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Association of serum periostin levels with clinical features in children with asthma

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Abstract

Background: The aim of this study was to investigate the association of serum periostin levels with clinical features in children with asthma.

Methods: Children with physician-diagnosed asthma who attended regularly to an outpatient pediatric allergy and asthma center were enrolled in the study along with control subjects. Asthma severity and control status of the patients were evaluated according to the recent GINA guidelines.

Results: A total of 158 children (125 with asthma and 33 age- and sex-matched control subjects) with a median age of 10.2 years (range 5.9-17.0) were enrolled. Asthma severity was mild in 41 (32.8%), moderate in 63 (50.4%), and severe in 21 (16.8%) children. Children with asthma had significantly higher periostin levels than controls (53.1 ± 13.1 vs 43.0 ± 11.2 ng/mL, $P < .001$). The mean serum periostin levels in children with severe asthma (63.8 ± 10.8) were significantly higher than in children with moderate asthma (53.3 ± 12.7) and mild asthma (47.4 ± 11.1) ($P < .001$). Results of multivariable logistic regression analysis demonstrated an association between serum periostin levels and asthma severity in children (OR, 1.10; 95% CI, 1.04-1.15, $P < .001$). When analyzed for the best cut-off value with the highest combined sensitivity and specificity, a cut-off value of 52 ng/mL for serum periostin level was obtained with sensitivity, specificity, PPV, and NPV of 100%, 50%, 29%, and 100%, respectively.

Conclusion: Although serum periostin levels are higher in children with asthma, its diagnostic role in identifying children with severe asthma is limited.

KEYWORDS

asthma, biomarker, children, periostin, severe asthma

1 | INTRODUCTION

Asthma is one of the most common chronic diseases of childhood, and type 2 airway inflammation is the major feature of the disease.

The emergence of biomarkers associated with the underlying airway inflammation is an active research area in adults and children. Up to date, only a limited number of biomarkers have been routinely used in daily clinical practice in patients with asthma and there is still a

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need for a reliable biomarker not only for the prediction, diagnosis, or follow-up of asthma, but also as a candidate target for the treatment options in the future.¹

Periostin is an extracellular matrix protein expressed in fibroblasts and airway epithelial cells and has emerged as a novel biomarker in the pathogenesis of T helper 2-type allergic diseases in the last years. It plays a key role in development and repair within the biologic matrix of the lung, and interacts with other extracellular matrix proteins to regulate the composition of the matrix in the lung. Its association with airway remodeling and airflow limitation has been highlighted in several adult studies.² However, there are limited studies with inconclusive data about the relationship of periostin with severity or inflammatory pattern in children with asthma.³

The aim of this study was to investigate the association of serum periostin levels with several clinical features in children with asthma.

2 | METHODS

2.1 | Study design, setting, and participants

Children aged 6-17 with physician-diagnosed asthma who were regularly followed up in the Pediatric Allergy and Asthma Unit of Gulhane School of Medicine between 2014 and 2017 were enrolled in the study along with age- and sex-matched control subjects without any physician-diagnosed asthma who admitted to outpatient department of our unit for various symptoms. The children in the control group had no history of wheezing or infection during the last 4 weeks before the study enrollment.

Asthma was defined as current symptoms (wheeze and cough) and positive bronchodilator responsiveness (improvement of FEV₁ by 12% or more following administration of 200 mcg salbutamol), and/or a positive response to a trial of therapy with inhaled or oral corticosteroids.⁴ Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations in the last year according to GINA guidelines. "Mild asthma" is asthma that is well controlled with Step 1 or Step 2 treatment; "moderate asthma" is asthma that is well controlled with Step 3 treatment; and "severe asthma" is asthma that requires Step 4 or 5 treatment. Asthma control status of the patients was also evaluated according to GINA guidelines.⁴ Patients with an acute exacerbation of asthma requiring systemic corticosteroids during the previous 3 months and other known systemic disorders were excluded.

The study was approved by the institutional review board of Gulhane School of Medicine, and written informed consent was obtained from parents.

2.1.1 | Study measurements

Skin tests

All children underwent skin prick testing (SPT) to common aeroallergens for our region,⁵ including house-dust mites (*Dermatophagoides*

Key Message

Serum levels of periostin, which has emerged as a novel biomarker in the pathogenesis of T helper 2-type allergic diseases in the last years, are higher in children with asthma; however, its role in identifying children with severe asthma is limited.

pteronyssinus and *Dermatophagoides farinae*), grass pollen mix (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, and *Avena eliator*), weed pollen mix (*Artemisia*, *Urtica*, *Taraxacum*, *Plantago*), tree pollen mix (*Alnus glutinosa*, *Corylus avellana*, *Populus alba*, *Ulmus minor*, *Betula alba*), molds (*Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*), and animal dander (cat and dog). Histamine (10 mg/mL of histamine phosphate) and 0.9% saline were used as positive and negative controls, respectively. Weal 3 mm greater than negative control was considered a positive reaction.

Anthropometric measures

Children were weighed wearing minimal clothes and without shoes. Height was rounded to the nearest 0.1 cm, and weight was rounded to the nearest 0.1 kg. Subsequently, BMI (body mass index) was calculated as weight (kilograms) divided by height (meters)-squared. BMI z-scores of participants were also calculated.⁶

Blood eosinophil counts and serum total IgE levels

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leukocyte measurements. Total serum IgE level was measured using ImmunoCAP (Phadia AB, Uppsala, Sweden).

Serum periostin levels

Measurement of serum periostin levels was made with an enzyme-linked immunosorbent assay (ELISA) at Shino-Test (Kanagawa, Japan), as described previously.⁷

Pulmonary function tests

Pulmonary function tests were performed using Zan 100 spirometer (nSpire Health, Oberthulba, Germany) according to the recommendations by the European Respiratory Society.⁸ FEV₁, FEV₁/FVC, and FEF₂₅₋₇₅ were recorded.⁹

2.2 | Statistical analysis

Analyses were performed using SPSS Statistics v21.0 (IBM, Chicago, IL, USA). Normally distributed continuous data were expressed as mean and standard deviation, and non-normally distributed continuous data as median and inter-quartile ranges (IQR). Group comparisons were carried out using Student's *t* test, Mann-Whitney *U* test, ANOVA, or Jonckheere-Terpstra test as appropriate for the

continuous, and the chi-square test or Fisher's test for categorical variables. The correlation coefficients between serum periostin level and other clinical variables were determined using Spearman's rank correlation coefficient. Association of severe asthma classes with clinical variables was examined using regression models adjusted for potential confounders, including age, aeroallergen sensitization, BMI z-score, blood eosinophil count, and serum periostin level. The odds ratio (OR) and 95% confidence interval (CI) were reported. The diagnostic performances of serum periostin levels to identify children with severe asthma were determined by receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the selected cut-off point. A P level $<.05$ was considered significant.

3 | RESULTS

3.1 | Descriptive statistics

A total of 158 children (125 with asthma and 33 age- and sex-matched control subjects) with a median age of 10.2 years (range 6.0-17.0) were enrolled. Characteristics of the study groups are presented in Table 1. There were no significant differences between the children with asthma and control groups in terms of age, sex, body mass index, and total IgE levels. The prevalence of aeroallergen sensitization was significantly higher in children with asthma, and they had significantly higher blood eosinophil counts. Children with asthma had significantly higher periostin levels than controls (53.1 ± 13.1 vs 43.0 ± 11.2 ng/mL, $P < .001$) (Figure 1A).

3.2 | Clinical features of children with asthma

Clinical characteristics of the children with asthma according to asthma severity are presented in Table 2. Of these 125 children

with asthma, 41 (32.8%) had mild, 63 (50.4%) had moderate, and 21 (16.8%) had severe asthma. Asthma was controlled in 58.4% of the patients. 69 children (55.2%) were under regular asthma controller treatment with inhaled corticosteroids, and 52 children (41.6%) had an asthma exacerbation in the last year. 87 children (69.6%) had an aeroallergen sensitization. The frequencies of controller treatment with inhaled corticosteroids and asthma exacerbation in the last year were significantly higher in children with severe asthma (Table 2). There were no differences between groups in terms of accompanying allergic diseases, asthma control status, BMI z-score, eosinophils, total IgE levels, aeroallergen sensitization, and lung function parameters.

3.3 | Correlation between serum periostin levels and clinical variables related to asthma

Serum periostin levels were found to be significantly correlated with asthma severity (Spearman's rho [r] = .41, $P < .001$) and BMI z-score ($r = -.31$, $P < .001$) (Figure S1), whereas no correlations were found with age, disease duration, accompanying atopic diseases such as allergic rhinitis and atopic dermatitis, asthma control status, total IgE levels, blood eosinophil counts, and lung function parameters (Table 3).

3.4 | Serum periostin levels and asthma

The mean serum periostin levels of children with severe asthma (63.8 ± 10.8) were significantly higher than in children with moderate asthma (53.3 ± 12.7) and mild asthma (47.4 ± 11.1) ($P < .001$) (Figure 1B). No significant differences in serum periostin levels were found in children with asthma when compared according to gender, asthma control status, aeroallergen sensitization, and presences of allergic rhinitis or atopic dermatitis (Table 4).

TABLE 1 Demographic and laboratory characteristics of the study groups (n = 158)

	Asthma (n = 125)	Control (n = 33)	P- value
Age (y)	10.2 (7.8-12.7)	11.4 (7.5-13.9)	.53
Male sex (%)	75.2	66.7	.32
BMI (kg/m ²)	19.8 $\pm$ 4.1	19.4 $\pm$ 4.1	.72
BMI z-score	0.45 $\pm$ 1.25	0.44 $\pm$ 1.08	.97
Aeroallergen sensitization (%)	69.6	18.2	<.001
Serum periostin (ng/mL)	53.1 $\pm$ 13.0	43.3 $\pm$ 11.2	<.001
Eosinophils, %	3.4 (2.1-5.6)	2.1 (1.4-3.9)	.007
Eosinophils (/mL)	255 (150-428)	120 (80-230)	<.001
Total IgE (IU/mL)	71 (20-167)	27 (11-138)	.12

Note: Data are presented as percentage, median (inter-quartile range), or mean $\pm$ standard deviation.

Abbreviation: BMI, body mass index.

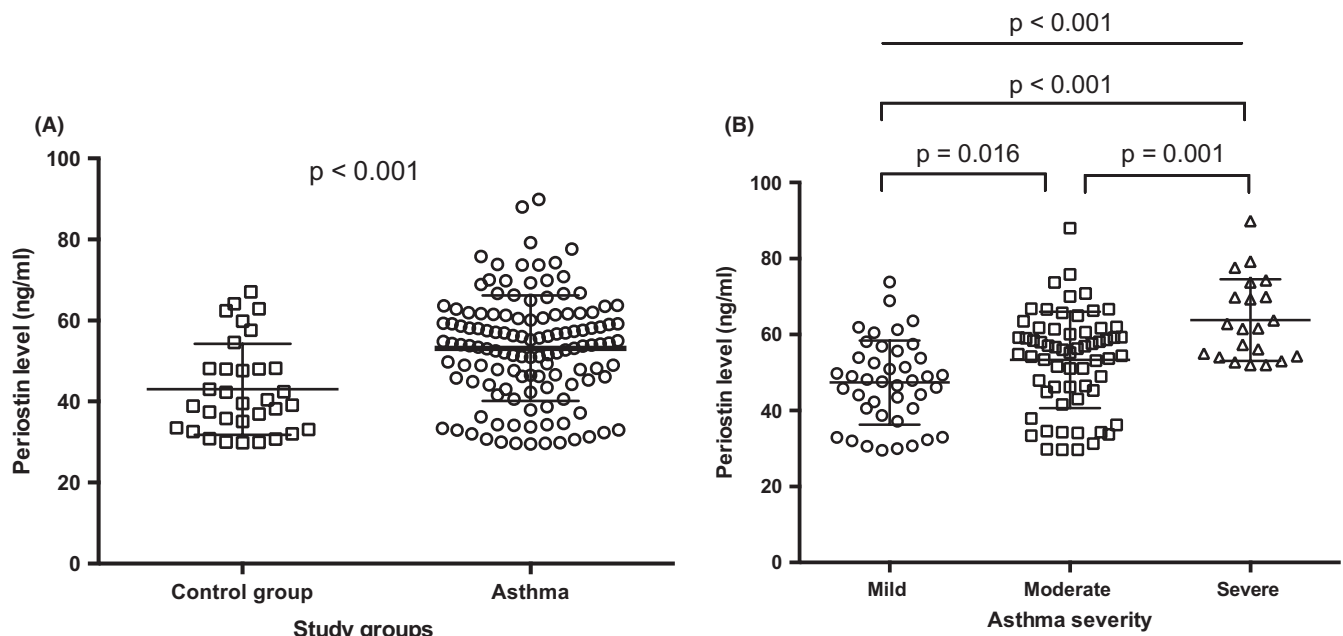


FIGURE 1 Comparison of serum periostin levels in study groups. (A) Asthma vs control group. (B) Asthma group according to severity

3.5 | Multivariable regression and ROC analyses for severe asthma

Results of multivariable logistic regression analysis revealed that serum periostin levels were associated with severe asthma in children (OR, 1.10; 95% CI, 1.04-1.15, $P < .001$) (Table 5).

Analysis using ROC curves identified the role of serum periostin levels in determining children with severe asthma (AUC: 0.77, 95% CI: 0.67-0.87, $P < .001$). When analyzed for the best cut-off value with the highest combined sensitivity and specificity, a cut-off value of 52 ng/mL for serum periostin level was obtained with sensitivity, specificity, PPV, and NPV of 100%, 50%, 29%, and 100%, respectively.

4 | DISCUSSION

In this cross-sectional study, we found that serum periostin levels were significantly higher in children with asthma when compared to children in the control group. Our results also found out an association between serum periostin levels and asthma severity independent from the confounding factors such as BMI and accompanying allergic diseases. However, the role of serum periostin in identifying children with severe asthma is limited.

4.1 | Periostin levels and asthma

Results of several previous childhood studies have demonstrated an association between serum periostin levels and asthma. Song et al¹⁰ have found that serum periostin levels were higher in children with asthma and associated with airway hyper-reactivity. Inoue

et al¹¹ have also found significantly higher serum periostin levels in children with asthma compared with children without any allergic disease in their cross-sectional study, and they indicated the possible role of serum periostin in the diagnosis of childhood asthma. On the other hand, Inoue et al¹² did not detect any increase in serum periostin levels in school-age children with allergic diseases including asthma in comparison with healthy children. The serum periostin levels were found to be significantly higher in children than those in healthy adults. They have speculated that the high baseline levels of serum periostin due to increased bone metabolism in childhood might have masked the possible further increase due to allergic diseases. In our study, serum periostin levels were higher in children particularly with moderate and severe asthma.

4.2 | Predictive role of periostin for asthma

Several attempts were made to investigate the role of periostin to predict the development of asthma in the future. Anderson et al¹³ have prospectively followed up the children from COAST (Childhood Origins of ASThma Study) cohort and longitudinally investigated the role of several biomarkers of type 2 inflammation such as aeroallergen sensitization, blood eosinophils, and serum periostin levels in the development of asthma during the childhood period. They have found that, along with other variables, high serum periostin level at the age of 2 years is a risk factor for asthma by school age. However, they have also addressed a concern regarding the possible confounder effect of the linear growth on serum periostin levels during the early-childhood phase. Castro-Rodriguez et al¹⁴ have performed a case-control study in preschoolers with recurrent wheezing episodes and compared periostin levels according to their asthma predictive index result. No significant difference was found

TABLE 2 Clinical and laboratory characteristics of the children with asthma according to severity

	Total (n = 125)	Mild (n = 41)	Moderate (n = 63)	Severe (n = 21)	P
Age, y	10.2 (7.8-12.7)	12.6 (9.0-13.9)	8.4 (7.1-11.8)	10.2 (9.4-11.7)	.004
Male sex	75.2	73.2	76.2	76.2	.94
Allergic rhinitis	61.6	70.7	60.3	47.6	.20
Atopic dermatitis	13.6	14.6	11.1	19.0	.64
Controller therapy	55.2	29.3	63.5	81.0	<.001
Exacerbation in last year	41.6	22.0	47.6	66.7	.002
Uncontrolled asthma	20.8	24.4	17.5	23.8	.44
BMI z-score	0.45 ± 1.25	0.40 ± 1.27	0.55 ± 1.19	0.26 ± 1.39	.63
Eosinophils, %	3.4 (2.1-5.6)	3.5 (2.7-6.6)	3.4 (2.1-5.6)	3.3 (0.9-6.3)	.18
Eosinophils (/mL)	255 (150-428)	230 (165-510)	260 (150-420)	280 (100-590)	.50
Total IgE (IU/mL)	71 (20-167)	46 (18-301)	72 (21-149)	79 (23-139)	.77
Serum periostin (ng/mL)	53.1 ± 13.0	47.4 ± 11.1	53.3 ± 12.7	63.8 ± 10.9	<.001
FEV ₁ , pred %	93.8 ± 12.9	96.1 ± 11.3	93.4 ± 13.7	90.5 ± 13.3	.26
FEV ₁ /FVC ratio	88.5 ± 6.9	87.9 ± 7.2	89.3 ± 6.7	87.2 ± 7.1	.38
FEF ₂₅₋₇₅ , pred %	89.6 ± 21.1	93.9 ± 23.5	89.0 ± 19.3	84.3 ± 21.6	.24
Aeroallergen sensitization	69.6	70.7	71.4	61.9	.70
Grass pollens	57.6	61.0	60.3	42.9	.33
House-dust mites	18.4	22.0	14.3	23.8	.48
Cat dander	11.2	12.2	9.5	14.3	.81
Mold	8.0	7.3	9.5	4.8	.77
Dog dander	6.4	7.3	6.3	4.8	.93
Tree pollens	4.0	0.0	6.3	4.8	.27
Weed pollens	3.2	4.9	3.2	0.0	.59

Note: Data are presented as percentage, median (inter-quartile range), or mean ± standard deviation.

Abbreviation: BMI, body mass index.

in periostin levels between children with positive and negative asthma predictive index. Recently, Guvenir et al¹⁵ investigated the role of periostin in young children with wheezing episodes for the prediction of asthma development. However, their results did not reveal periostin as a predictive factor for future asthma in young children, either.

4.3 | Association between asthma control and periostin

There are conflicting results about the relationship between serum periostin levels and asthma control status in children. El Basha et al¹⁶ have found significantly higher serum periostin levels in children during an asthma exacerbation compared with children with stable asthma and healthy controls. In contrast to these findings, Mena et al¹⁷ have found an inverse association with lower serum periostin levels in children with uncontrolled asthma. Licari et al¹⁸ did not find an association between asthma control and serum periostin levels in 121 children with allergic asthma. In our study, serum periostin was not associated with

asthma control, either. Asthma control status is determined according to the symptoms in the last 4 weeks, and it can be different in every clinical visit. However, asthma severity is based on the step of medications to control asthma symptoms in the last year and it can be a better instrument in search of a biomarker that reflects the degree of inflammation in a chronic disease such as asthma.

4.4 | Association between asthma severity and periostin

There are also inconsistent results from the studies that investigated the association between asthma severity and serum periostin levels. The results of Licari et al¹⁸ and Konradsen et al¹⁹ did not reveal an association between asthma severity and serum periostin levels. On the other hand, Song et al¹⁰ have explored the relationship between periostin and airway hyper-responsiveness (AHR) in children with asthma and found a significant correlation between the degree of AHR and periostin levels. Similarly, Cho et al²⁰ found significantly higher periostin levels in children with positive exercise and

TABLE 3 Spearman's correlation coefficients between serum periostin level and other clinical variables in children with asthma

	Serum periostin (ng/mL)	
	<i>r</i>	<i>P</i> -value
Age, y	-.15	.11
Disease duration, y	-.06	.56
Asthma severity	.41	<.001
Asthma control status	-.01	.92
Atopic dermatitis	.11	.23
Allergic rhinitis	.04	.70
ICS therapy	.02	.85
BMI, z-score	-.31	<.001
Total IgE (IU/mL)	.03	.78
Eosinophils (%)	-.18	.06
Eosinophils (/mL)	-.18	.05
FEV ₁ , pred %	.04	.66
FEV ₁ /FVC ratio	.10	.26
FEF ₂₅₋₇₅ , pred %	.04	.69

Abbreviations: BMI, body mass index; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume during the first second; FVC, forced vital capacity; ICS, inhaled corticosteroids.

TABLE 4 Comparison of serum periostin levels according to clinical variables in children with asthma

	Serum periostin (ng/mL)	<i>P</i> -value
Gender		
Boys	53.8 ± 13.5	.36
Girls	51.3 ± 11.6	
Asthma severity		
Mild	47.4 ± 11.1	<.001
Moderate	53.3 ± 12.7	
Severe	63.8 ± 10.8	
Asthma control status		
Controlled	52.9 ± 13.4	.18
Partially controlled	56.7 ± 12.1	
Uncontrolled	50.1 ± 12.4	
Aeroallergen sensitization		
Yes	54.3 ± 12.9	.13
No	50.4 ± 12.9	
Atopic dermatitis		
Yes	55.7 ± 12.5	.38
No	52.7 ± 13.1	
Allergic rhinitis		
Yes	53.6 ± 12.4	.61
No	52.4 ± 14.1	

Note: Data are presented as mean ± standard deviation.

mannitol tests when compared to children with asthma and negative results. Recently, the findings of Knihtilä et al²¹ have demonstrated a significant correlation between serum periostin levels, airway

TABLE 5 Multivariable logistic regression analysis for severe asthma

Variable	OR (95% CI)	<i>P</i> -value
Age	1.11 (0.91-1.34)	.31
Aeroallergen sensitization	0.44 (0.15-1.32)	.14
BMI, z-score	1.01 (0.65-1.58)	.96
Eosinophils (/mL)	1.01 (0.99-1.01)	.23
Serum periostin level	1.10 (1.04-1.15)	<.001

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

hyper-reactivity, and bronchodilator responsiveness in 49 children with asthmatic symptoms. In our study, we found a significant and independent correlation between asthma severity and serum periostin levels. A serum periostin value of 52 ng/mL was emerged as the best cut-off level to differentiate children with severe asthma with high sensitivity and negative predictive values, whereas the specificity and positive predictive value for this cut-off were not satisfactory. There are patients with mild-moderate asthma and "high" serum periostin values along with patients with severe asthma and "low" serum periostin levels. Solanki et al²² have found out that treatment with inhaled corticosteroids reduces the serum periostin concentration in adults with asthma. Nevertheless, there was no correlation between inhaled corticosteroid treatment and serum periostin levels in our study. Asthma is a disease with different "endotypes" classified according to the common underlying mechanisms and results of several studies emerged periostin as a biomarker to distinguish Th2 endotype from Th2-low subjects.^{23,24} The unsatisfactory results regarding the role of serum periostin in identifying children with severe asthma may be due to endotype diversity in childhood asthma.

4.5 | Body mass index and serum periostin

In accordance with the previous adulthood studies,^{25,26} we found a negative correlation between serum periostin levels and body mass index in children with asthma along with controls. In our previous studies, we have demonstrated associations between anthropometric measures and asthma severity along with pulmonary functions.²⁷ In the current study, our results did not reveal an independent association between body mass index and asthma severity. The different study design and the lack of control group with obese children is the most plausible explanation. Addition of serum periostin measurement into the studies can help us to better understand the interaction between obesity and asthma in the future.

4.6 | Limitations and strengths

There are several limitations in the present study. First, the diagnostic performance of serum periostin in identifying children with

severe asthma was relatively low. It seems that further studies including more children particularly with severe asthma can help to determine different cut-off values with better statistical performances. Furthermore, periostin is a bone-derived extracellular matrix protein that is secreted by osteoblasts, and in growing children, the indicative role of periostin related to the airway inflammation and consequently asthma severity may be affected due to the fast-linear growth in school-age children. On the other hand, it was performed in a center, which was specialized for children with asthma and allergic diseases. The diagnostic procedures and the longitudinal follow-up of the patients were made by pediatric allergy and asthma specialists conforming with the international standard GINA guidelines. Its controlled design with the inclusion of patients with different severity grades who were under regular follow-up enabled us to demonstrate the possible interactions between features related to childhood asthma and periostin.

5 | CONCLUSION

In conclusion, we demonstrated a significant and independent association between serum periostin and asthma severity in children. However, the performance of serum periostin in identifying children with severe asthma was not satisfactory. According to our findings, it can be postulated that low serum periostin levels may aid clinicians better in excluding severe asthma in children. Several further studies are needed to elaborate the role of periostin in the asthma pathogenesis and clinical utility for the physicians dealing with children with asthma.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

S. Tolga Yavuz: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (equal); supervision (lead); writing-original draft (lead); writing-review & editing (lead). **Soyhan Bagci:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); project administration (equal); supervision (equal); writing-original draft (supporting); writing-review & editing (supporting). **Ahmet Bolat:** Conceptualization (supporting); data curation (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing-original draft (supporting); writing-review & editing (supporting). **Onur Akin:** Conceptualization (supporting); data curation (supporting); investigation (supporting); methodology (supporting);

project administration (equal); supervision (supporting); writing-original draft (supporting); writing-review & editing (supporting). **Rainer Ganschow:** Investigation (supporting); project administration (equal); supervision (supporting); writing-original draft (supporting); writing-review & editing (supporting).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Figure S1.

Correlation between BMI z-score and serum periostin

