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Objective Laboratory Parameters in Assessment of Asthma Control in Children

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The initial findings of this study were presented through an oral presentation at the 12th Pediatric Allergy and Asthma Congress.

ABSTRACT

Objective: Accurate decisions regarding the asthma control level are critical in asthma management. However, an objective laboratory parameter has not yet been defined for detecting asthma control levels in children.

Materials and Methods: We aimed to determine objective laboratory parameters that can be used in evaluating the asthma control level. To achieve this, we compared the Global Initiative for Asthma (GINA)-defined asthma control scale with the Pediatric Asthma Control Test and laboratory parameters including serum periostin, tryptase, urinary leukotriene E4, and fractional exhaled nitric oxide levels in determining the control level of asthma in 160 children with asthma.

Results: The serum periostin level and FeNO level were significantly high and the median Pediatric Asthma Control Test score was significantly low in uncontrolled patients ($p<0.001$, $p=0.003$, $p<0.001$, respectively). After ROC analysis, p-ACT (AUC:0.914, %95CI:0.86-0.97, $p<0.001$), serum periostin (AUC:0,669, %95CI:0.59-0.75, $p=0.001$) and FeNO (AUC:0.755, %95CI:0.67-0.84, $p<0.001$) were found to be predictive in the assessment of asthma control. There was inconsistency between the GINA-defined asthma control scale and the Pediatric Asthma Control Test in 28.7% of the study group. Within the patients having controlled asthma according to both the GINA-defined asthma control scale and Pediatric Asthma Control Test, 8.7% had high levels of periostin and FeNO. Besides, serum periostin levels and FeNO levels were both normal in 25.0% of the patients with uncontrolled asthma according to the GINA-defined asthma control scale and the Pediatric Asthma Control Test.

Conclusion: The asthma control status demonstrated a correlation with FeNO and serum periostin levels. We hold the belief that incorporating objective laboratory parameters, such as FeNO and serum periostin, for the assessment of asthma control levels may have the potential to mitigate both overtreatment and undertreatment in the management of asthma.

Keywords: Asthma control, fractional exhaled nitric oxide, urinary leukotriene E4, periostin, tryptase

INTRODUCTION

Asthma is the most frequent inflammatory airway disease in childhood (1). Accurate assessment of asthma control is crucial for ensuring effective treatment. Studies have indicated that nearly two-thirds of children diagnosed with asthma have experienced at least one asthma attack within the last 12 months, highlighting the inadequate control of childhood asthma (1, 2). Assessment of childhood asthma control is typically based on the Global Initiative for Asthma (GINA)-defined asthma control scale and the Pediatric Asthma Control Test (p-ACT). Nevertheless, both scales rely on historical data provided by the patient or caregivers and the physician's interpretation, incorporating subjective parameters (1). Consequently, there is a need for objective parameters in the evaluation of asthma control.

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Although multiple studies have explored objective parameters for assessing asthma control, the evaluation continues to rely on the aforementioned methods, with even fewer investigations conducted specifically in the pediatric population. It has been demonstrated that fractional exhaled nitric oxide (FeNO), serum periostin levels, and urinary leukotriene E4 levels are elevated in patients with allergic asthma (3-5). The combination of FENO and ACT (Asthma Control Test) has been found useful in determining the level of asthma control in adults (6). In a single-center study aimed at exploring the association between asthma control levels and serum periostin levels in children, high periostin levels were linked to poor asthma control (7). Nonetheless, there remains a scarcity of research concerning the role of these parameters in determining asthma control during childhood. Existing studies have indicated a correlation between basal tryptase levels and IgE-mediated allergic diseases. In patients with food allergy, basal tryptase levels were observed to be higher than in controls, and basal tryptase levels were shown to correlate with the severity of anaphylaxis (8, 9). Serum basal tryptase levels have been demonstrated to have the potential to serve as a supportive parameter in indicating disease severity in childhood asthma (10). Nevertheless, there is insufficient research available that investigates the correlation between tryptase levels and asthma control levels.

This study endeavors to identify objective laboratory parameters that can complement the Global Initiative for Asthma (GINA)-defined asthma control and Pediatric Asthma Control Test (p-ACT) scales for the evaluation of asthma control in children. To achieve this objective, we assessed FeNO, serum periostin, tryptase, and urinary leukotriene E4 levels to determine their potential in assessing the status of asthma control in children.

MATERIALS and METHODS

Study Population

The study enrolled patients aged between 7-17 years with physician-diagnosed asthma for 12 months or more based on GINA guidelines (1). Patients with cystic fibrosis, bronchiectasis, bronchopulmonary dysplasia, bronchiolitis obliterans, chronic lung disease, congenital heart disease, and immunodeficiency were not enrolled in the study. Additionally, patients who experienced an asthma exacerbation treated with systemic steroids or had either an upper or lower respiratory tract infection within the last 4 weeks were excluded from the study.

Ethical Issues

The study was approved by the Clinical Research Ethics Committee. (Ref No:2015/154). A written informed consent form was received from all participants and caregivers.

Survey Instruments and Clinical Data

A comprehensive clinical history was elicited from all participants and/or their caregivers. Information regarding prenatal and postnatal asthma risk factors, exacerbation history, and medications used were inquired. The level of asthma control was assessed using the GINA-defined asthma control scale and p-ACT (1, 11).

The following laboratory investigations were conducted on all subjects: epidermal skin prick tests, lung function tests, total blood count, absolute eosinophil count, and total IgE, FeNO, serum periostin, serum tryptase, and urinary leukotriene E4 levels. Blood and urine samples were collected to detect serum tryptase and periostin levels, as well as urinary leukotriene E4 levels, and were subsequently frozen at -80 ºC for analysis.

Asthma Control Level

The assessment of the asthma control level was accomplished using the GINA-defined asthma control scale.

GINA-defined asthma control scale: The control status of asthma was evaluated by a pediatric allergist (who was blinded to the p-ACT scores) based on specific criteria, including the frequency of asthma symptoms, any nocturnal awakenings due to asthma, the extent of limitation in daily activities, and frequency of reliever medication use for symptom relief (1).

p-ACT: Children and their caregivers completed the respective sections of the validated Turkish version of the p-ACT. The overall p-ACT score is obtained by summing the scores from the two sections, with scores ranging from 0 (indicating the poorest asthma control) to 27 (reflecting optimal asthma control) (11).

Skin Prick Test

Prick tests were performed using prevalent airborne allergens, encompassing animal dander (cat, dog), cockroach, house dust mite, molds (Alternaria, Aspergillus, Cladosporium), and pollens (mixed tree and mixed grass pollen). After 20 minutes, the reactions were assessed, and

a test was considered positive if the diameter of the wheal was at least 3 mm greater than the negative control.

Spirometry

Lung function tests were performed with a spirometer (Minispir®, Rome, Italy) to meet American Thoracic Society standards [20].

Fractional Exhaled NO

FeNO measurement was performed according to the ATS/ERS recommendations (15817806). The patient sat without a nose clip, inhaled to total lung capacity, and then exhaled at a constant flow rate of 50 mL/s. The FeNO level was measured three times (NObreath, Maidstone, England), and the mean of these three measurements was determined as Parts per million (ppm).

Tryptase levels (ImmunoCAP, Uppsala, Sweden) were tested by the fluoroimmunoassay method.

Serum periostin levels (Cusabio, Baltimore, USA) and *urine leukotriene E4 levels* (Cayman, Michigan, USA) were tested by the micro-ELISA (Mikro Enzyme-Linked Immunosorbent Assay) technique.

Statistical Analysis

The participants were categorized into three groups as controlled, partially controlled, and uncontrolled, based on the GINA-defined asthma control scale. The chi-square test was employed to compare categorical variables between these groups. For continuous variables, the One-way ANOVA or Kruskal-Wallis tests were used, depending on the normal distribution of the data. By using posthoc analysis for parameters whose p variable is smaller than 0.05, p values of $p < 0.016$ were considered significant in paired comparison.

After the first analyses, uncontrolled and partially controlled patients according to the GINA-defined asthma control scale were gathered in one group (uncontrolled), and the patients were divided into two groups as controlled and uncontrolled. Categorical variables between the two groups were compared by the chi-square test. If continuous variables between the groups showed a normal distribution, they were compared by Student's T-Test while non-normally distributed variables were compared by the Mann-Whitney U Test. It was considered significant that the p value was below 0.05. The statistically significant continuous variables, which could be utilized to predict asthma control, underwent ROC analysis and cut-off values were determined.

Correlation analyses were conducted to assess the relationship between two variables. In cases where both variables were continuous and exhibited a normal distribution, Pearson correlation analysis was utilized. However, in situations where at least one of the variables did not conform to a normal distribution, Spearman correlation analysis was employed. When one variable was continuous and the other was nominal, Point-Biserial Correlation analysis was employed.

RESULTS

Among the 160 pediatric patients included in the study, the mean age was 10.6 ± 3.7 years. Of the total participants, 52.5% were female, 47.5% were male, and 83.1% demonstrated aeroallergen sensitization. The clinical characteristics are presented in Table I.

The Level of Asthma Control and the Laboratory Findings

Fourteen percent of patients exhibited non-compliance with corticosteroid (CS) treatment. Among the patients, fifty-one (31.9%) were categorized as having "controlled" asthma, as per the GINA-defined asthma control scale. The median p-ACT score was 20. When evaluating exacerbation risk factors, 73.1% of participants had passive smoke exposure, 16.9% were obese, 14.4% exhibited non-compliance with ICS treatment, and only 1 (0.06%) patient had a history of low FEV-1 and endotracheal intubation. Laboratory results of the patients are presented in Table I.

Comparison of the Participants According to the GINA-Defined Asthma Control Scale

Patients were categorized into three groups based on their asthma control level according to the GINA-defined asthma control scale: 1) Controlled, 2) Partially Controlled, and 3) Uncontrolled. The three groups were compared according to the clinical and laboratory findings. Median p-ACT, FeNO, and periostin levels exhibited statistically significant differences among the three groups ($p<0.001$, $p<0.001$, and $p=0.003$, respectively) (Table II).

Post-hoc analysis revealed that FeNO levels were significantly higher in the uncontrolled and partially controlled groups compared to the controlled group ($p<0.001$), but

Table I: General characteristics and laboratory results of the participants.

Age, year, mean ±SD	10.6±3.7
Sex, female n (%)	84 (52.5)
GINA-defined asthma control status, n (%)	
Controlled	51 (31.9)
Partially controlled	58 (36.3)
Uncontrolled	51 (31.9)
Aeroallergen-sensitized, n (%)	133 (83,1)
p-ACT score, median (IQR)	20 (6)
Risk factors for exacerbation, n (%)	
Uncontrolled asthma	51 (31.9)
Non-compliance with ICS treatment	23 (14.4)
High-dose use of SABA	1 (0.6)
Smoke exposure	117 (73.1)
Allergen exposure	113 (70.6)
Obesity	27 (16.9)
Food allergy	1 (0.6)
Rhinosinusitis	72 (45)
Eosinophilia	89 (55.6)
≥ 1 heavy exacerbation in the last year	25 (15.6)
Intubation / Hospitalization to PICU	1 (0.6)
Low FEV-1 *	1 (0.6)
FeNO, median (IQR) (ppm)	30 (39)
Periostin, mean ± SD (ng/ml)	73.0±27.0
Tryptase, median (IQR) (µg/L)	5.0 (2.3)
Leukotriene E4, median (IQR) (pg/mg CR)	83.3 (3.5)
Total Eosinophil Count, mean ±SD	465±421
Total IgE, mean ± SS (IU/ml)	237±194
FEV-1, (%), mean ± SD	99.4±16.1
FEV-1/FVC, (%), mean ± SD	115±45

FeNO: Fractional exhaled nitric oxide, **GINA:** Global Initiative for Asthma, **ICS;** inhaled corticosteroids, **IgE:** Immunoglobulin E, **IQR:** Interquartile range, **FEV-1:** Forced expiratory volume at the first second, **FVC:** Forced vital capacity, ***:** FEV-1<%60; SABA; short acting beta agonist.

there was no difference between the controlled and partially controlled groups (p=0.846). Periostin levels were significantly higher in the uncontrolled and partially controlled groups compared to the controlled group (p=0.004 and p=0.002, respectively), but no significant difference was observed between the controlled and partially controlled groups (p=0.576).

Subsequently, we assembled a cohort comprising patients with partially controlled and uncontrolled asthma into a single group and compared this group with patients exhibiting controlled asthma. The findings from this comparative analysis closely resembled those obtained from the three-group comparison. Notably, levels of p-ACT, periostin, and exhaled nitric oxide (NO) exhibited substantial differences between the two groups, signifying their clinical significance in distinguishing asthma control statuses. Conversely, no statistically significant distinctions were observed in relation to the remaining parameters under investigation (Table III).

Compatibility Between the GINA-Defined Asthma Control Scale and p-ACT

ROC analyses revealed that p-ACT had diagnostic value in predicting uncontrolled asthma (AUC:0.914, %95CI:0.86-0.97, p<0.001) (Table IV, Figure 1A).

GINA-Defined Asthma Control Scale and FeNO

After ROC analysis, it was determined that a cut-off value of 17.5 ppm for exhaled NO had diagnostic value in predicting uncontrolled asthma (AUC:0.755, %95CI:0.67-0.84, p<0.001) (Table V, Figure 1B).

GINA-Defined Asthma Control and Periostin

In ROC analysis for periostin, a cut-off value of 75 ng/ml was found to be a diagnostic value in predicting uncontrolled asthma (AUC:0.669, %95CI:0.59-0.75, p=0.001) (Table VI, Figure 1C).

Correlation Between GINA-Defined Asthma Control and P-AKT, FeNO, Periostin

The GINA-defined asthma control status was strongly negatively correlated with p-ACT (p<0.001, r=-0.704), weakly negatively correlated with FeNO (p<0.001, r=-0.208), and very weakly negatively correlated with periostin (p=0.027, r=-0.174) (Figure 2A-C). Additionally, a strong positive correlation was detected between periostin and FeNO (p<0.001, r=0.650) (Figure 2D).

Subclinical Inflammation

In order to assess the occurrence of subclinical inflammation, we conducted an evaluation to determine the proportion of patients classified as "Controlled" based on GINA guidelines and p-ACT scores, yet exhibiting elevated levels of serum periostin and FeNO. Among the sub-

Table II: Comparison of laboratory parameters between the three control levels according to the GINA-defined asthma control scale.

Characteristic	Controlled N=51	Partially Controlled N=58	Uncontrolled N=51	P value
Sex (Male), n (%)	27 (52.9)	28 (48.3)	21 (41.2)	0.487
Age, year, mean ±SD	10.1±4.0	11.3±3.6	10.4±3.4	0.176
BMI, mean ± SD	19.6±4.4	19.6±4.4	19.4±4.0	0.695
p-ACT score, median (IQR)	24 (2)	20 (3)	16 (6)	<0.001
FeNO, median (IQR)	9.5 (26)	36 (52)	37.5 (46)	<0.001
Periostin, median (IQR)	62.9 (20.5)	70.6 (40.7)	73.5 (29.7)	0.003
Tryptase, median (IQR)	5.0 (2.2)	5.2 (2.1)	4.6 (2.4)	0.533
Leukotriene E4, median (IQR)	83.3 (4.0)	83.3 (2.8)	84.0 (3.8)	0.804
Total eosinophil count, median (IQR)	402.5 (409.7)	380.5 (413)	278.0 (543.5)	0.409
Total IgE, median (IQR)	200.2(370)	169.4 (372.1)	129.8 (414.5)	0.765
FEV-1%, mean ± SS	99.5±14.5	100.3±16.3	98.3±17.6	0.809
FEV-1/FVC%, median (IQR)	114 (15)	111 (31)	105 (24)	0.284

FeNO: Fractional exhaled nitric oxide, **GINA:** Global Initiative for Asthma, **IgE:** Immunoglobulin E, **IQR:** Interquartile range, **FEV-1:** Forced expiratory volume at the first second, **FVC:** Forced vital capacity.

Table III: Comparison of "Controlled" and "Uncontrolled" groups according to the GINA-defined asthma control scale.

Characteristic	Controlled N=51	Uncontrolled N = 109	P value
Sex (Male), n (%)	27 (52.9)	49 (45.0)	0.346
Age, year, mean ±SD	10.1 ± 4.0	10.9 ± 3.5	0.393
BMI, mean ± SD	19.6 ± 4.4	19.6 ± 4.4	0.993
p-ACT score, median (IQR)	24 (2)	18 (6)	<0.001
FeNO, median (IQR)	9.5 (26)	36.5 (45)	<0.001
Periostin, median (IQR)	62.9 (20.5)	72.0 (33.8)	0.001
Tryptase, median (IQR)	5.0 (2.2)	5.0 (2.3)	0.806
Leukotriene E4, median (IQR)	83.3 (4.0)	82.3 (3.3)	0.662
Total eosinophil count, median (IQR)	402.5 (409.7)	33.5 (448.8)	0.990
Total IgE, median (IQR)	200.2 (370)	150.2 (399)	0.495
FEV-1%, mean ± SS	99.5 ± 14.5	101 (25)	0.059
FEV-1/FVC%, median (IQR)	114 (15)	107.3 (28)	0.135

FeNO: Fractional exhaled nitric oxide, **GINA:** Global Initiative for Asthma, **IgE:** Immunoglobulin E, **IQR:** Interquartile range, **FEV-1:** Forced expiratory volume at the first second, **FVC:** Forced vital capacity.

group of patients deemed "Controlled" according to both GINA and p-ACT criteria, a total of 8.7% displayed NO and periostin levels surpassing the defined cut-off values. Conversely, 25% of patients categorized as "Uncontrolled" by both methods demonstrated NO and periostin levels that fell below the predetermined cut-off values

DISCUSSION

In our study, we found that p-ACT as well as FeNO and serum periostin levels could be used to determine asthma control status. Also, serum periostin and FeNO levels seem to be objective laboratory parameters that can be used both for the detection of subclinical inflammation and the prevention of overtreatment.

Table IV: Sensitivity-specificity values for pediatric ACT (p-ACT) cut-off values.

Cut-off values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
18	55	94.1	95.2	49.5	0.396
19	61.5	92.2	94.4	52.8	0.448
20	70.6	90.2	93.9	59.0	0.533
21	84.4	90.2	94.8	73.0	0.702
22	89.0	82.4	91.5	77.8	0.702

NPV: Negative predictive value, **PPV:** Positive predictive value.

Table V: Sensitivity-specificity values for FeNO cut-off values.

Cut-off values (ppm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
17.5	73.4	68.6	83.3	54.7	0.394
20	69.7	70.6	83.5	52.2	0.369
22.5	69.7	72.5	84.4	52.9	0.385
25	67.9	74.5	85.1	52.1	0.380

NPV: Negative predictive value, **PPV:** Positive predictive value.

Table VI: Sensitivity-specificity values for Periostin cut-off values.

Cut-off values (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
60	74.3	43.1	73.6	44.0	0.175
65	63.3	56.9	75.8	42.0	0.184
70	53.2	74.5	81.7	42.7	0.231
75	49.5	84.3	97.1	43.9	0.272
80	41.3	92.2	91.8	42.3	0.255
85	35.8	92.2	90.7	40.2	0.208

NPV: Negative predictive value, **PPV:** Positive predictive value.

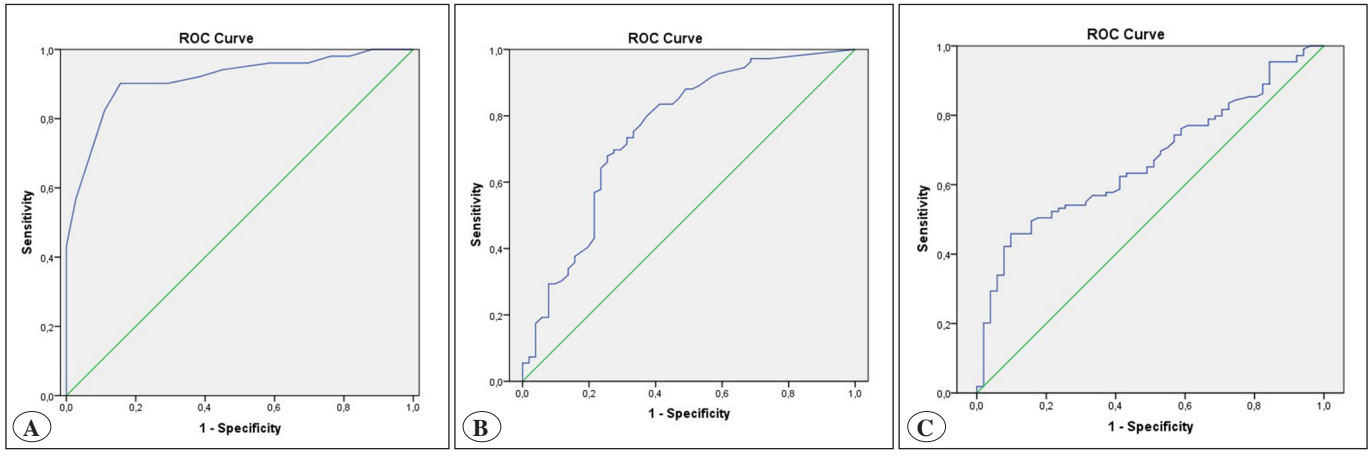

Figure 1. A) p-ACT-GINA ROC curve in predicting asthma control. **B)** FeNO-GINA ROC curve in predicting asthma control. **C)** Periostin-GINA ROC curve in predicting asthma control.

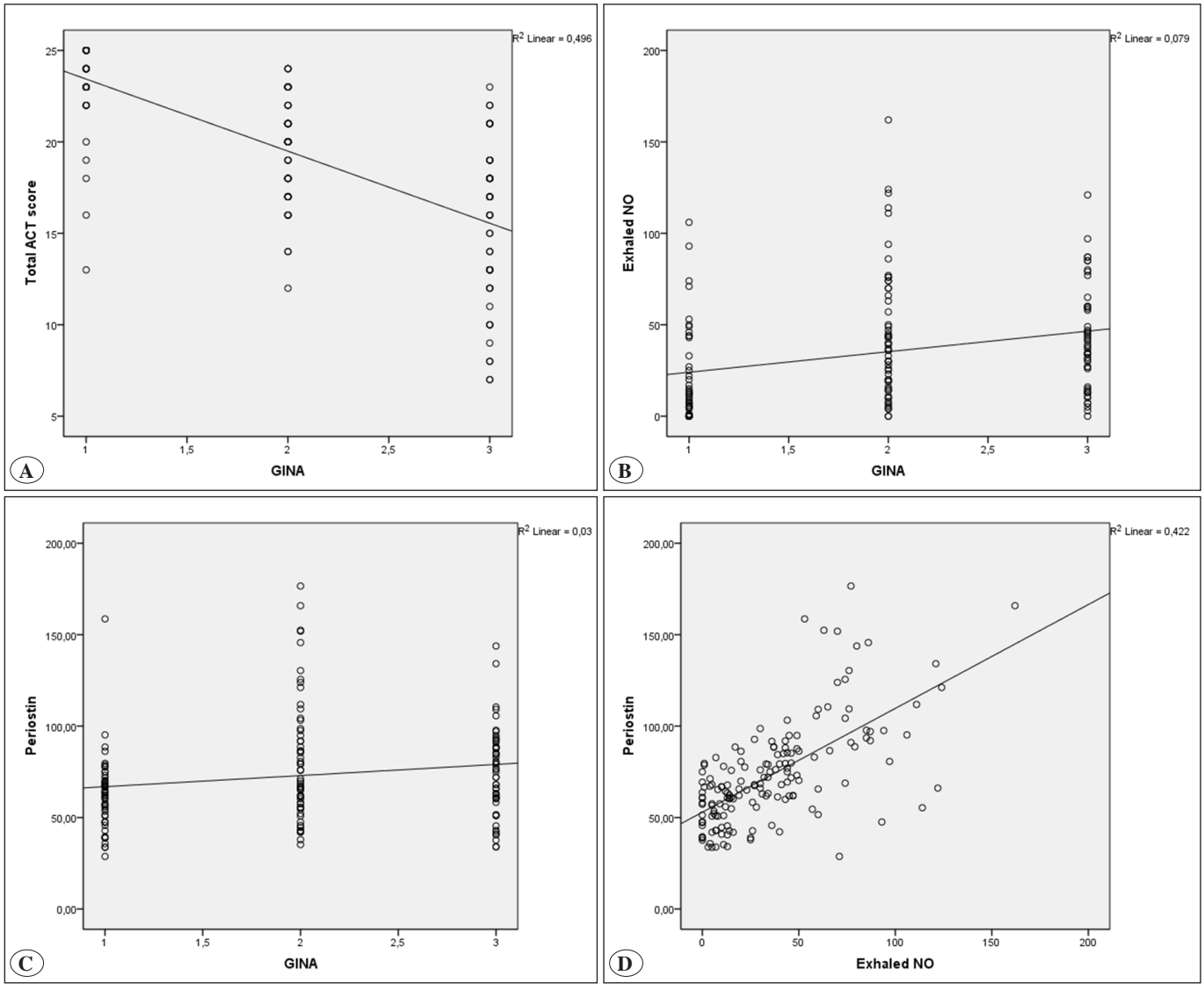

Figure 2. A) p-ACT-GINA correlation graphic. **B)** FeNO-GINA correlation graphic. **C)** Periostin-GINA correlation graphic. **D)** FeNO-Periostin correlation graphic.

The GINA assessment scale is based on the history that is given by the family or patient and it is mostly made up of subjective parameters (1). Pediatric ACT is a test commonly used with a GINA-defined asthma control scale and is similarly a scaling method based on the patient declaration. Although the GINA-defined asthma control scale and p-ACT are generally compatible in evaluating the level of asthma control, there may be inconsistencies in a significant proportion (12-14). A mismatch between GINA and p-ACT was determined in 28.7% in our study. The GINA-defined asthma control scale (categorical) and p-ACT (numerical) are two different measurement tools; GINA categorizes symptoms based on frequency, while p-ACT assesses both frequency and severity, involving separate parent and child sections, and this divergence could explain the discrepancies observed (12, 15-17). As a result, both methods are based on patients' and families' statements. Therefore, in addition to these methods, objective laboratory parameters are needed to evaluate asthma control. Exhaled NO measurement is a simple, non-invasive test that is an indirect indicator of airway inflammation. It has been shown that the FeNO level is decreased in a dose-dependent manner with inhaled corticosteroid treatment and correlated with eosinophil count in induced sputum (18, 19). Different results have been reported in studies that investigate the importance of FeNO in the evalua-

tion of asthma control. In a study evaluating 207 asthmatic children between the ages of 5 and 15 years, FeNO was not found to be adequate in distinguishing between controlled and uncontrolled asthma (20). While FeNO levels were found to be higher in patients with uncontrolled asthma than patients with controlled asthma in ICS untreated cases by Visitsunthorn N et al. (21), no association was found between the value of FeNO and the degree of asthma control in a recent study (22). In our study, the FeNO level was significantly higher in the uncontrolled group compared to the controlled group. These findings suggest that FeNO is an objective parameter and may be used in addition to the GINA-defined asthma control scale to evaluate asthma control.

Periostin is a matrix protein produced by fibroblasts and epithelial cells and has been proposed as a type 2 inflammation biomarker. In previous studies, a correlation between periostin and bronchial obstruction and increased FeNO levels and eosinophilia has been shown (23, 24). In a study conducted in children aged 5-14 years with uncontrolled asthma according to the GINA-defined asthma control scale, serum periostin levels were found to be higher than in previous studies, but this study did not reveal the role of periostin in the controlled and uncontrolled asthma group because there was no controlled asthma group (25). In a recent study, Licari A et al. reported that serum periostin was not associated with the asthma control level and did not correlate with blood eosinophils and FeNO (26). In our study, serum periostin levels were significantly higher in the uncontrolled asthma group than in the controlled asthma group. The inconsistency with a previous study by Licari et al could depend on the dissimilarity of the enrolled populations, including for asthma severity, gender, and the measured variables. Although our results indicate that periostin is an objective parameter that may be used to assess asthma control status, the clinical value of serum periostin in asthma management is still debated and controversial, and extensive studies are needed in this regard.

The parameters used in GINA and p-ACT are based on the patient's or their caregiver's statement. The perceptions and attitudes of patients and their caregivers regarding illnesses and symptoms may vary. They may exaggerate the symptoms or conceal them. In this respect, the use of objective parameters in addition to these scales will enable us to make more accurate control decisions. In our study, we found that 7.8% of the patients who were controlled according to both GINA and p-ACT had FeNO and serum periostin levels above the cut-off values. In addition, FeNO and serum periostin levels were within normal limits in 24.8% of the patients who were uncontrolled according to both scales. While the reason for these findings could be that some of the patients cannot express or hide their symptoms, it shows that some of them perceive their symptoms as exaggerated. This situation may give rise to overtreatment and undertreatment. We believe that using objective laboratory parameters such as the serum periostin level and FeNO as well as GINA and p-ACT in determining asthma control status may contribute to the prevention of inappropriate treatment.

The mast cell is one of the most important cells to take part in the pathogenesis of asthma. The correlation of tryptase, a protease released from mast cells, with various allergic diseases has been investigated. It has been shown that the level of tryptase is correlated with the severity of hypersensitivity reactions, and high basal tryptase levels are a risk factor for severe systemic reactions in venom allergy (27, 28). It was also found that tryptase levels were higher in patients with chronic urticaria compared to controls (29, 30). Studies in asthmatic patients have shown high levels of tryptase in BAL and high levels of tryptase in adult patients with moderate to severe asthma at the time of diagnosis (31, 32). On the other hand, low serum tryptase was observed to increase the risk of exacerbation, and low serum tryptase was associated with a corticosteroid-resistant and refractory non-type 2 asthma phenotype. These findings give rise to the thought that there may be a correlation between the asthma control level and the total tryptase level. When we investigated this correlation in our study, we determined that total tryptase levels did not differ between controlled and uncontrolled asthma patients. However, the determination of a weak correlation between the total tryptase level, serum periostin level, and total eosinophil count indicate that additional studies are needed in this regard.

Cysteinyl leukotrienes, which are produced by the cyclooxygenase pathway, take part in both early and late allergic inflammation (33). Leukotriene E4 is the measurable stable end product of this pathway. In studies investigating the relationship between leukotriene E4 levels and asthma, it has been shown that children having an acute asthma exacerbation have increased LTE4 levels in the urine. It has also been shown that the urine LTE4 level is correlated with exacerbation severity (34). These studies

indicate that the urine LTE4 level may be a good predictor to evaluate the control level of asthma. We did not find a significant correlation between the urine LTE4 levels and asthma control levels. This finding shows that the urine LTE4 level might not be a good predictor to determine the asthma control level.

CONCLUSION

We found a significant correlation between the asthma control levels and the FeNO and serum periostin levels. We believe that the use of objective laboratory parameters such as FeNO and serum periostin, as well as the GINA-defined asthma control scale and p-ACT in the determination of the asthma control level may help to decrease overtreatment and undertreatment in asthma.

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Conflict of Interest

The authors assert that they possess no conflicts of interest pertaining to the subject matter discussed in this paper. The authors have meticulously examined and granted their approval for the final version of this manuscript to be submitted for publication. Furthermore, we affirm that this article is an original piece of work and has not been previously submitted to any other scholarly journal.

Author Contributions

Concept: **Melek Yorgun Altunbas, Mustafa Erkocoglu,** Design: **Melek Yorgun Altunbas, Mustafa Erkocoglu,** Data collection or processing: **Melek Yorgun Altunbas, Mustafa Erkocoglu,** Analysis or Interpretation: **Melek Yorgun Altunbas, Mustafa Erkocoglu, Seyda Ozsoy Karabork,** Literature search: **Melek Yorgun Altunbas, Mustafa Erkocoglu, Seyda Ozsoy Karabork,** Writing: **Melek Yorgun Altunbas, Mustafa Erkocoglu, Seyda Ozsoy Karabork,** Approval: **Melek Yorgun Altunbas, Mustafa Erkocoglu, Seyda Ozsoy Karabork.**

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