishiuji Y, Katsuta M, et al. Role of eosinophil relative count and neutrophil-to-lymphocyte ratio in the assessment of severity of atopic dermatitis. *Acta Derm Venereol.* 2021;101(7):adv00491.
15. Hon KL, Wang SS, Pong NH, Leung TF. Circulating immunoglobulins, leucocytes and complements in childhood-onset atopic eczema. *Indian J Pediatr.* 2013;80(2):128-131.
16. Altaş U, Ünlü DA, Güllüce H, et al. Evaluation of the relationship between laboratory parameters and allergy tests in children with atopic dermatitis: laboratory parameters and allergy tests in children with atopic dermatitis. *Chron Precis Med Res.* 2023;4(2):168-171.
17. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol.* 2007;157(4):645-648.
18. Topal E, Celiksoy MH, Catal F, Karakoç HT, Karadağ A, Sancak R. The platelet parameters as inflammatory markers in preschool children with atopic eczema. *Clin Lab.* 2015;61(5-6):493-496.
19. Gayret ÖB, Erol M, Şener A, Nacaroğlu HT. Neutrophil-lymphocyte ratio and the platelet parameters as biomarkers of atopic dermatitis severity in children. *Iranian Red Crescent Med J.* 2019;21(7):e91594.
20. Sanli Gunes H, Ozkars MY, Ipek S. The evaluation of mean platelet volume in infants with atopic dermatitis. *Ann Med Res.* 2019;26(5):899-903
21. Oztas Kara R, Solak B. Assessment of venous blood leukocyte profiles and immunoglobulin e levels in atopic dermatitis patients. *Dermatitis.* 2022;33(6S):S69-S72.
22. Dogru M, Citli R. The neutrophil-lymphocyte ratio in children with atopic dermatitis: a case-control study. *Clin Ter.* 2017;168(4):e262-e265.
23. Jiang Y, Ma W. Assessment of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in atopic dermatitis patients. *Med Sci Monit.* 2017;23:1340-1346.
24. Akcal O, Taskırdı İ. Do platelet count and mean platelet volume have a predictive role as a marker in children with atopic dermatitis?. *Indian J Dermatol.* 2022;67(6):688-692.
25. Hu Y, Liu S, Liu P, Mu Z, Zhang J. Clinical relevance of eosinophils, basophils, serum total IgE level, allergen-specific IgE, and clinical features in atopic dermatitis. *J Clin Lab Anal.* 2020;34(6):e23214.
26. Zühre KA. Tam kan sayım çıktılarının yorumlanması. *Dicle Med J.* 2013;40(3):521-528.
27. Cansever M, Oruç Ç. What plays a role in the severity of atopic dermatitis in children?. *Turk J Med Sci.* 2021;51(5):2494-2501.
28. Kuo HC, Chu CH, Su YJ, Lee CH. Atopic dermatitis in Taiwanese children: The laboratory values that correlate best to the SCORAD index are total IgE and positive Cheddar cheese IgE. *Medicine (Baltimore).* 2020;99(30):e21255.