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The peripheral blood inflammatory patterns in the control levels of asthma in children

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ABSTRACT

Objective: Asthma is the most common chronic inflammatory disease of childhood, but there are no useful and easily accessible laboratory tests routinely used in the diagnosis and follow-up of this disease in children. Therefore, this study aimed to investigate the roles of white blood cell (WBC) count, platelet count, mean platelet volume (MPV), and eosinophil percentage as full blood count inflammatory markers in evaluating the control level and follow-up of asthma in the pediatric age group.

Methods: A retrospective review of patient records and files of 3,580 patients diagnosed with asthma at the University of Health Sciences in Ankara, Turkey was performed. Patients who met inclusion/exclusion criteria were divided into two groups based on the asthma control level: controlled and uncontrolled. Laboratory data were compared according to the asthma control levels, drug use status, and atopy status of the patients.

Results: A total of 348 patients between 4 and 18 years of age, who were followed-up with the diagnosis of asthma, were included in this study. A significant difference was found between the controlled and uncontrolled groups of asthma patients in terms of the eosinophil percentage (mean $\pm$ SD, respectively; 3.493 ± 2.24 ; 4.992 ± 3.43 ; $p = .003$). When patients were grouped according to their asthma control levels and atopy status, only the eosinophil percentages were different in the logistic regression analysis (odds ratio = 1.276, 95% confidence interval = 1.113–1.462).

Conclusion: Our study showed that the percentage of eosinophils can be used as an asthma control parameter, but additional prospective studies would be desirable to confirm our results.

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Introduction

Asthma is the most common chronic inflammatory disease of childhood, and the interaction between genetic and environmental factors contributes to its pathogenesis (1). The atopic clinical form of bronchial asthma (BA) is the most well-known because of its relationships with allergic disease history and reversible airway obstruction (2–4). When allergens contact the airway epithelium, they disrupt the integrity of the epithelium as a physical barrier and trigger the release of cytokines, uric acid, adenosine triphosphate, colony-stimulating factor, and other substances (5,6). These agents can cause the activation of natural immune cells (dendritic cells, granulocytes, and monocytes) in the bloodstream, eventually leading to lung inflammation (4,6–8). Asthma severity also

affects the functioning of peripheral blood cells. In its severe form, the number of granulocytes in the blood and bronchoalveolar lavage and the expression profile of proinflammatory cytokines are changed (8–13). In patients with BA, the peripheral blood granulocytes have a higher metabolic response than healthy donor cells and a higher susceptibility to bacterial or viral agents (14–18). Excessive granulocyte activity is considered to be a complication and exacerbation factor in asthma cases (19).

Although many proinflammatory cytokines and innate immune cells are involved in the pathogenesis of asthma, there are no useful and easily accessible laboratory tests that can be used routinely in the diagnosis and follow-up of the disease. To address this challenge, several complete blood count parameters, such as white blood cell (WBC) count, presence of

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eosinophilia, platelet (PLT) count, and mean PLT volume (MPV), have been studied to determine the asthma phenotype, evaluate recurrent hospitalization incidences and response to corticosteroid treatment, and determine the severity of asthma and the asthma attack. In one study, high WBC count levels were observed in uncontrolled asthma cases (20). In another study, the PLTs were shown to have effects on bronchoconstriction, airway inflammation, the bronchial response, and remodeling in asthma (21). In chronic inflammatory conditions in which the production of PLTs increases, the MPV has been shown to increase, depending upon the rise in young PLTs (22). More recently, increased blood eosinophil levels in adult asthmatic patients have been found to be related to the recurrent hospitalization incidence (23).

For follow-up of the disease in pediatric patients, physical examination and pulmonary function tests are used as objective parameters, but they may be compromised due to varying degrees of compliance by children. Noninvasive tests, such as asthma control questionnaires and asthma control tests (ACTs), offer subjective data in patient follow-up as they are dependent on patients' or parents' input. Therefore, we aimed to investigate the availability of blood parameters as objective data for the assessment of asthma control levels in children. In this context, our study aimed to investigate the complete blood count parameters, including the WBC count, eosinophilia percentage, PLT count, and MPV, at the level of asthma control.

Materials and methods

From January 2011 through September 2015, the patient records and files of 3,580 patients who received a diagnosis of asthma at the Department of Pediatric Allergy and Immunology at the University of Health Sciences in Ankara, Turkey were screened retrospectively. The diagnoses were made in accordance with the Global Strategy for Asthma Management and Prevention Guidelines developed by the Global Initiative for Asthma (GINA). In patients under five years of age, the Martinez modified asthma predictive index was used to diagnose asthma (24).

The exclusion criteria for the study were as follows: a history of infection and/or acute asthma attack and need for systemic corticosteroid and/or montelukast use in the last three months, children having any chronic infection, inflammatory disease, autoimmune disease, endocrine system disease, gastrointestinal system disease, kidney disease, urinary tract disease,

hematological, metabolic, neurological disease and/or mental motor retardation, as well as any medication for chronic diseases (except for inhaled steroids and/or short – long-acting Beta2-agonists for asthma control), and children who smoke.

In addition to patients excluded for these reasons ($n=1,963$), asthmatic patients with atopic diseases, such as concomitant allergic rhinitis ($n:853$), eczema ($n:315$), and food allergy ($n:101$) were also excluded (Figure 1).

In our department, complete blood counts (performed using an LH 780 Hematology Analyzer; Beckman Coulter, Brea, CA) and pulmonary function tests (performed using a Zan 100 Spirometer; nSpire Health GmbH, Oberthulba, Germany) are routinely requested during the outpatient checkups of asthmatic patients. For those children meeting our study criteria, the WBC count ($10^3/\text{microliters}$), PLT count ($10^3/\text{microliters}$), MPV (femtoliter), eosinophilia percentage (%), forced expiratory volume in 1s (FEV1) (%), forced vital capacity (FVC) (%), FEV1/FVC (%), and regular or irregular drug use were screened by the same investigators (NE and OC) from our hospital patient registry system, and the results were recorded. Also, the detailed demographic characteristics and symptom starting ages of these patients were determined. If sufficient data could not be obtained from the hospital registry system, the patient's parents were called or invited to the clinic to complete the missing data.

Our study subjects were divided into two main groups: controlled and uncontrolled asthma. The degree of asthma control was assessed using the Asthma Control Test (ACT), which consists of five questions regarding daytime and nighttime asthma symptoms, rescue medication use, and daily activity impairment level due to asthma. An ACT score of 25 points was considered to be full control, 20–24 points indicated partial control, and <20 points was uncontrolled. To determine if the asthma was under control, the ACT score was measured at least three months after the last exacerbation. For this study, the partially controlled asthmatic patients were included in the uncontrolled asthma group. All of the asthmatic patients were divided into subgroups based on their drug use (regular and irregular subgroups) and history of atopy (atopic asthma and non-atopic asthma subgroups). The regular medication group consisted of children who were using daily, inhaled steroids and/or short/long-acting Beta2-agonists for the last three months, at doses determined according to their age and asthma severity (1). Regular drug use by our

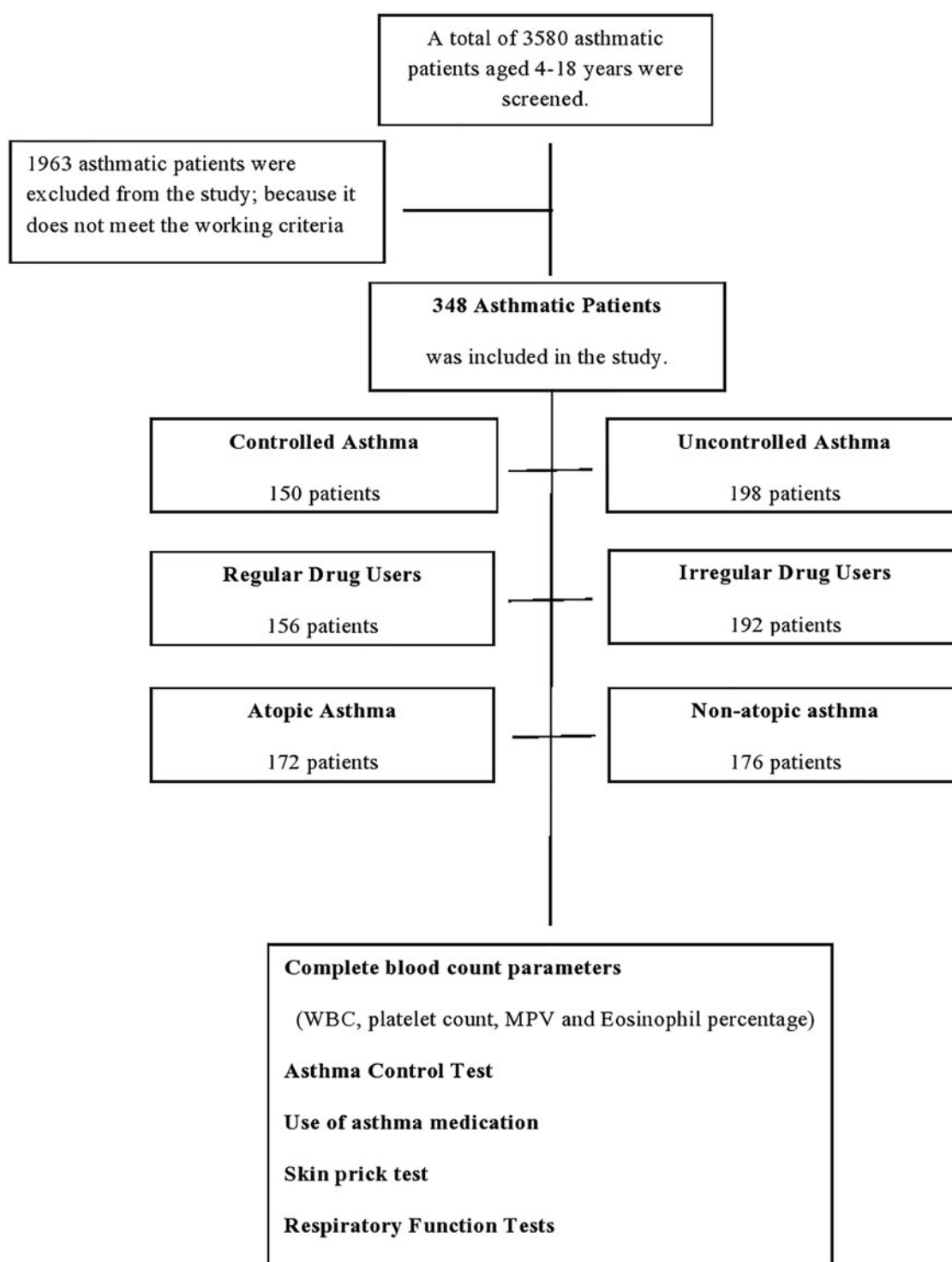


Figure 1. The flow chart of the study.

patients was followed using two methods: those who used a drug in the numerator brought their medication with them when they came to each visit, and the drug dose count was done by the physician. Patients who used non-numerator drugs were given a drug use control schedule and were asked to bring it with them when they came to each visit.

Atopy was classified as at least one positive reaction to an allergen sensitivity using the skin prick test (SPT) with a clinical correlation. The SPTs were applied to the anterior surface of the forearm when it was appropriate to test the subject (i.e. not taking antihistamines). SPTs for the following common aero-allergens were performed using an SPT device

(Stallerpoint, Antony, France): *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, a mixture of grass pollens (*Lolium perenne*, *Dactylis glomerata*, *Phleum pratense*, *Anthoxanthum odoratum*, *Poa pratensis*, *Festuca elatior*, *Agrostis vulgaris*, *Holcus lanatus*, *Cynodon dactylon*, *Avena sativa*, *Avena fatua*, and *Lotus corniculatus*), *Artemisia vulgaris*, *Parietaria officinalis*, a mixture of grain pollens (oats, wheat, barley, and corn), a mixture of tree pollens (*Acer pseudoplatanus*, *Aesculus hippocastanum*, *Robinia pseudoacacia*, *Tilia platyphyllos*, and *Platanus vulgaris*), Cupressus, Betulaceae, Salicaceae, *Alternaria alternaria*, Cladosporium, cockroaches (*Blattella germanica*), latex, and cat and dog dander (Allergopharma GmbH & Co. KG, Reinbek, Germany). Histamine (10 mg/ml) and physiological saline were used as positive and negative references, respectively. The skin reactions were evaluated 20 min after the SPT. A positive reaction was characterized as a wheal diameter of ≥ 3 mm. If the results were inconsistent with the patient's allergic complaints, serum specific IgE tests for either perennial allergens (mites, molds, and animal epithelia) or seasonal allergens (grass pollen, weed pollen, and early-middle-late flowering tree pollens) were performed to show the presence of atopy.

First and foremost, in this study, the relationships between the asthma control level and the WBC count, PLT count, MPV, and eosinophilia percentage were evaluated. Second, the effects of regular and irregular drug use and the atopy status based on the inflammatory parameters of a complete blood count were evaluated in asthmatic patients.

The study was approved with the permission of the Dr. Sami Ulus Education Planning Commission (Sept 15, 2015; approval number: 73799008).

Statistical analysis

IBM SPSS Statistics for Windows Version 23.0 (IBM Corp., Armonk, NY) was used for the statistical analysis of the findings obtained in this study. Descriptive statistical methods (mean, standard deviation, and frequency) were used for evaluating the data, and the quantitative data were compared. The independent samples *t*-test was used for the comparisons of the parameters with normal distributions, and the Mann–Whitney *U* test was used for the comparisons of the parameters that did not show normal distribution. Statistical significance was accepted as a *p* value $< .05$. A logistic regression analysis was used to evaluate the use of the data as a marker.

Results

A total of 348 patients between the ages of 4 and 18 who did not have an acute asthma attack, and/or did not use any systemic steroids in the preceding three months were enrolled in the study. The mean age ($\pm$ standard deviation) of these patients was 8.77 ± 2.83 years old. The study group consisted of 220 (63.2%) males. The demographic characteristics of the patients are summarized in Table 1.

There were no statistically significant relationships between the age of the patients and the age at which their asthma symptoms started and whether the asthma was under control ($p = .829$ and $p = .322$, respectively).

The FVC percentage measurements of the children with and without asthma control ($p > .05$) are shown in Table 2. There were no statistically significant correlations between the FEV1 values and the WBC, PLT, and eosinophil values, but there was a negative correlation with the MPV variable ($r = -.234$).

Patients with uncontrolled asthma had higher WBC counts than patients with asthma control, and the difference was statistically significant ($p = .001$) (Table 3). The Hosmer–Lemeshow test results were $X^2 = 9.35$ ($p = .314$). The fact that the result of this test was insignificant ($p > .05$) indicates that the model-data fit was adequate. When the WBC and eosinophil predictor variables were analyzed together, the asthma control explained 20.7% of the variance in the predicted variable (Nagelkerke $R^2 = 0.207$). A one-unit increase in the WBC count did not lead to a change

Table 1. Demographic characteristics of asthmatic children.

Total number of patients (N, %)	348 (%100)
Gender (N, %)	
Female	128 (%36.8)
Male	220 (%63.2)
Age (years) (mean $\pm$ SD ^a)	8.77 $\pm$ 2.83
Age of onset of asthma symptoms (years $\pm$ SD ^a)	3.84 $\pm$ 3.2
Atopy (N, %)	
Yes	172 (%49.4)
No	176 (%50.6)
Regular drug use (N, %)	
Yes	156 (%44.8)
No	192 (%55.2)
Asthma control level (N, %)	
Controlled	150 (%43.1)
Uncontrolled	198 (%56.9)

N: number of patients, mean $\pm$ SD: mean standard deviation.

^aIndependent samples *t*-test.

Table 2. The results of respiratory function tests according to control of the disease asthma in children with asthma.

	Asthma control level		* <i>p</i>
	Controlled	Uncontrolled	
Fev1% (mean $\pm$ SD)	97 $\pm$ 13,012 (13.35)	92.38 $\pm$ 15,582 (13.35)	.058
Fvc% (mean $\pm$ SD)	89.74 $\pm$ 12,825 (13.35)	87.24 $\pm$ 15,265 (13.35)	.323

Table 3. The relation of complete blood parameters with asthma control in children with asthma.

	Asthma control		^a <i>p</i>
	Controlled	Uncontrolled	
Wbc ^b (mean ± SD)	7074.40 ± 1543.14	8140.91 ± 2085.79	.001
Platelet count ^c (mean ± SD)	308946.67 ± 65573.74	327909.09 ± 73613.45	.150
MPV ^d (mean ± SD)	7.763 ± 0.82	7.858 ± 0.81	.677
Eosinophils (%) (mean ± SD)	3.493 ± 2.24	4.992 ± 3.43	.003

^aMann-Whitney *U* test.^bWhite blood cells (10³/microlitre).^cPlatelet count (10³/microlitre).^dMean platelet volume (femtolitre).

Mean ± SD: average standard deviation.

Table 4. Change of full blood parameters by drug use in children with asthma.

	Regular drug use		^a <i>p</i>
	Yes	No	
Wbc ^b (mean ± SD)	7603.59 ± 2050.422	7744.27 ± 1853.957	.476
Platelet count ^c (mean ± SD)	311820.51 ± 68831.008	26166.67 ± 71886.851	.277
MPV ^d (mean ± SD)	7.795 ± 0.7300	7.834 ± 0.8908	.817
Eosinophils (%) (mean ± SD)	4.788 ± 3.0077	3.986 ± 3.0777	.016

^aMann-Whitney *U* test.^bWhite blood cells (10³/microlitre).^cPlatelet count (10³/microlitre).^dMean platelet volume (femtolitre).

Mean ± SD: average standard deviation.

Table 5. The relation of complete blood parameters with atopy in children with asthma.

	Atopy		^a <i>p</i>
	Yes	No	
Wbc ^b (mean ± SD)	7305.47 ± 1917.01	8048.41 ± 1901.99	.008
Platelet count ^c (mean ± SD)	307906.98 ± 61250.42	331295.45 ± 77453.30	.056
MPV ^d (mean ± SD)	7.870 ± 0.89	7.765 ± 0.74	.370
Eosinophils (%) (mean ± SD)	4.503 ± 3.12	4.192 ± 3.01	.368

^aMann-Whitney *U* test.^bWhite blood cells (10³/microlitre).^cPlatelet count (10³/microlitre).^dMean platelet volume (femtolitre).

Mean ± SD: average standard deviation.

in the odds of uncontrolled asthma [odds ratio (OR) = 1.000, 95% confidence interval (CI) = 1.000–1.001]. In comparison, a one-unit increase in the eosinophil variable resulted in a 27.6% increase in the odds of uncontrolled asthma (OR = 1.276, 95% CI = 1.113–1.462). The PLT and MPV variables were not included in the model because they did not cause a significant difference in the model compliance.

A significant difference was found between the controlled and uncontrolled groups of asthma patients in terms of the eosinophil percentage (values as mean ± SD, respectively; 3.493 ± 2.24; 4.992 ± 3.43; *p* = .003). In addition, there was a statistically significant relationship between the age of onset of symptoms and regular drug use (*p* = .047). The eosinophil percentages were higher in the asthmatic patients with regular medication than in the patients without drug use (*p* = .016) (Table 4). However, in the logistic regression analysis, the changes in WBC, PLT, MPV,

and eosinophil values did not make a significant difference with regard to drug use (*p* > .05).

There were statistically significant relationships between the age of the patients and the age of onset of the symptoms and atopy (*p* = .047 and *p* = .001, respectively). When children with asthma were evaluated for the presence of atopy, the number of WBCs was found to be statistically higher in those children without atopy (*p* = .008) (Table 5). When the logistic regression analysis for the atopy relationship was performed, the predictor variable explained 4.9% of the variance (Nagelkerke *R*² = 0.049), and a one-unit increase in the WBC count did not lead to a change in the OR of the presence of atopy (OR = 1.000, 95% CI = 1.000–1.000).

Discussion

There are no objective parameters for the evaluation of asthma control, and while pulmonary function tests

and peak expiratory flow (PEF) meter follow-ups are still in use, they are usually patient dependent. To address this challenge, we evaluated the availability of the complete blood count inflammatory parameters, such as the WBC count, PLT count, MPV, and eosinophil percentage, as inexpensive and easily accessible objective parameters for the follow-up of asthma patients. The results of our study verified our hypothesis that patients with uncontrolled asthma had higher eosinophil percentages when compared to patients with asthma under control. Therefore, we suggest the use of the eosinophil percentage as a marker for monitoring asthmatic children.

In our study group, no statistically significant differences were found between the PLT count, MPV, and eosinophilia percentages in the children with and without atopy. Therefore, these data do not contribute to the differentiation between atopy and non-atopy. Yet, when the advanced statistical analysis was performed, according to the Kruskal–Wallis H test, there was a significant difference in eosinophil values between the uncontrolled asthma patients with atopy and the non-atopic controlled asthma group. When the control group was compared with the uncontrolled group, regardless of atopy status, the eosinophil value was higher in the uncontrolled patients.

Based on the results of our study, the eosinophil value is significant in distinguishing between controlled and uncontrolled asthma. In the logistic regression analysis, we showed that a one-unit increase in the eosinophil percentage led to a 27.6% increase [(1.276–1) 0.100] in the odds of uncontrolled asthma (OR = 1.276, 95% CI = 1.113–1.462). Based on these results, the high percentage of eosinophils supports the notion that it can be used as a parameter for predicting the clinical course independently of atopy. Price et al. reported that patients with asthma and blood eosinophil counts greater than 400 cells per μL have a 42% higher incidence rate of severe asthma exacerbations, and 28% higher rate of acute respiratory events, and have poorer asthma control than those with less than 400 cells per μL . The authors suggest that the assessment of blood eosinophils could add predictive value to a traditional control-based assessment using the GINA criteria (25). Nadif et al. reported that high eosinophilia levels (EOShi = 250 eosinophils/mm analyzed three times) were positively correlated with uncontrolled asthma in a cross-sectional analysis of adult asthmatic patients. After adjusting for age and sex, the associations were found to be significant in the participants without respiratory infections over the previous four weeks, those

with allergic sensitization, and in non/ex-smokers. However, it was shown that these associations did not remain significant after further adjustment for current smoking status and inhaled corticosteroid (ICS) treatment (26). Kerkhof et al. conducted a study that evaluated the relationship between the blood eosinophil count and the readmission risk of asthmatic patients. That study established the fact that a high blood eosinophil count in the year before an asthma-related hospitalization was associated with an increased risk of readmission within the following year (23). Our study aligns with the literature as it also supports the role of blood eosinophilia as a potential biomarker in determining the control level of asthma. Similar to our study, Ferguson et al., in their recent trial, prespecified subgroup analysis to investigate the relationship between blood eosinophil counts and treatment effects on lung function and exacerbation rates (27).

In our study, in the uncontrolled asthmatic group, the WBC count was higher than that of the controlled group. However, as a result of the regression analysis, it was determined that a one-unit increase in the WBC count did not cause any changes in the odds of uncontrolled asthma. In the logistic regression analysis of the effect of regular drug use on the number of WBCs, there was shown to be no contribution. Nacaroglu et al. compared asthmatic children during their asymptomatic and acute episodes with healthy controls (64% atopic and 36% non-atopic) according to their complete blood count parameters (28). They found that the total leukocyte levels of the children with asthma in both the acute attack and asymptomatic period cases were higher than those in the control group; however, they did not evaluate this parameter using an advanced statistical method. In the Epidemiological study on the Genetics and Environment of Asthma, Nadif et al. found that the association between a high neutrophil inflammation level and asthma control remained significant after further adjustment for the eosinophil count (OR = 2.95, 95% CI = 1.74–5.00 and OR = 3.08, 95% CI = 1.42–6.69 for partly controlled and uncontrolled asthma, respectively). Associations between neutrophil inflammation and poor asthma control (partly controlled or uncontrolled versus controlled) were consistently observed in the participants without respiratory infections over the previous four weeks and after stratification according to current smoking status or ICS treatment (26).

We found that the total leukocyte count in children with non-atopic asthma was also higher than that in the atopic asthmatic patients in our study, but this

value was within normal limits for children aged 4–18 years old. When the logistic regression analysis was performed for the atopy relationship, the WBC predictor variable explained 4.9% of the variance in the predicted variable of atopy (Nagelkerke $R^2 = 0.049$). In other words, a one-unit increase in the WBC did not cause a change in the OR of atopy (OR = 1.000, 95% CI = 1.000–1.000). Recently, in Tikhonova et al.'s developmental study of a biomarker that could be used in the follow-up of adult atopic BA patients, they found that the leukocyte count and blood cell ratios (monocytes, eosinophils, and segmented neutrophils) of atopic BA patients during their asymptomatic period were not different from those of the healthy controls (29). Similarly, in our study, there was no difference in the percentage of eosinophils between the atopic and non-atopic patients.

We detected that asthma was under control in 43.1% of the 348 pediatric patients who met the study criteria for asthma. In the literature, it has been reported that the pulmonary function tests of uncontrolled asthmatic patients are more variable than in controlled patients (1). In our study, we found no statistically significant differences in the FEV1, FVC, and FEV1/FVC percentages between the controlled and uncontrolled asthmatic groups, in accordance with the literature; however, during the clinical follow-up of patients with asthma, we observed that patients in the pediatric age group had greater difficulty in expressing themselves and defining individual health changes than adults typically do. There were no statistically significant correlations between the FEV1 values and the WBC, PLT, and eosinophil values, but there was a negative correlation with the MPV variable ($r = -.234$). Similarly, in the study by Nacaroglu et al., the MPV values were only higher during the asymptomatic period in the cases of severe persistent asthma when compared to the other asthma groups (mild and moderate asthma and asthma attack groups) ($p = .025$) (28).

In our study, no significant differences were recorded according to the atopy and control status of the children when the thrombocyte count and MPV values were examined. Tuncel et al. reported that the MPV values of asthmatic patients in both acute asthmatic attacks and asymptomatic periods showed no difference when compared to the healthy controls ($p > .05$). The presence of atopy, infection, eosinophilia, and elevated immunoglobulin E and the severity of the acute asthmatic attack did not influence the mean PLT volume values (30). Nacaroglu et al. found that the PLT counts of children with asthma, during both acute

attacks and asymptomatic periods, were statistically significantly higher than in the control group ($p = .001$) (28). However, in their study, the MPVs of the patients with asthma in both cases were not statistically different from those of the healthy control group. Moreover, they showed that various factors, such as immunotherapy, infection, atopy, asthma severity, eosinophil count, and the severity of the asthma exacerbation, did not impact the MPV values of asthma patients during both exacerbation and remission.

The strengths of our study were the inclusion of patients who were regularly followed up in our clinic and were evaluated continuously for comorbid diseases. The interpretation of our cases according to the subgroups may help illuminate the contradictory results published in the literature.

There are several limitations to our study. It was a retrospective and cross-sectional study, it lacked a healthy control group, and the frequency and number of asthma attacks of the study patients were unreported. Another limiting factor is the fact that we did not mention the patients with uncontrolled asthma who suffered an acute asthma attack despite changing the drug dose.

Conclusion

We believe that the eosinophil percentage in pediatric asthma cases may be used as an effective marker in the follow-up, treatment, and control of asthma. However, it is advisable to confirm the same parameters with additional prospective studies in order to obtain more precise results.

Disclosure statement

The presented work was conducted at Health Sciences University, Dr. Sami Ulus Obstetrics, Children's Health and Diseases Training and Research Hospital, Department of Pediatric Immunology and Allergy, Ankara/Turkey.

Dr. Orhan, Dr. Nazlı, and Dr. İlknur confirmed that they have no conflicts of interest or financial ties to disclose.

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