Research Article

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The prevalence of asthma-COPD overlap (ACO) among COPD patients and the role of prostaglandin D2 (PGD2) in differential diagnosis

KOAH hastaları arasında astım-KOAH overlap (AKO) sıklığı ve ayırıcı tanıda prostaglandin D2 (PGD2)' nin rolü

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Abstract

Purpose: Asthma-COPD overlap (ACO) is a disease similar to Chronic Obstructive Pulmonary Disease (COPD) with some features of asthma. In the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, it is defined as “asthma and COPD symptoms accompanying each other at similar rates in cases with persistent airflow limitation (postbronchodilator FEV1/FVC<70%)”. We aimed to investigate the frequency of patients with ACO according to GINA and GOLD criteria among those we followed with the diagnosis of COPD and to compare their clinical features and laboratory findings. We evaluated prostaglandin D2 (PGD2) levels in these patients and investigated whether it could be used as a parameter in the differential diagnosis of ACO.

Materials and methods: Patients with COPD who applied to the chest diseases outpatient clinics of 3 hospitals in Denizli were examined between October 2021 and May 2022. Patients aged 40 years and older, who were followed up and treated with COPD by a pulmonologist for at least one year and who gave consent were included in the study. The presence of reversibility was investigated by pulmonary function test (PFT) in all patients. If the postbronchodilator FEV1/FVC was <70% in the patients included in the study and the reversibility was positive, it was considered as ACO. Patients divided into two groups as COPD and ACO were compared in terms of clinical, laboratory, PFT and hospital admissions.

Results: A total of 166 COPD patients were included in the study. 158 of the patients were male and 8 were female, and their mean age was 61.48 (40-84). 30 (18.07%) patients included in the study with the diagnosis of COPD were diagnosed with ACO. While the mean blood eosinophil percentage in ACO patients was higher than in COPD patients, the mean blood neutrophil counts and percentages were lower than in COPD patients (p=0.02, p=0.02, and p=0.03, respectively). Total IgE level of the COPD group was higher than the ACO group (p=0.006).

Conclusion: In our study, PGD2 was ineffective in differentiating ACO patients from COPD patients; mean blood eosinophil percentages and mean blood neutrophil percentages were useful but insufficient.

Keywords: Prostaglandin D2, asthma-COPD overlap, prevalence.

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Öz

Amaç: Astım-KOAH overlap (AKO) bazı özelikleri ile astım bazı özellikleri ile Kronik Obstruktif Akciğer Hastalığına (KOAH) benzeyen bir hastalıktır. Astım için Küresel İnsiyatif (Global Initiative for Astma, GINA) ve KOAH için Küresel İnisiyatif (Global Initiative for Chronic Obstructive Lung Disease, GOLD) rehberlerinde “persistan hava akımı kısıtlanması (postbronkodilatör FEV1/FVC<%70) olan olgularda astım ve KOAH özelliklerinin birbirine yakın oranlarda eşlik etmesidir” şeklinde tanımlanmıştır. KOAH tanısıyla takip ettiğimiz hastalardan GINA ve GOLD kriterlerine göre AKO olan hastaların sıklığını araştırmayı, klinik özelliklerini ve laboratuvar bulgularını karşılaştırmayı amaçladık. Bu hastalarda prostaglandin D2 (PGD2) düzeylerini değerlendirerek AKO ayırıcı tanısında bir parametre olarak kullanılıp kullanılamayacağını araştırdık.

Gereç ve yöntem: Çalışmaya Ekim 2021-Mayıs 2022 tarihleri arasında Denizli’deki 3 hastanenin göğüs hastalıkları polikliniklerine başvuran, en az bir yıldır KOAH tanısıyla takip ve tedavi altındaki 40 yaş ve üzeri hastalar dahil edildi. Tüm hastalarda solunum fonksiyon testi (SFT) ile reversibilite araştırıldı. Hastalarda postbronkodilatatör FEV1/FVC<%70 ve reversibilite pozitifliği bulunması AKO olarak değerlendirildi. KOAH ve AKO olarak ikiye ayrılan hastalar klinik, laboratuvar, SFT ve hastane başvuruları bakımından karşılaştırıldı.

Bulgular: Çalışmaya alınan 166 KOAH hastasının 158’i erkek, 8’i kadındı ve yaş ortalamaları 61,48 (40-84) idi. KOAH tanısıyla çalışmaya alınan 30 (%18,07) hastaya AKO tanısı konuldu. AKO hastalarının ortalama kan eosinofil yüzdesi KOAH’lılardan daha yüksekken, ortalama kan nötrofil sayı ve yüzdeleri KOAH’lılardan

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daha düşüktü (sırasıyla *p*=0,02, *p*=0,02 ve *p*=0,03). KOAH grubunun total IgE düzeyi AKO grubuna göre daha yüksekti (*p*=0,006).
Sonuç: Çalışmamızda AKO hastalarını KOAH'lılardan ayırmada PGD2'nin faydasız; ortalama kan eosinofil yüzdeleri ve ortalama kan nötrofil yüzdelerinin ise faydalı, ancak yetersiz oldukları sonucuna varılmıştır.

Anahtar kelimeler: Prostaglandin D2, astım-KOAH overlap, prevalans.

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Introduction

Asthma-COPD overlap (ACO) is a condition that resembles asthma in some characteristics and Chronic Obstructive Pulmonary Disease (COPD) in others. The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define the situation as "the co-existence of asthma and COPD characteristics in patients with persistent airflow limitation (post-bronchodilator FEV1/FVC<70%) at comparable rates." In the GINA and GOLD guidelines, individuals possessing three or more characteristics of asthma and COPD are identified as presenting ACO. A stepwise approach has been presented to distinguish ACO. ACO is a term newly introduced into the literature and may be overlooked. However, given the available data, the rate is by no means negligible [1, 2]. Based on this, we compared the clinical characteristics and laboratory results of individuals presented with ACO in accordance with GINA and GOLD criteria with COPD.

Furthermore, there is no consensus regarding the biomarkers to be used in the diagnosis of ACO in the available studies [3-8]. One of the biomarkers that can assist in the diagnosis of ACO is Prostaglandin D2 (PGD2). Prostaglandin D2 (PGD2) is an important prostanoid primarily produced by mast cells in various allergic diseases, including asthma. The effects of PGD2 in causing vasodilation and increased vascular permeability are notable in allergic inflammation, and it is a potent bronchoconstrictor [9]. However, the literature evaluating Prostaglandin D2 (PGD2) in ACO is not adequate. In our study, we investigated the prevalence of ACO in COPD patients who visited chest diseases outpatient clinics and whether PGD2 can be utilized as a parameter in differential diagnosis.

Materials and methods

We included consecutive patients diagnosed with COPD who applied to the pulmonary diseases outpatient clinics of three hospitals in Denizli province between October 1, 2021 and May 1, 2022. Patients aged 40 and above, who have been under follow-up and treatment for at least one year with a diagnosis of COPD by a thoracic disease specialist, were included. When the sample size was calculated using the formula for unknown population size, assuming a margin of error of d=0.05 and a prevalence of 9% [10], it was determined that at least 126 participants meeting the inclusion criteria should be included in the study. Among these patients, those with lung diseases other than COPD (asthma, bronchiectasis, pneumonia, pulmonary embolism, interstitial lung disease, and lung cancer diagnosis) and pregnant women were excluded from the study. Patients with COPD were evaluated using the stepwise approach related to ACO in the GINA and GOLD guidelines. General characteristics of asthma and COPD and determination of the probability of ACO diagnosis are shown in Table 1. The presence of reversibility in all patients was investigated using a pulmonary function test. Patients included in the study were evaluated as having ACO if their post-bronchodilator FEV1/FVC was <70% and reversibility was positive. Patients classified into COPD and ACO groups were compared in terms of clinical, laboratory, pulmonary function tests (PFT), and hospital admissions. Complete blood counts were measured in venous blood samples taken from patients in EDTA tubes using an Abbott Cell-Dyn Ruby device. Venous blood samples taken from participants in yellow-capped gel-lined tubes were centrifuged at 4100 rpm for 10 minutes, and the serum was separated. Total IgE was measured using the immunoturbidimetric method

using an Abbott Achitect İ2000SR (U.S.A.) device. The remaining serum was placed in 0.5 cc Eppendorf tubes and stored at -80°C in a Nüve (Türkiye) brand deep freezer. On the day of the study, the samples were vortexed and allowed to reach working temperature. Serum Prostaglandin D2 levels were measured in the Medical Biochemistry Research Laboratory of PAU Faculty of Medicine using a BT-Lab brand commercial ELISA kit (catalog no: EA0185Hu) on a Biotek ELx800 Absorbance Microplate Reader. The levels of PGD2 in patients with ACO and COPD were measured to determine whether the difference between both groups was significant in distinguishing them.

Approval for the study was obtained from the Non-Invasive Clinical Research Ethics Committee of Pamukkale University (06/10/2020-E.60671).

Table 1. Determining the general characteristics of asthma and COPD and the probability of ACO diagnosis (1)

Characteristics	Asthma	COPD
Onset	▪ <40 years	▪ >40 years
Respiratory symptoms	▪ Symptom variability over minutes, hours, and days ▪ Symptoms worsen at night and in the morning ▪ Symptoms that occur with triggers	▪ Persistence of symptoms despite treatment ▪ Sometimes better, sometimes worse, but always daily symptoms and exertional dyspnea ▪ Chronic cough and sputum production ▪ Dyspnea unrelated to triggers
Respiratory functions	▪ Variable expiratory airflow limitation	▪ Persistent airflow restriction (Post-BD FEV1/FVC<0,7)
PFT during symptom-free periods	▪ Normal	▪ Abnormal
CV and family history	▪ Diagnosis of asthma in childhood or currently ▪ Family history of asthma or allergies	▪ Diagnosis of COPD, chronic bronchitis, or emphysema ▪ History of tobacco or biomass exposure
Clinical Course	▪ No worsening of symptoms over time ▪ Seasonal or year-to-year variability ▪ Spontaneous or treatment-induced improvement ▪ Rapid response to bronchodilators or response to ICS within weeks	▪ Slow progression over years ▪ Partial relief with bronchodilators
Chest X-ray	▪ Normal	▪ Severe air trapping

Post-BD: Post-bronchodilator, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity
COPD: Chronic obstructive pulmonary disease, ACO: Asthma-COPD overlap, ICS: Inhaled corticosteroid

Statistical analysis

The data were analyzed using SPSS 25.0 (IBM SPSS Statistics 25 software package, Armonk, NY: IBM Corp.). Continuous variables are expressed as mean±standard deviation, median, 25th-75th percentiles (interquartile range-IQR), and categorical variables are expressed as count (n) and percentage (%). The conformity of the data to a normal distribution was examined using the Shapiro-Wilk test. In the examination of independent group differences, when the assumptions for parametric tests were met, the independent samples t-test was used; and when the assumptions were not met, the Mann-Whitney U test was utilized. The Chi-square analysis was utilized in examining the differences between categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of PGD2 levels, eosinophil percentage, neutrophil percentage, and their combined model in distinguishing asthma–COPD overlap (ACO) from COPD. ROC curves and area under the curve (AUC) values were generated using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The diagnostic accuracy of each parameter was assessed based on AUC values. In all analyses, $p<0.05$ was considered statistically significant.

Results

A total of 166 patients diagnosed with COPD were included in the study. Of the patients, 158 were male, 8 were female, and their mean age was 61.48 (range: 40-84). Among the patients included in the study with a diagnosis of COPD, 30 patients (18.07%) were diagnosed with ACO. The demographic characteristics and laboratory results of the patients are shown in Table 2.

In the ACO group, the mean eosinophil percentage was higher at 2.87% compared to the mean eosinophil percentage of 2.02% in the COPD group ($p=0.02$). The diagnostic performance of the eosinophil percentage was evaluated with ROC analysis, and it was determined that its use as a parameter alone would not be sufficient to distinguish ACO (AUC: 73%, $p=0.028$). The ROC curve for the eosinophil percentage is shown in Figure 1.

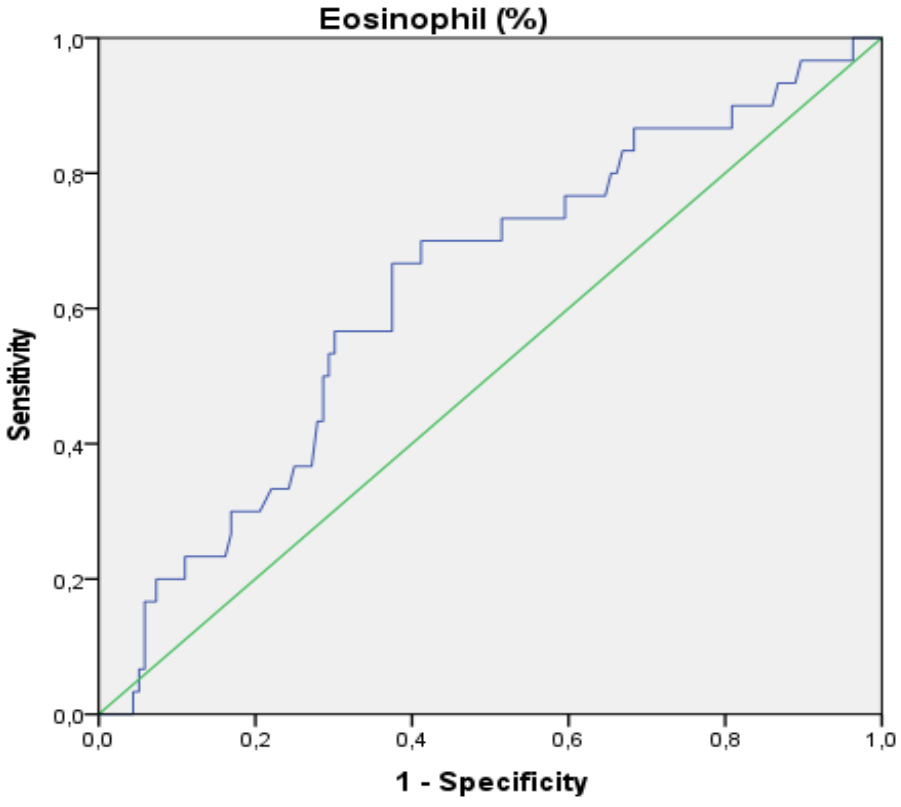

Figure 1. The ROC curve for the eosinophil percentage

The mean neutrophil counts and mean neutrophil percentages in patients with COPD were significantly higher compared to those with ACO (p=0.02 and p=0.03, respectively). An evaluation of neutrophil percentages showed that patients with COPD had a higher average of 62.58% compared to the average level of 58.68% in patients with ACO. When the diagnostic performance of the neutrophil percentage was evaluated using ROC analysis, it was considered that its use alone as a parameter for distinguishing ACO would not be sufficient (AUC: 72%, p=0.047). The ROC curve for the percentage of neutrophils is shown in Figure 2.

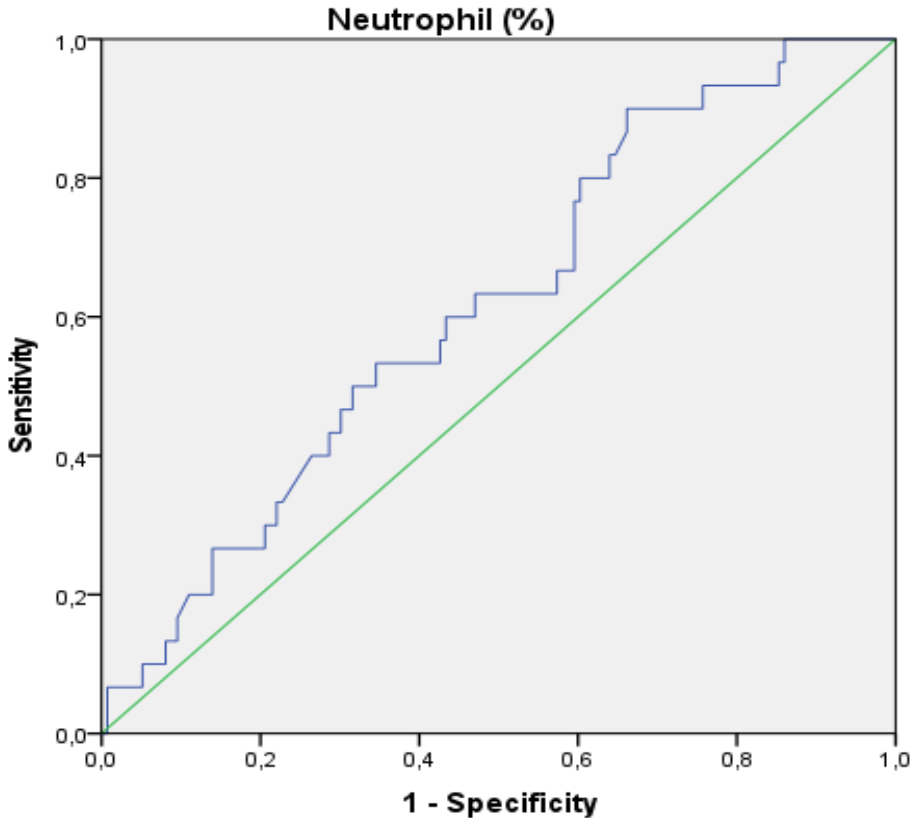

Figure 2. The ROC curve for the percentage of neutrophils

When the mean eosinophil and neutrophil percentages are jointly modeled with ROC analysis for the diagnosis of ACO, it was found that this did not provide any additional benefit in terms of specificity compared to their individual evaluations (AUC: 72%, p=0.037). The combined ROC curve is shown in Figure 3.

In our study, the mean PGD2 levels of ACO patients were 255.37 (154.2-219.94), and the mean PGD2 levels of COPD patients were 244.68 (159.26-213.1), with no significant difference between the groups (p=0.858) (Table 2). The diagnostic performance of PGD2 was evaluated using ROC analysis, and we concluded that it was not successful in distinguishing patients with ACO (AUC: 51%, p=0.858). The ROC curve for the PGD2 levels is shown in Figure 4.

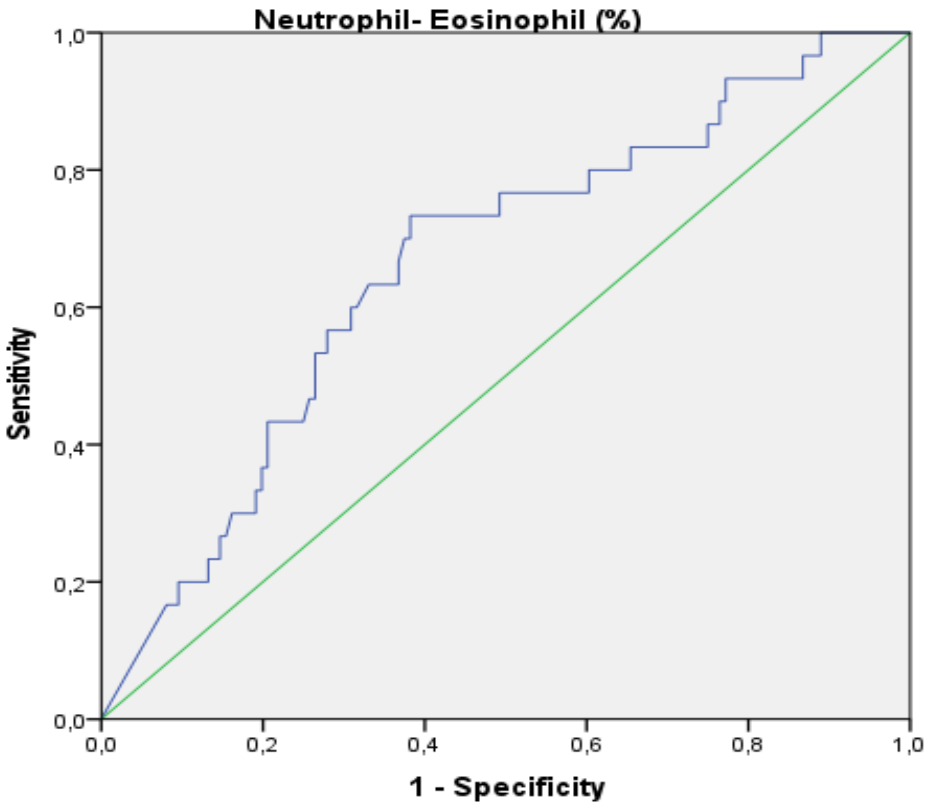

Figure 3. The combined ROC curve of mean neutrophil and eosinophil percentage

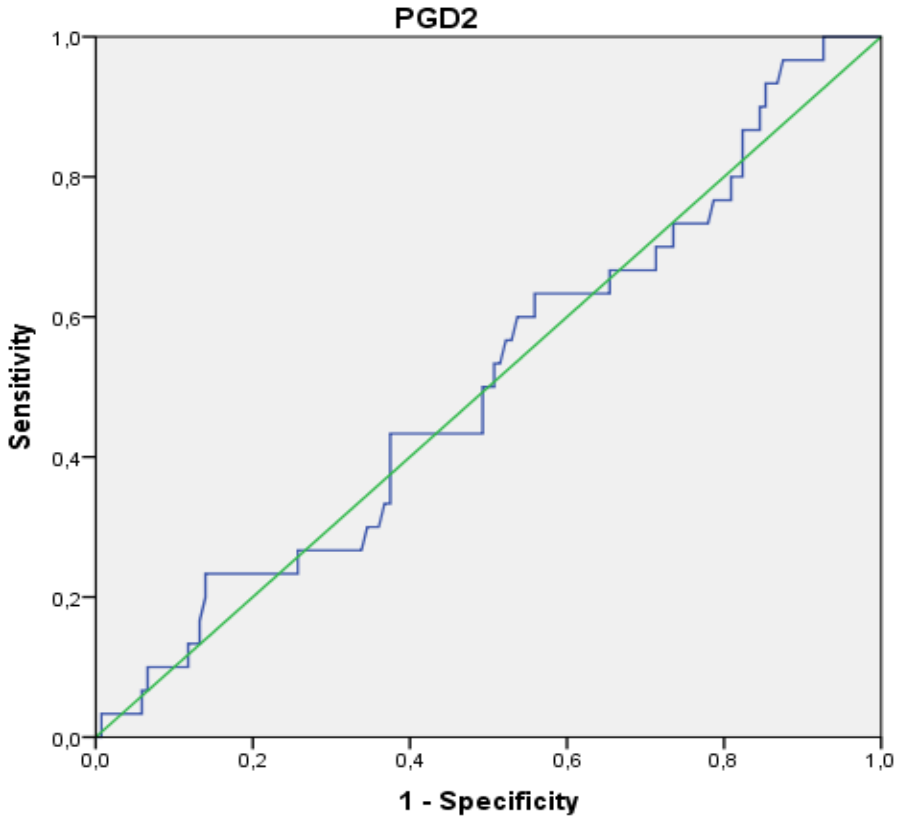

Figure 4. The ROC curve for the PGD2 levels

Table 2. Demographic characteristics and laboratory results of COPD and ACO patients

	COPD (n:136)		ACO (n:30)		
	Mean±SD	**Median (IQR)**	**Mean±SD**	**Median (IQR)**	***p***
Age (year)	62.56±9.5	63(56-69)	63.73±8.18	64.5 (57-70.25)	0.531 (t=-0.627)
Height (cm)	166.4±10.75	166.5 (163-172)	163.2±20.16	166.5 (161.5-172.25)	0.814 (z=-0.235)
Weight (kg)	75.68±15.23	74.5 (64-85)	81.9±15.87	78 (69.5-95.5)	0.057 (z=-1.904)
BMI (kg/m²)	27.02±4.78	26.22 (23.25-29.74)	29.9±4.46	30.11 (25.55-33.83)	0.002* (z=-3.114)
Cigarette (package/year)	44.24±29.33	40 (30-50)	40.5±22.1	40 (30-50)	0.914 (z=-0.108)
FEV1 (L)	1.55±0.67	1.4 (0.99-2)	1.37±0.51	1.45 (0.93-1.68)	0.385 (z=-0.869)
FEV1%	55.7±20.27	57 (38.25-71.75)	52±16.65	52 (36-64.25)	0.352 (t=0.933)
FVC (L)	3.12±5.59	2.47 (1.95-3.3)	2.42±0.66	2.5 (1.84-2.85)	0.324 (z=-0.986)
FVC%	76.6±20.28	76.5 (62-91)	72.1±18.12	72 (59.25-88)	0.265 (t=1.12)
FEV1/FVC%	57.49±9.06	59.65 (49.43-64.95)	57.89±8.27	57.75 (52.83-63.73)	0.915 (z=-0.107)
FEF25-75 (L)	0.89±0.44	0.80 (0.53-1.23)	0.82±0.34	0.88 (0.51-0.97)	0.687 (z=-0.403)
FEF25-75%	30.87±12.89	31 (19.25-40)	29.2±11.39	29.50 (18.75-36.25)	0.472 (z=-0.72)
Post FEV1 (L)	1.63±0.71	1.45 (1.06-2.08)	1.71±0.46	1.74 (1.28-1.91)	0.462 (t=-0.74)
Post FEV1%	58.19±20.53	58 (43-75)	64.1±16.55	63 (53.75-73.75)	0.171 (z=-1.37)
Delta FEV1 (L)	0.08±0.08	0.07 (0.01-0.13)	0.32±0.12	0.26 (0.22-0.44)	0.0001* (z=-8.1)
Delta FEV1%	5.97±5.78	4.5 (1-9.75)	26.43±19.36	19 (14-26.25)	0.0001* (z=-7.801)
Eosinophil (10^3/uL)	0.22±0.2	0.18 (0.1-0.3)	0.25±0.17	0.23 (0.13-0.31)	0.16 (z=-1.405)
Eosinophil (%)	2.88±6.09	2.02 (1.1-3.17)	2.88±1.56	2.87 (1.71-3.95)	0.028* (z=-2.199)
Neutrophil (10^3/uL)	6.17±2.43	5.76 (4.4-7.15)	5.13±1.8	5.02 (3.71-5.91)	0.025* (z=-2.237)
Neutrophil (%)	62.58±9.44	62.21 (56-67.93)	58.68±7.81	58.03 (52.92-64.91)	0.036* (t=2.109)
Total IgE (IU/mL)	234.75±773.32	51.3 (21.73-126.25)	59.23±103.63	22.8 (6.23-54.4)	0.006* (z=-2.771)
PGD2 (ng/mL)	244.68±262.51	187.23 (159.26-213.1)	255.37±274.88	186.16 (154.2-219.94)	0.858 (z=-0.178)

T-test and Mann-Whitney U test were used in independent groups. Mean: Arithmetic mean; SD: Standard deviation; Med (IQR): Median (25th–75th percentiles),FEV1: Forced expiratory volume in one second FVC: Forced vital capacity, FEF25-75: Forced expiratory flow at 25% and 75% of the pulmonary volume, Post-FEV1: Post-bronchodilator FEV1

Discussion

No definitive rate has been reported for the prevalence of ACO in epidemiological studies. The prevalence of ACO has been reported to range between 11% and 55%, depending on the diagnostic criteria such as the history and/or functional parameters used in the study, as well as whether the study is retrospective or prospective [11]. The reasons for such variability in prevalence can be attributed to differences in the definition of ACO, the characteristic features of different populations, and variations in study conditions. In the COPDGene study, which included 915 patients with COPD, 13% of the patients were identified as presenting ACO; while in the PLATINO study, 12% of the patients were diagnosed with ACO, and in another study, 17.4% of the patients were reported to have ACO [11-13]. A recent meta-analysis evaluated seventeen studies and reported that 27% of patients diagnosed with and followed up for COPD had ACO [14]. In the study conducted by Özdemir in 2021 [15], the ratio of COPD patients diagnosed with ACO was found to be 19%. As part of examining the prevalence of ACO in patients included in the present study, it was found that 18.07% of our patients diagnosed with COPD were also diagnosed with ACO, which was found to be similar to those reported in previous studies.

While neutrophilic inflammation predominates in patients with COPD, eosinophilic inflammation is more prevalent in asthma patients [1, 2]. However, as a large number of asthma patients with moderate to severe symptoms have been found to have a significant amount of neutrophils in their airways, an increase in the count of eosinophils in sputum and peripheral blood has been observed in 30% to 40% of patients diagnosed with COPD [16]. Since ACO patients exhibit characteristics of both asthma and COPD, both neutrophilic and eosinophilic inflammation can be observed together. In another study comparing ACO and COPD patients, the peripheral eosinophil percentage was found to be higher in ACO patients than in COPD patients [17]. In a study conducted in the United States, the mean eosinophil percentage in patients with COPD was 2.73%, while the mean eosinophil percentage in patients with ACO was reported to be 3.18% [18]. In our study, the peripheral eosinophil percentage in patients with ACO (2.87%) was significantly higher compared to those with COPD (2.02%). The mean peripheral neutrophil count (5.76) and percentage (62.21%) in the COPD group were significantly higher compared to the ACO group (5.02 and 58.03%), which was in line with other studies. However, both individual and combined modeling ROC analyses demonstrated that the diagnostic performance of the eosinophil percentage and neutrophil percentage was inadequate (respectively, AUC: 73%, 72%, 72%, respectively).

ACO is a recently introduced term in the literature. A biomarker that can be used to distinguish ACO patients from asthma and COPD patients has not yet been identified. PGD2 is an inflammatory mediator primarily produced in mast cells in many allergic diseases, including asthma, which triggers vasodilation and an increase in vascular permeability. It leads to an increased mucus secretion in the respiratory tract and inflammation [19]. In the literature, there are very few studies regarding PGD2 levels in patients with ACO. In the study conducted by Uzan et al. [20] investigating PGD2 levels in patients with ACO, it was concluded that PGD2 could be a biomarker capable of distinguishing patients with ACO from those with chronic obstructive pulmonary disease (COPD). In a study by Özdemir [15], the PGD2 value in patients with ACO was reported to be 215.99 ng/mL on average, while in patients with COPD it was an average of 62.19 ng/mL, and this difference was statistically significant. The diagnostic performance of PGD2 was assessed using ROC analysis, and it was concluded that it could be used to distinguish patients with ACO. The sensitivity value of PGD2 in ACO patients was 75%, and the specificity value was 82.4%. The cutoff value for PGD2 to be used in diagnosis, as evaluated by the Youden index, was determined to be 71.4 ng/mL [14]. In our study, no significant difference was found between the PGD2 levels of patients with ACO and COPD. In the literature, there is no other study evaluating PGD2 as a biomarker to distinguish patients with ACO from those with COPD other than our study, the study by Özdemir [15], and the one conducted by Uzan et al. [20]. Therefore, further studies are

required on PGD2 and other biomarker levels in distinguishing ACO patients from COPD patients. Such studies will contribute to the literature to facilitate differential diagnosis.

The most significant limitation of our study is that it was conducted during the COVID-19 pandemic, which resulted in a lower number of patient consultations and patients. Secondly, specific IgE could not be measured. The third limitation is the presence of subjective data due to the fact that much of the data has been obtained through questionnaires.

In conclusion, the frequency of ACO has been found to be significant among patients diagnosed with COPD. The recognition of this patient group and close monitoring gain importance as it requires a treatment tailored to the patient and oversight of treatment adherence. Our study concluded that PGD2 is ineffective in distinguishing ACO patients from COPD patients, whereas the mean blood eosinophil percentages and mean blood neutrophil percentages are useful but insufficient. Larger scale randomized controlled studies with larger patient numbers are needed on this subject.

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Author contributions: S.H.A. and Y.E. collected the data and contributed to the discussion. They reviewed and edited the manuscript and contributed to the discussion.

Conflict of interest: The authors have declared that no competing interest exists.

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