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To cite this article: Gulfidan Cakmak Uzan, Sermin Borekci, Yasemin Erdogan Doventas, Macit Koldas & Bilun Gemicioglu (2019): The relationship between inflammatory markers and spirometric parameters in ACOS, Asthma, and COPD, Journal of Asthma, DOI: [10.1080/02770903.2019.1652644](https://doi.org/10.1080/02770903.2019.1652644)

To link to this article: <https://doi.org/10.1080/02770903.2019.1652644>



Published online: 12 Aug 2019.



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The relationship between inflammatory markers and spirometric parameters in ACOS, Asthma, and COPD

Gulfidan Cakmak Uzan, MD^a , Sermin Borekci, MD^b , Yasemin Erdogan Doventas, MD^c, Macit Koldas, MD^c, and Bilun Gemicioglu, MD, PhD^b 

^aHaseki Training and Research Hospital, Department of Pulmonology, University of Health Sciences, Istanbul, Turkey; ^bCerrahpasa Medical Faculty, Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Istanbul, Turkey; ^cHaseki Training and Research Hospital, Department of Biochemistry, University of Health Sciences, Istanbul, Turkey

ABSTRACT

Objective: The inflammatory mechanisms underpinning asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) have not been fully elucidated. Here, we examined the levels of cysteinyl leukotrienes (cys-LTs), prostaglandin D2 (PG-D2), prostaglandin E2 (PG-E2), interleukin 5 (IL-5), and a disintegrin and metalloprotease domain (ADAM 33) in ACOS patients to determine the relationship between levels of these inflammatory markers and pulmonary functions.

Methods: Blood samples were obtained from asthma, COPD, and ACOS patients who received combined therapy and were stable for the last month to measure cys-LTs, PG-D2, PG-E2, IL-5, and ADAM33 levels. Differences between groups and their correlations with pulmonary function tests were evaluated.

Results: In total, 24 ACOS, 27 asthma, and 35 COPD patients were included. PG-D2 levels were higher in ACOS (120.9 ± 117.2 ng/L) and asthma (119.6 ± 111.7 ng/L) patients than in COPD (82.6 ± 46.7 ng/L) patients ($p = 0.036$ and $p = 0.038$, respectively). In ACOS patients, PG-D2, cys-LTs, and ADAM33 levels were negatively correlated with FEV1/FVC% values ($p = 0.021$, $p = 0.008$, and $p = 0.028$, respectively). In COPD patients, a negative correlation was detected between PG-E2 and FEV1/FVC% ($p = 0.007$), whereas positive correlations were detected between IL-5 and pulmonary function tests, including FVC, FVC%, FEV1, FEV1%, FEF25-75, and FEF25-75% ($p = 0.047$, $p = 0.005$, $p = 0.002$, $p = 0.002$, $p = 0.010$, and $p = 0.005$, respectively). In asthma patients, cys-LTs levels were negatively correlated with FEV1 and FEF25-75 values ($p = 0.045$ and $p = 0.037$, respectively).

Conclusions: PG-D2 levels may be a valuable biomarker to differentiate COPD in asthma and ACOS patients.

ARTICLE HISTORY

Received 31 May 2019

Revised 29 July 2019

Accepted 31 July 2019

KEYWORDS

Asthma; COPD; ACOS; inflammation; cys-LTs; prostaglandin; interleukin; ADAM 33; matrix metalloprotease

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are airway diseases characterized by chronic inflammation. While differentiating asthma and COPD in most patients is straightforward, the fundamental characteristics of asthma and COPD may co-exist, especially in the elderly. These cases are evaluated as asthma-COPD overlap syndrome (ACOS) or asthma-COPD overlap, as indicated in the 2018 Global Initiative for Asthma (1). Currently, there are no universally recognized or approved criteria for the diagnosis of ACOS. ACOS is an umbrella term encompassing neutrophilic inflammation and irreversible airway obstruction experienced in COPD, eosinophilic, or smoking asthma patients (2). These three disease groups show differences

in clinical and pathological features, quality of life, exacerbation, progression, hospitalization, pulmonary functions, and mortality; distinguishing these groups is therefore crucial. Nevertheless, this can be challenging. As the fundamental feature in all three disease groups is airway inflammation, diagnosis based on inflammatory markers has been attempted in recent years. Arachidonic acid metabolites cys-LTs (LT C4, LT D4, LT E4), prostaglandin D2 (PG-D2), and prostaglandin E2 (PG-E2) are the most commonly studied markers.

In addition to inflammation, genetics also plays a role in the pathogenesis of COPD (3). A disintegrin and metalloprotease domain (ADAM) is a gene family that in recent years has been identified to underpin a predisposition to asthma and bronchial hyperreactivity

(3). ADAM33 is present in tracheal smooth muscle and epithelial cells, and it is considered to be responsible for airway remodeling (3). ADAM33 is associated with pulmonary functions and the course of respiratory functions in asthma and COPD cases (3). It increases protease activity and mucus secretion, matrix metalloproteinase 33 (MMP 33) release, and development of resistance to glucocorticoids (3). MMP is a wide protease enzyme family. MMP2 and MMP9 have been the most extensively studied in the context of asthma and COPD. They are present at low levels in healthy lung tissue and are highly expressed in pulmonary diseases such as asthma, COPD, and cystic fibrosis (3,4).

The purpose of this study was to investigate how the levels of inflammatory markers such as cys-LTs, PG-D2, PG-E2, interleukin (IL)-5, and ADAM33 play a role in the differentiation of ACOS, asthma, and COPD, and their relationship with spirometric values.

Methods

This study was conducted in patients with asthma and COPD using a cross-sectional design in two centers of the Pulmonology Department of the city. The local ethical committee approved the study protocol (No: 1567).

Patients

In total, 86 patients were included in the study between May 2014 and December 2016. The order of patients was standardized as one female case following five male cases among patients older than 18 years old who visited the clinic after May 2014. Patients who had been stable for at least 3 months, were receiving inhaled steroids and long-acting bronchodilator combination treatment but had not used these in the last 15 h were included in the study. Patients with additional diseases or conditions that may have affected biomarkers (e.g., aspirin hypersensitivity, known coronary artery disease, and/or renal pathology) were excluded.

Biochemical analysis

After 8-h fasting, blood samples were obtained in the morning for biochemical parameters. Samples were quickly centrifuged at 4,000 rpm for 10 min to separate the plasma and serum. Serum samples were kept at -80°C . Subsequently, all parameters were assessed in the same serum sample.

For measuring ADAM 33 levels, sandwich enzyme-linked immunosorbent assay (ELISA) method was

applied using commercial kits (Sunred, catalog no.: 201-12-3060, Shanghai Sunred Biological Technology Co. Ltd., Shanghai, China) with a lower limit of detection (0.092 ng/L) obtained as per the manufacturer's instructions and assay range (0.1–30 ng/mL).

Concentrations of PGE2, PGD2, and cys-LTs were measured using an ELISA kit with a commercially available system (Eastbiopharm, Hangzhou Eastbiopharm Co. Ltd. China, REF: CK-E11569, CK-E10744, CK-E10768). Absorbances were read spectrophotometrically at 450 nm in the ELX800 ELI-SA reader. For plate washing, Biotek ELX50 (BioTek Instruments, USA) was used as an automatic washer.

Spirometric evaluation

The forced vital capacity (FVC), FVC%, forced expiratory volume in the first second (FEV1), FEV1%, post bronchodilator FEV1 (Post FEV1), FEV1/FVC, Forced expiratory flow over the middle half of the FVC (FEF25-75), and FEF25-75% were checked using the Jaeger Master Scope (version 4.5) (SensorMedics Vmax 229; Sensor Medics Corporation, Yorba Linda, CA, USA) in compliance with ERS/ATS 2005 criteria.

Statistical analysis

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were denoted as number and percentage for categorical variables; and mean, standard deviation, minimum, and maximum for numeric variables. For numeric variables, comparison of more than two independent groups was performed with one-way analysis of variance (ANOVA) if values were normally distributed and Kruskal-Wallis test if they did not meet a normal distribution. Sub-group analyses were performed with Tukey HSD test for parametric testing and Mann-Whitney *U*-test for non-parametric testing. Data were interpreted with Bonferroni correction. The relationships between numeric variables were examined with Spearman correlation analysis, as parametric test conditions were not met. Intergroup rate of categorical variables was tested with chi-square analysis. Monte Carlo simulation was applied when conditions were not met. Statistical significance was set at $p < 0.05$.

Results

A total of 24 patients diagnosed with ACOS (19 males and five females; mean age, 60.3 ± 9.3 years), 27 patients diagnosed with asthma (21 males and six

Table 1. Demographic characteristics.

		ACOS	Asthma	COPD	<i>p</i>
Age (years)					
Mean $\pm$ SD (Min-Max)		60.3 $\pm$ 9.3 (42–80)	54.7 $\pm$ 12.6 (23–81)	59.4 $\pm$ 7.2 (42–69)	0.087
Gender					
<i>n</i> (%)	Male	19 (79.2)	21 (77.8)	35 (100)	0.004*
	Female	5 (20.8)	6 (22.2)	0 (0.0)	
Symptom					
<i>n</i> (%)	Dyspnea	8 (33.3)	8 (29.6)	14 (40.0)	<0.001*
	Dyspnea + coughing	9 (37.5)	1 (3.7)	17 (48.6)	
	Coughing	7 (29.2)	18 (66.7)	4 (11.4)	
Smoking					
Mean $\pm$ SD (Min-Max)		27.8 $\pm$ 10.3 (12–48)	18.1 $\pm$ 6.1 (10–40)	33.6 $\pm$ 8.8 (15–50)	<0.001*

females; mean age, 54.7 $\pm$ 12.6 years), and 35 male patients diagnosed with COPD (mean age, 59.4 $\pm$ 7.2 years) were included in the study. The difference among groups in ratio of genders was statistically significant ($p=0.004$). There was no significant difference in mean age among groups ($p=0.087$). Symptom ratios of disease groups were significantly different ($p<0.001$). With regard to symptoms, coughing was high in the asthma group, while dyspnea and dyspnea + coughing were high in the COPD group. Mean smoking rates were significantly different among groups ($p<0.001$). Smoking rates were significantly higher in ACOS and COPD patients than in asthma patients (both $p<0.001$). There was no significant difference in mean smoking rates between ACOS and COPD patients (Table 1).

Mean pulmonary function test parameters of disease groups were all significantly different (all $p<0.001$). Apart from POST FEV1% in asthma patients compared to that in ACOS patients, mean results of all tests were significantly higher than those for COPD patients (all $p<0.001$). Mean FEV1%, FEV1/FVC%, FEF25-75, FEF25-75%, and POST FEV1% were significantly higher in ACOS patients than in COPD patients ($p=0.018$, $p=0.006$, $p=0.015$, $p=0.003$, and $p=0.001$, respectively).

Among the inflammatory markers evaluated in disease groups, mean PG D2 was significantly different among groups ($p=0.045$). PG D2 was significantly higher in asthma and ACOS patients than in COPD patients ($p=0.045$ and $p=0.036$, respectively) (Table 2).

Among the parameters evaluated in ACOS patients, PG D2 was negatively associated with cys-LTs, ADAM33, and FEV1/FVC% ($p=0.021$, $p=0.008$, and $p=0.028$, respectively) (Table 3). Among the parameters evaluated in asthma patients, cys-LTs was negatively related to FEV1 and FEF25-75 ($p=0.045$ and $p=0.037$, respectively) (Table 4). Among evaluated parameters, PG E2 was negatively associated with FEV1/FVC% and positively associated with IL-5 FVC,

FVC%, FEV1, FEV1%, FEF25-75, and FEF25-75% in COPD patients ($p=0.047$, $p=0.005$, $p=0.002$, $p=0.002$, $p=0.010$, and $p=0.005$, respectively) (Table 5).

Discussion

In our study investigating the role of inflammatory markers (cys-LTs, PG-D2, PG-E2, IL-5, and ADAM33 levels) in the differentiation of ACOS, asthma, COPD, and their relationship with spirometric values, it was determined that PG-D2 may be used as a distinctive biomarker for distinguishing asthma and ACOS cases from COPD. FEV1/FVC value was associated with PG-D2 and cys-LTs levels in ACOS cases, FEV1/FVC value was associated with PG-E2 in COPD cases, and cys-LTs levels were negatively related to FEV1 and FEF25-75 values in asthma cases.

Among the inflammatory markers evaluated in disease groups, mean PG D2 was significantly different among groups in our study ($p=0.045$). PG D2 was significantly higher in asthma and ACOS patients than in COPD patients ($p=0.045$ and $p=0.036$, respectively). In contrast to our results, Montuschi and colleagues observed similar PG D2 levels in COPD and control groups in their study (5). Further, Fajit et al. assessed PG D2 in bronchoalveolar lavage (BAL) fluid in severe and uncontrolled asthma patients. Yoshimura et al. investigated PG D2 in nasal mucosa in asthma patients with chronic rhinosinusitis and nasal polyps, and O'Sullivan et al. examined PG D2 metabolites in urine in aspirin-induced asthma patients; PG D2 levels were increased in all of these studies (6–8). In our study, we assessed PG D2 blood levels, and we propose that they may be a sign of systemic inflammation in ACOS.

In their study, Mastalerz et al. investigated PG E2 levels in aspirin-induced and aspirin tolerant asthma patients, and found them to be similar. Blood PG E2 levels and excretion in urine increased after aspirin administration in aspirin tolerant asthma patients (9).

Table 2. Comparison of inflammatory markers.

	ACOS Mean $\pm$ SD (Min–Max)	Asthma Mean $\pm$ SD (Min–Max)	COPD Mean $\pm$ SD (Min–Max)	<i>p</i>
PG E2 (pg/mL)	566.6 $\pm$ 639.5 (160.1–2516.2)	534.9 $\pm$ 545.1 (237.0–2389.3)	405.2 $\pm$ 287.9 (197.2–1525.3)	0.496
PG D2-MOX (ng/L)	120.9 $\pm$ 117.2 (34.1–503.2)	119.6 $\pm$ 111.7 (54.4–491.4)	82.6 $\pm$ 46.7 (48.8–258.1)	0.045*
Cys-LTs (ng/L)	222.9 $\pm$ 170.2 (63.8–671)	211.3 $\pm$ 165.5 (86.9–671)	164.3 $\pm$ 83.5 (87.3–462.9)	0.205
ADAM33 (ng/mL)	13.9 $\pm$ 12.2 (4.2–51)	13.6 $\pm$ 11.8 (6.5–51)	9.6 $\pm$ 3.4 (6.14–21.9)	0.167
IL-5 (pg/mL)	29.5 $\pm$ 49.9 (3.4–215.5)	31.7 $\pm$ 99.5 (2.2–524.6)	34.2 $\pm$ 92.8 (2.9–524.6)	0.529

Table 3. Relationship between inflammatory markers and spirometric parameters in ACOS patients.

	PG E2		PG D2-MOX		cys-LTs		ADAM33		IL-5	
ACOS	rho	<i>p</i>	rho	<i>p</i>	rho	<i>P</i>	rho	<i>p</i>	rho	<i>p</i>
Age	0.048	0.825	−0.064	0.766	−0.152	0.477	0.047	0.826	−0.269	0.204
Smoking	−0.006	0.977	−0.084	0.697	−0.118	0.583	−0.047	0.827	0.183	0.392
FVC (mL)	−0.046	0.845	−0.125	0.590	0.044	0.849	−0.070	0.762	0.043	0.853
FVC%	0.079	0.733	0.081	0.726	0.283	0.213	0.232	0.311	−0.184	0.426
FEV1 (mL)	−0.143	0.537	−0.316	0.163	−0.122	0.598	−0.209	0.363	−0.071	0.760
FEV1%	0.020	0.931	−0.049	0.834	0.101	0.664	0.101	0.664	−0.315	0.164
FEV1/FVC %	−0.332	0.141	−0.502	0.021*	−0.563	0.008*	−0.478	0.028*	−0.141	0.541
FEF25-75 (mL)	−0.112	0.630	−0.291	0.201	−0.175	0.449	−0.219	0.340	−0.187	0.416
FEF25-75%	−0.005	0.982	−0.266	0.244	−0.150	0.517	−0.146	0.527	−0.371	0.098
POST FEV1%	−0.139	0.549	−0.253	0.268	−0.326	0.149	−0.323	0.153	−0.186	0.421

Table 4. Relationship between inflammatory markers and spirometric parameters in asthma patients.

	PG E2		PG D2-MOX		Cys-LTs		ADAM33		IL-5	
Asthma	rho	<i>p</i>	rho	<i>p</i>	rho	<i>p</i>	rho	<i>p</i>	rho	<i>p</i>
Age (years)	0.199	0.320	0.093	0.645	0.172	0.390	0.031	0.880	−0.056	0.780
Smoking (package-year)	0.032	0.873	0.039	0.846	0.013	0.948	0.065	0.746	0.239	0.230
FVC (mL)	−0.178	0.374	−0.236	0.236	−0.338	0.084	−0.221	0.268	0.218	0.274
FVC%	0.104	0.605	−0.049	0.808	−0.168	0.403	−0.081	0.689	0.006	0.976
FEV1 (mL)	−0.224	0.262	−0.283	0.153	−0.390	0.045*	−0.280	0.157	0.240	0.227
FEV1%	0.058	0.775	−0.122	0.545	−0.212	0.289	−0.153	0.446	0.015	0.940
FEV1/FVC%	−0.013	0.951	−0.161	0.423	−0.237	0.233	−0.208	0.298	0.120	0.551
FEF25-75 (mL)	−0.194	0.333	−0.308	0.118	−0.402	0.037*	−0.292	0.139	0.313	0.112
FEF25-75%	−0.128	0.523	−0.270	0.173	−0.336	0.086	−0.268	0.177	0.233	0.241
POST FEV1%	−0.015	0.942	0.204	0.307	0.135	0.503	0.184	0.359	−0.234	0.239

Table 5. The relationship between inflammatory markers and spirometric parameters in COPD patients.

	PG E2		PG D2-MOX		CysLTs		ADAM33		IL-5	
COPD	rho	<i>p</i>	rho	<i>p</i>	rho	<i>p</i>	rho	<i>p</i>	rho	<i>p</i>
Age (years)	0.100	0.567	0.102	0.562	−0.024	0.892	0.157	0.369	−0.011	0.951
Smoking (package-year)	0.305	0.075	0.147	0.399	0.152	0.383	0.158	0.366	−0.075	0.669
FVC (mL)	−0.186	0.316	−0.212	0.252	−0.323	0.076	−0.176	0.344	0.360	0.047*
FVC%	−0.068	0.717	−0.041	0.825	−0.160	0.389	−0.040	0.833	0.493	0.005*
FEV1 (mL)	−0.149	0.423	−0.109	0.560	−0.199	0.283	−0.102	0.584	0.544	0.002*
FEV1%	−0.151	0.416	−0.072	0.700	−0.181	0.331	−0.044	0.814	0.524	0.002*
FEV1/FVC%	−0.473	0.007*	−0.248	0.179	−0.242	0.190	−0.235	0.203	0.231	0.211
FEF25-75 (mL)	−0.253	0.169	−0.224	0.225	−0.243	0.188	−0.154	0.410	0.454	0.010*
FEF25-75%	−0.236	0.201	−0.161	0.388	−0.226	0.221	−0.094	0.617	0.487	0.005*
POST FEV1%	0.026	0.889	−0.156	0.394	−0.017	0.926	−0.111	0.546	0.057	0.757

Montuschi stated that LT B4 concentration increased and PG E2 decreased in exhaled air in COPD patients (5). In contrast to previous studies, we examined blood PG E2 levels in our study and did not observe them to be high in the ACOS group.

Among the parameters evaluated in ACOS patients in our study, PG D2 was negatively associated with cys-LTs, ADAM33, and FEV1/FVC%. Cys-LTs FEV1 was negatively associated with FEF25-75. Among evaluated parameters, PG E2 was negatively associated

with FEV1/FVC% and positively associated with IL-5, FVC, FVC%, FEV1, FEV1%, FEF25-75, and FEF25-75% in COPD patients. In their study, Busse and Mostafavi-Pour-Manshadi investigated the most commonly studied parameters such as serum levels of eosinophil and IgE as well as exhaled nitric oxide levels and found them to be associated with FEV1 variability (10,11). Montuschi et al. reported increased exhaled PG E2 levels in COPD patients and increased LT E 4 levels in asthma patients in their study (12).

Csanky et al. reported a linear correlation with prostaglandin D2 levels in BAL fluid and pulmonary functions (13). Hanazawa et al. did not detect a correlation between LTD4 and FEV1 (%) (14). Jang et al. observed a significant correlation between sputum eosinophil count, IL5 levels, FEV1 and FEV1/FVC ratio (15). In contrast, Samitas et al. observed a negative correlation between cys-LTs and FEV1 in their study (16).

Gross-Sondej and colleagues observed high LT E4 levels in COPD exacerbation (17), whereas Montuschi et al. reported high-exhaled LT E4 levels in children with atopic asthma in their study (18). Choi et al. investigated cys-LTs and ECP levels in nasal lavage fluid in aspirin-exacerbated respiratory disease and aspirin tolerant asthma patients, and observed them to be high in the aspirin-sensitive group (19). After determining allergens in patients with untreated asthma in their study, Bartoli et al. observed high LT E4 levels in urine which were decreased with ICS treatment (20). Baulay et al. reported similar cys-LT levels in induced sputum in asthma patients with or without rhinitis (21). Dal Negro et al. observed high LTE4 urine levels which were decreased with erdos-teine (22). In contrast, we investigated blood cys-LT levels in our study and observed higher cys-LT levels in ACOS patients than in COPD and asthma groups.

Kips et al. examined blood IL5 levels in asthma, COPD, and ACOS patients in their study, and determined that it was highest in asthma and lowest in COPD patients (23). Pérez-de-Llano et al. detected similar blood IL5 levels between eosinophilic COPD patients and smoking asthma patients without complete reversibility (24). Bafadhel and colleagues reported that the levels of proinflammatory mediators IL-6 and IL-8 were increased in COPD, and the expression of cytokines IL-4, IL-5, and IL13 was increased in asthma. (25). Jang et al. observed higher sputum IL5 and ECP levels in asthma patients than in the control group (15). In contrast, IL5 levels were highest in COPD and lowest in ACOS patients in our study.

It has been suggested that matrix metalloproteinases (MMPs) are the main proteolytic enzymes that induce remodeling of the airway in asthma and COPD (26,27). MMP-2 and MMP-9 are the most widely studied MMPs in asthma and COPD. MMP-9 expression is high in COPD patients. It is released from neutrophils and alveolar macrophages (28), and is associated with emphysema (4,29). Perng et al. reported that sputum MMP-9 levels were high in COPD patients, and they decreased with anti-

inflammatory treatment (30). Iwamoto et al. performed a study on ACOS but did not report high levels in ACOS patients (31). In contrast to past studies, we assessed MMP33 levels in our study. We observed that ADAM33 was not different among groups, possibly due to bronchial hyperreactivity and the presence of this parameter, which is associated with remodeling, in all three groups.

There are few studies on inflammation in ACOS. Gao et al. assessed IL-13, myeloperoxidase (MPO), neutrophil gelatinase-associated lipocalin (NGAL), chitinase-like protein (YKL-40), and IL-6 levels in sputum in asthma, COPD, and ACOS patients. They reported that NGAL levels were high in the ACOS group and were correlated with FEV1% (32). Iwamoto et al. examined blood and sputum levels of surfactant protein A (SP-A), soluble receptor for advanced glycation end-products (sRAGE), myeloperoxidase (MPO), and NGAL in COPD, and determined high NGAL levels in ACOS patients (31). Chen and Karampitsakos reported high fractional exhaled nitric oxide (FeNO) levels in ACOS patients (33,34). In contrast to past literature, we evaluated PG D2, PG E2, cys-LTs, IL-5, and ADAM 33 levels in our study. Among these, we observed significantly higher PG D2 levels in the ACOS group.

A positive aspect of our study is that we assessed biomarkers different from those in the literature. A limitation of our study is the small number of patients. Evaluation of significant parameters with larger patient groups may lead to clearer information. Further, examination of bronchoalveolar lavage and exhaled breath condensate samples using similar methods will help to guide new studies.

Conclusions

PG-D2 may be used as a distinctive biomarker in distinguishing asthma and ACOS cases from COPD. FEV1/FVC levels, which are used to show obstruction, were associated with PG-D2 and cys-LTs levels in ACOS patients, and PG-E2 levels in COPD patients. FEV1 levels were negatively related to FEF25-75 values and cys-LTs level in asthma patients.

Declaration of interest

The authors report no conflicts of interest.

Funding

This work was supported by the Haseki Training and Research Hospital Thesis and academic studies commission.

ORCID

Gulfidan Cakmak Uzan  <http://orcid.org/0000-0003-2330-9433>

Sermin Borekci  <http://orcid.org/0000-0002-0089-1312>

Bilun Gemicioglu  <http://orcid.org/0000-0001-5953-4881>

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