Original paper

Clinical characteristics of asthma-chronic obstructive pulmonary disease overlap phenotypes

Özge Atik[1], Fatma Merve Tepetam[1], Şeyma Özden[1], Ayşe Ezgi Ak[2]

[1]Department of Immunology and Allergy, University of Health Sciences Süreyyapasa Chest Disease and Chest Surgery Training and Research Hospital, Istanbul, Türkiye
[2]Department of Chest Disease, University of Health Sciences Süreyyapasa Chest Disease and Chest Surgery Training and Research Hospital, Istanbul, Türkiye

Adv Dermatol Allergol 2025; XLII (3): 283–290
DOI: https://doi.org/10.5114/ada.2025.152082

Abstract

Introduction: Asthma-chronic obstructive pulmonary disease overlap (ACO) patients are categorized as those with persistent airflow limitation and features of asthma and chronic obstructive pulmonary disease (COPD).
Aim: This study aimed to identify ACO subgroups based on atopy, bronchodilator response (BDR), and eosinophil count.
Material and methods: From 2021 to 2024, we conducted a retrospective study on patients with asthma and/or COPD who underwent BDR testing. An ACO diagnosis required persistent airflow limitation, a history of asthma before the age of 40 or significant BDR, and at least one minor criterion. Patients were grouped by atopy status, BDR presence, and eosinophil count. We compared demographic, laboratory, spirometry, and medication data across subgroups.
Results: The study included 109 ACO patients with a mean age of 49.5 ±10.7 years. Atopic ACO patients showed a higher increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent (ΔFEV_1BDR) and higher total IgE levels than non-atopic patients (200 ml vs. 100 ml, $p = 0.034$; 211 IU/ml vs. 60 IU/ml, $p = 0.002$). Eosinophil counts were higher in the BDR-positive group (360/µl vs. 195/µl, $p = 0.047$). High eosinophilic ACO patients also had elevated IgE levels (323 IU/ml vs. 80 IU/ml, $p = 0.001$). BDR-positive and eosinophilic groups demonstrated better spirometric results. Atopic ACO patients used more leukotriene receptor antagonists, while BDR-negative ACO patients used antimuscarinics.
Conclusions: Higher ΔFEV_1BDR in atopic ACO indicates they may respond better to bronchodilators. Elevated eosinophil counts in BDR-positive patients support their classification and suggest less severe disease progression.

Key words: asthma, asthma-chronic obstructive pulmonary disease overlap, chronic obstructive pulmonary disease, phenotype.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) rank among the most prevalent chronic lung conditions. On average, one in every twelve individuals globally is affected by either asthma or COPD [1, 2].

Asthma is a condition characterized by chronic inflammation in the airways. This inflammation causes symptoms like cough, wheezing, shortness of breath, and chest tightness, which vary in intensity [1]. It involves airflow limitation caused by the increased activity of eosinophils and mast cells. This leads to thickening of the airway walls and smooth muscle hypertrophy, ultimately causing airway remodelling [3, 4].

COPD is a preventable and treatable condition marked by lung disorders that cause persistent, often progressive airflow limitation. It includes symptoms like shortness of breath, cough, and expectoration resulting from airway (bronchitis, bronchiolitis) and/or alveolar (emphysema) abnormalities [1, 5]. COPD typically develops after the age of forty due to tobacco use. Airflow limitation may be reversible with bronchodilators but can also be persistent and irreversible. Small airway remodelling in COPD is characterized by airway wall fibrosis and squamous metaplasia, driven by immune cells like neutrophils and macrophages [6, 7]. Asthma and COPD are respiratory diseases with similar symptoms but different underlying mechanisms, making it difficult to

Address for correspondence: Özge Atik MD, University of Health Sciences Süreyyapasa Chest Disease and Chest Surgery Training and Research Hospital, Maltepe, Istanbul, Türkiye, phone: +905334685700, fax: +90 2164214130, e-mail: drozgeatik@gmail.com
Received: 13.12.2024, **accepted:** 26.01.2025, **online publication:** 12.06.2025.

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distinguish between them in some patients. The GINA and GOLD guidelines recognize individuals with features of both conditions, leading to the definition of asthma-COPD overlap syndrome (ACOS) [8]. However, since ACOS reflects various clinical phenotypes, the term "asthma-COPD overlap (ACO)" is preferred [9]. ACO is diagnosed in patients with persistent airflow limitation (FEV_1/FVC < 70%) and symptoms of both asthma and COPD. Prevalence rates vary widely, ranging from 0.9% to 66%, depending on the population. ACO symptoms are variable, improving intermittently and triggered by different factors [10, 11]. A history of childhood asthma or pre-40 asthma diagnosis, smoking, or toxin exposure is common. Pulmonary tests show persistent airflow limitation and bronchodilator response (BDR) (≥ 12% and ≥ 200 ml for FEV_1), with high reversibility (> 15% and > 400 ml) often seen. ACO should also be considered in COPD patients with eosinophilia [12, 13].

The natural progression and long-term outcomes of ACO are not well understood. Patients often face frequent, severe exacerbations, leading to hospitalizations and emergency visits, which worsen the quality of life and increase healthcare costs [14]. Despite attempts to differentiate patients based on factors like age of onset, smoking history, risk factors, pulmonary tests, and chest radiographs, diagnosing and treating ACO remains challenging [11, 15, 16].

Patients diagnosed with ACO based solely on pulmonary function tests are heterogeneous and can be further categorized by their phenotypic characteristics. Few clinical studies have explored ACO phenotypes, which are influenced by factors like exposure to toxic substances, BDR, atopy, and eosinophilic inflammation [17–19]. Each phenotype has distinct pathophysiology, characteristics, and prognoses, making individualized treatment essential. Understanding these phenotypes helps define the condition and guide therapeutic strategies.

Aim

This study aimed to identify subgroups of ACO patients based on atopy, BDR, and eosinophil count.

Material and methods

The study included all patients diagnosed with asthma and/or COPD and had been followed up in our clinic between 2019 and 2023. Patients with missing data (unknown smoking history, no reversibility test, no atopic evaluation) and patients with comorbid diseases such as malignancy, rheumatological disease, vasculitis, sarcoidosis, a1-antitrypsin deficiency, previous tuberculosis, pulmonary infections, bronchopulmonary aspergillosis, or interstitial lung disease and pregnancy were excluded.

ACO was diagnosed according to a global expert panel discussion in 2016. The panel comprised various specialists from North America, Western Europe, and Asia. They reported a consensus on ACO based on major and minor clinical, spirometry, and laboratory criteria, as stated below [20].

Major criteria

1. Persistent airflow limitation (post-bronchodilator FEV_1/FVC < 0.70) in individuals of 40 years of age or older;
2. At least 10 pack-years of tobacco smoking;
3. Documented history of asthma before 40 years of age or BDR of > 400 ml in FEV_1 (FEV_1 increase > 400 ml over baseline, 20 min after inhalation of 400 µg of salbutamol).

Minor criteria

1. Documented history of atopy;
2. A BDR of FEV_1 ≥ 200 ml and 12% from baseline values observed on two or more visits;
3. Eosinophil count of ≥ 300 cells/µl.

The committee recommends that all three primary criteria and at least one minor criterion be present for diagnosing ACO (Figure 1).

From the computerized hospital data of the patients, age, gender, body mass index (BMI), and pulmonary function test results (FEV_1 ml, FEV_1%, FEV_1/FVC ratio, FEF25/75%), an increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent (ΔFEV_1BDR: absolute vol-

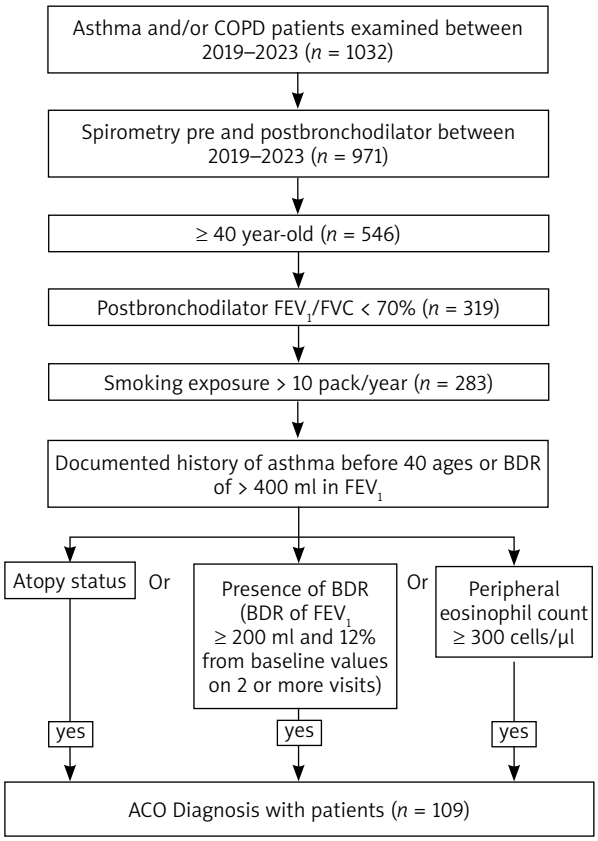


Figure 1. Flow chart of study design

Table 1. Baseline demographic, clinical, and laboratory features of patients diagnosed with ACO

Parameter	Total ACO (*n* = 109)
Age [years] mean ± SD	49.5 ±10.7
Gender female, *n* (%)	73 (57.8)
BMI [kg/m^2] median (IQR)	25.83 (6.24)
FEV_1 [ml] mean ± SD	1810.55 ±725.53
FEV_1 (%), median (IQR)	63 (21)
FEV_1/FVC, median (IQR)	63.10 (10.85)
$FEF_{25–75}$ (%), mean ± SD	30.17 ±11.43
ΔFEV_1BDR [ml] median (IQR)	160 (205)
ΔFEV_1%, median (IQR)	11 (10)
Peripheral eosinophil count [cells/µl] median (IQR)	280 (500)
Total IgE [IU/ml] median (IQR)	249 (350)

BMI – body mass index, IQR – interquartile range, SD – standard deviation, ΔFEV_1BDR, ml – an increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent, ΔFEV_1% – of the initial FEV_1.

Table 2. Radiological findings and medications of patients diagnosed with ACO

Parameter	Total ACO (*n* = 109)
Thorax CT, *n* (%)	53 (48.6)
Bronchial wall thickening	19 (17.4)
Mosaic perfusion	7 (6.4)
Bronchiectasis	18 (16.5)
Emphysema	4 (3.7)
Medications, *n* (%)	
Intranasal corticosteroids and/or oral antihistamines	21 (19.3)
Anti-leukotrienes	25 (22.9)
ICS + LABA	58 (53.2)
LAMA	38 (35)
SABA	28 (25.6)
SAMA	14 (12.8)

CT – computed tomography, ICS – inhaled corticosteroids, LABA – long-acting inhaled beta-agonists, LAMA – long-acting anti-muscarinic drugs, SABA – short-acting inhaled beta two agonists, SAMA – short-acting anticholinergics.

Table 3. Comparison of characteristics of ACO phenotype groups according to atopy status

Parameter	Atopic (*n* = 77)	Non-atopic (*n* = 32)	*P*-value
Age [years] mean ± SD	48.5 ±10.0	52.2 ±11.7	0.096
Gender, female, *n* (%)	46 (59.7)	17 (53.1)	0.524
BMI [kg/m^2] median (IQR)	25.83 (6.29)	25.67 (5.29)	0.793
FEV_1 [ml] mean ± SD	1867.79 ±748.77	1672.81 ±657.00	0.203
FEV_1 (%) median (IQR)	64 (22)	59 (20)	0.232
FEV_1/FVC median (IQR)	63.60 (10.60)	61.80 (10.80)	0.235
FEF25/75 (%), mean ± SD	30.90 ±11.90	28.41 ±10.20	0.303
ΔFEV_1BDR [ml] median (IQR)	200 (215)	100 (177)	0.034
ΔFEV_1%, median (IQR)	11 (10)	7 (11)	0.208
Peripheral eosinophil count [cells/µl] median (IQR)	310 (535)	220 (295)	0.316
Total IgE [IU/ml] median (IQR)	211 (448)	60 (246)	0.002

IQR – interquartile range, SD – standard deviation, BMI – body mass index, ΔFEV_1BDR, ml – an increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent, ΔFEV_1% – of the initial FEV_1.

ume change (ml), ΔFEV_1%: of the initial FEV_1), atopy status (skin prick test or allergen-specific IgE results), radiological findings, medication (inhaled corticosteroid (ICS), long-acting bronchodilator (LABA), short-acting inhaled beta two agonists (SABA), long-acting muscarinic antagonist (LAMA), short-acting anticholinergics (SAMA), combination of ICS-LABA, anti-leukotrienes, intranasal corticosteroids, oral antihistamines) and laboratory findings (total IgE, peripheral eosinophil count) were recorded.

Classification of ACO phenotypes

We divided the patients into groups considering the presence of 3 minor criteria: the atopy status (atopic or non-atopic ACO), the presence of BDR (BDR positive or negative ACO) and peripheral eosinophil count (high eosinophilic ACO: ≥ 300 cells/µl or low eosinophilic ACO: < 300 cells/µl).

Considering these three categories, the atopic vs. non-atopic ACO, BDR positive vs. negative ACO, and high eosinophilic vs. low eosinophilic ACO subgroups were compared in terms of demographic-clinic characteristics, spirometric measurements, peripheral eosinophil count-total IgE levels, and medication categories.

Statistical analysis

SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL, USA) was used. Parametric variables were

Table 4. Comparison of characteristics of ACO phenotype groups according to presence of BDR

Parameter	BDR positive (*n* = 53)	BDR negative (*n* = 56)	*P*-value
Age [years] mean ± SD	45.5 ±7.7	53.4 ±11.6	< 0.001
Gender female, *n* (%)	31 (58.5)	32 (57.1)	0.887
BMI [kg/m^2] median (IQR)	25.31 (5.11)	26.35 (7.23)	0.406
Presence of atopy, *n* (%)	41 (77.4)	36 (64.3)	0.134
FEV_1 [ml] mean ± SD	2080 ±672	1555.54 ±685.76	< 0.001
FEV_1 (%), median (IQR)	66 (17)	57 (26)	0.002
FEV_1/FVC median (IQR)	64.00 (8.9)	60.55 (14.58)	0.044
$FEF_{25–75}$ (%), mean ± SD	34.02 ±9.51	26.52 ±11.98	< 0.001
ΔFEV_1BDR [ml] median (IQR)	280 (175)	70 (80)	< 0.001
ΔFEV_1% median (IQR)	13 (9)	5 (6)	< 0.001
Peripheral eosinophil count [cells/µl] median (IQR)	360 (460)	195 (482)	0.047
Total IgE [IU/ml] median (IQR)	126 (408)	169 (346)	0.709

IQR – interquartile range, SD – standard deviation, BMI – body mass index, ΔFEV_1BDR, ml – an increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent, ΔFEV_1% – of the initial FEV_1.

expressed as means and standard deviations, and non-parametric variables were expressed as medians and minimum-maximum values. Several cases and percentages were used for categorical variables. χ^2 or Fisher's exact test was used to analyse categorical variables. The normal distribution of continuous variables was determined by Kolmogorov-Smirnov test and histogram analyses. Normally distributed numerical variables were analysed using the Student *t*-test. Mann-Whitney *U* test was used to compare numerical variables that were not normally distributed. A *p*-value of 0.05 or less was generally considered statistically significant.

Results

ACO was diagnosed in 11.2% of 971 patients with asthma and/or COPD who were followed up in our clinic with recorded postbronchodilator spirometry results. A total of 109 ACO patients with a mean age of 49.5 ±10.7 years, 73 (57.8%) of whom were female, were included in the study. The mean value of FEV_1 was 1810.55 ml. The median for the FEV_1/FVC ratio was 63.10%, for ΔFEV_1BDR 160 ml, for peripheral eosinophil count 280 cells/µl, and for total IgE 249 IU/ml. Baseline characteristics of the patient groups and all ACO patients whose ACO diagnosis was confirmed, considering the atopy status or presence of BDR or eosinophil count, are given in Table 1.

Table 2 shows the distribution of radiological findings and drug categories used. The most common radiological findings are peribronchial thickening and bronchiectasis, and the most frequently used drug is ICS + LABA.

Considering the atopy status, it was determined that the ΔFEV_1BDR and total IgE level of the atopic ACO group were higher than those of the non-atopic ACO group (200 ml vs. 100 ml, $p = 0.034$; 211 IU/ml vs. 60 IU/ml $p = 0.002$, respectively) (Table 3).

When the ACO subgroups were compared according to the presence of BDR, the average age of BDR-positive patients was lower than that of BDR-negative patients (45.5 years vs. 53.4 years, $p < 0.001$). FEV_1 value and FEV_1 %, FEV_1/FVC ratio, $FEF_{25–75}$%, and peripheral eosinophil count of the BDR positive group were found to be statistically significantly higher than the BDR negative group (2080 ml vs. 1555 ml, $p < 0.001$; 66% vs. 57%, $p = 0.002$; 64.00% vs. 60.55%, $p = 0.044$, 34.02% vs. 26.52%, $p < 0.001$; 360 cells/µl vs. 195 cells/µl, $p = 0.047$, respectively) (Table 4).

When the high eosinophilic vs. low eosinophilic ACO subgroups were compared, the FEV_1 value, FEV_1/FVC ratio and total IgE level of the high eosinophilic ACO group were found to be statistically significantly higher than the low eosinophilic ACO group (1982 ml vs. 1659 ml, $p = 0.020$; 65.50% vs. 60.85%, $p = 0.023$; 323 IU/ml vs. 80 IU/ml, $p = 0.001$, respectively) (Table 5).

The characteristics of the atopic, BDR-positive, and eosinophilic ACO subgroups are presented in Figure 2. This figure contains detailed information about each subset's clinical, spirometric, and laboratory measurements.

Radiological findings were similar in ACO subgroups. When we look at the distribution of medication categories, ICS + LABA and SABA were used at similar rates in atopic vs. non-atopic ACO, BDR-positive vs. BDR-negative ACO, or high eosinophilic vs. low eosinophilic ACO. However, the use of leukotriene receptor antagonists and intranasal corticosteroids and/or oral antihistamines is higher in atopic ACO than in non-atopic ACO ($p = 0.036$). LAMA and SAMA were significantly higher in BDR-negative ACO than in BDR-positive ACO ($p < 0.001$).

Table 5. Comparison of characteristics of ACO phenotype groups according to peripheral eosinophil count

Parameter	High eosinophilic (eosinophil count ≥ 300 cells/µl) (*n* = 51)	Low eosinophilic (eosinophil count < 300 cells/ µl) (*n* = 58)	*P*-value
Age [year] mean ± SD	48.2 ±9.5	50.7 ±11.5	0.224
Gender female, *n* (%)	27 (52.9)	36 (62.1)	0.336
BMI [kg/m^2] median (IQR)	26.35 (5.22)	25.61 (8.21)	0.516
Presence of atopy, *n* (%)	40 (78.4)	37 (63.8)	0.094
FEV_1 [ml] mean ± SD	1982.16 ±690.50	1659.66 ±727.75	0.020
FEV_1 (%), median (IQR)	64 (21)	60 (23)	0.127
FEV_1/FVC median (IQR)	65.50 (9.4)	60.85 (10.75)	0.023
FEF25/75 (%), mean ± SD	31.88 ±10.70	28.66 ±11.93	0.142
ΔFEV_1BDR [ml] median (IQR)	210 (240)	110 (195)	0.080
ΔFEV_1% median (IQR)	13 (8)	8 (9)	0.107
Peripheral eosinophil count [cells/µl] median (IQR)	640 (690)	110 (112)	< 0.001
Total IgE [IU/ml] median (IQR)	323 (459)	80 (250)	0.001

IQR – interquartile range, SD – standard deviation, BMI – body mass index, ΔFEV_1BDR, ml – an increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent, ΔFEV_1% – of the initial FEV_1.

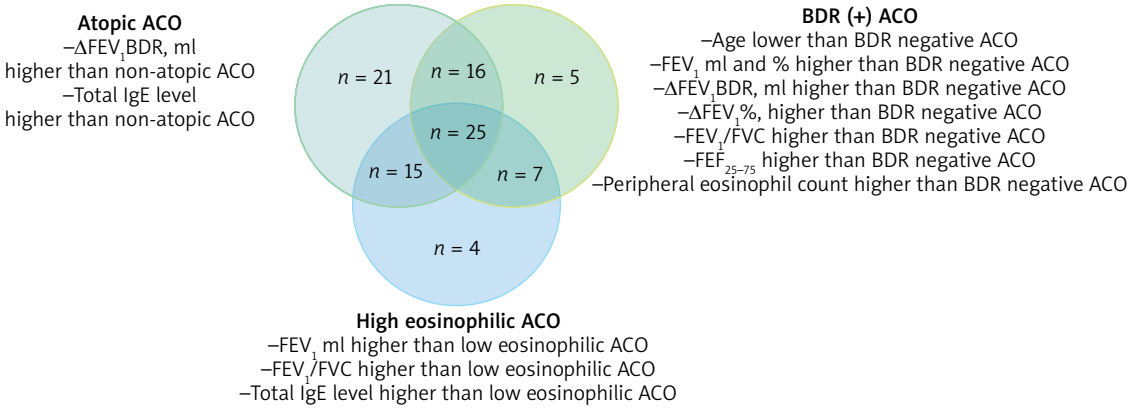


Figure 2. A Venn diagram illustrating the intersections between the three ACO subgroups and the clinical, spirometric, and laboratory measurements. Patients who meet more than one definition of ACO are those who overlap with more than one circumference BDR – bronchodilator response, High eosinophilic ACO – peripheral eosinophil count ≥ 300 cells/µl, Low eosinophilic ACO: < 300 cells/µl, ΔFEV_1BDR – an increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent (absolute volume change (ml)), ΔFEV_1% – an increase in FEV_1% of the initial FEV_1

Discussion

Although various definitions of ACO have been proposed in recent years, it essentially characterizes patients with a history of smoking (or other noxious irritants) and persistent airflow limitation that can often be reversed by β2-agonists, with an asthmatic component (previous or current diagnosis) and frequently accompanied by elevated blood and/or sputum eosinophils which are a marker of type 2 inflammation [20].

Few studies have explored the phenotype of ACO, with factors such as atopy, elevated eosinophil count (≥ 300 cells/µl), and smoking exposure considered in phenotyping [18, 21, 22]. While high BDR is typical in ACO patients, a high eosinophil count can also support the diagnosis when unmet BDR [23]. Our study is the first one to phenotype ACO based on atopy status, BDR, and elevated eosinophil count. This approach is valuable for several reasons: it highlights clinical heterogeneity in ACO, suggests that patient subgroups with distinct characteristics exist, and emphasizes that clinical traits may be more relevant for understanding outcomes than persistent airflow limitation alone. Additionally, it may provide insights into the disease's prognosis and future treatment strategies.

In our study, ACO was diagnosed in 11.22% of 971 patients with asthma and/or COPD who underwent the BDR test, following the criteria of the global expert panel discussion from 2016 [24]. Among 109 ACO pa-

tients, 77 had atopy, 53 had BDR positivity, and 51 had elevated eosinophil counts. Atopic ACO patients had higher ΔFEV_1BDR and total IgE levels than non-atopic patients. BDR-positive patients were younger, had higher spirometric measurements (FEV_1 ml, FEV_1%, FEV_1/FVC, FEF_{25-75}%), and had higher eosinophil counts than BDR-negative patients. Those with eosinophil counts ≥ 300 cells/µl had higher FEV_1, FEV_1/FVC ratio, and total IgE levels. Although radiological findings were similar across the subgroups, medication use varied: atopic patients more often used intranasal corticosteroids, oral antihistamines, and antileukotrienes, while BDR-negative patients used LAMA and SAMA more frequently.

The prevalence of ACO in our study was 11.22%. Previous studies have reported prevalence rates of ACO in the population ranging from 0.9% to 20% [25–29]. This variability can be attributed to differences in the patient populations studied, the diagnostic criteria employed, and the methodologies used in the studies.

It is unsurprising that our atopic ACO patients have higher total IgE levels as many studies have well established the relationship between atopy and total IgE [30, 31]. The finding that the ΔFEV_1BDR is nearly twice as high in the atopic ACO group compared to the non-atopic group (200 ml vs. 100 ml, $p = 0.034$) aligns with previous research [21, 22]. Rhee [21] suggested classifying ACO patients into four phenotypes based on atopy, eosinophilic inflammation, and smoking history. The C phenotype is characterized by allergic inflammation, features of asthma and COPD and is associated with high bronchial hyperreactivity (BHR). Additionally, studies have shown that COPD patients with elevated BHR are often atopic and show greater BDR in FEV_1 [32, 33]. Similarly, Haldar *et al*.'s cluster analysis of asthmatic patients found that atopic asthmatics had higher BDR in FEV_1 [34]. These findings suggest that atopy is linked to airway variability in asthma, COPD, and ACO patients.

BDR, measured by FEV_1, is commonly used in clinical practice to diagnose respiratory conditions like COPD and asthma, assess asthma control, and predict the effectiveness of inhaled treatments [35]. This is the first study to phenotype ACO patients based on BDR. Our results showed that BDR-positive patients were younger and had higher spirometric measurements, supporting the idea that, as asthma patients progress, both reversibility and spirometric measurements typically decline. A study on COPD patients found that BDR-positive individuals were younger and had higher post-bronchodilator FEV_1% and FVC%, which were associated with less advanced stages of COPD, consistent with our findings [36].

In our study, BDR-positive patients had higher eosinophil levels than BDR-negative patients (360 cells/µl vs. 195 cells/µl, $p = 0.047$). In COPD patients, an elevated eosinophil count has been identified as a predictor of a positive response to bronchodilator treatment [37, 38]. In the ADEPT cluster analysis of asthmatic patients, both the mixed granulocytic (eosinophilic + neutrophilic) and eosinophilic phenotypes showed high reversibility, supporting the link between eosinophilia and increased bronchodilator responsiveness [39].

A systemic inflammatory network analysis revealed that in ACO, the inflammatory pattern exhibited characteristics of both asthma and COPD, featuring the expression of Th2 cytokines (eosinophilic) alongside non-Th2 cytokines (neutrophilic) [40].

The results of all these studies reinforce the idea that ACO patients exhibit mixed granulocytic characteristics and consist of individuals with high reversibility.

Studies on ACO phenotypes based on eosinophil levels show varying results. Joo *et al*. [22] found that phenotype C, with high eosinophil counts, had higher FEV_1 levels than phenotype D (low eosinophil counts), although the difference was not statistically significant. Toledo-Pons *et al*. [41] classified ACO patients into three phenotypes (smoking asthmatics, COPD patients with high BDR and eosinophilic COPD patients). They observed a greater FEV_1/FVC ratio in the eosinophilic COPD phenotype, which also lacked statistical significance. Joo *et al*. [22] also noted that phenotype A, with eosinophil counts above 300 cells/µl, had the highest total IgE levels, but this difference was not statistically significant. Our findings, which show that FEV_1 levels, FEV_1/FVC ratio, and total IgE levels are higher in the high eosinophilic ACO group compared to the low eosinophilic group, align with these earlier studies [22, 41].

Consistent with previous research, ICS-LABA, primarily used for asthma, was the most frequently prescribed drug combination overall. The analysis revealed two predominant groups: one leaning towards asthma and the other towards COPD, with specialists tailoring prescriptions based on each group's characteristics. In line with other studies, antimuscarinics were more commonly prescribed for the COPD-predominant phenotype (BDR-negative group). At the same time, antileukotrienes were more frequently used in the asthma-predominant phenotype (atopic ACO) [18, 22].

This study aims to provide a clearer understanding of ACO by objectively validating patients and categorizing them into subgroups based on specific criteria, which aligns with the global expert panel discussion. Phenotyping ACO patients according to atopy, BDR positivity, and eosinophil levels offers valuable insights into their prognosis and response to bronchodilator therapy. This study has some potential clinical implications. In this research, we found that BDR-positive and highly eosinophilic asthma-chronic obstructive pulmonary disease overlap (ACO) groups showed better spirometric results. In addition, we showed that leukotriene receptor antagonists were more commonly used in the atopic ACO group, while antimuscarinic drugs were more commonly used in the BDR-negative group.

Consistent with other studies, antimuscarinics were more commonly prescribed for the COPD-dominant phenotype (BDR-negative group). A higher increase in FEV_1 after inhalation of 400 µg of salbutamol or the equivalent ($\Delta FEV_1 BDR$) in atopic ACO suggests that these patients may respond better to bronchodilators. We think that these results will contribute to the literature in terms of diagnosis and treatment. However, a limitation of our study is its retrospective nature, which restricts the assessment of symptoms, acute exacerbations, and inflammatory characteristics. Nonetheless, these findings can serve as a foundation for future research.

Conclusions

This research supports the definition of ACO based on global expert panel criteria, including persistent airflow limitation, cigarette exposure history, and asthma characteristics. We categorized patients into subgroups based on minor criteria that could confuse them. The high airway variability in atopic ACO suggests that these patients may be better candidates for bronchodilator therapy and may experience more frequent exacerbations. The elevated eosinophil levels in BDR-positive patients support the idea that eosinophilia could help define ACO in BDR-negative patients. Additionally, BDR-positive individuals typically have less advanced disease as shown by their superior baseline spirometric measurements/better baseline spirometric results. Eosinophilic ACO includes cases with high total IgE levels and, to some extent, better spirometric outcomes. Future studies considering clinical and inflammatory characteristics will allow for a more detailed analysis of these subgroups and may help identify biological agents for targeted therapies.

Funding

No external funding.

Ethical approval

This study was approved by the Local Ethics Committee of University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital with the decision dated 2023 and numbered 116.2017.R-284.

Conflict of interest

The authors declare no conflict of interest.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2023. Available from: www.goldcopd.org. Accessed at May 2023.
2. Levy ML, Bacharier LB, Bateman E, et al. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. NPJ Prim Care Respir Med 2023; 33: 7.
3. Holgate ST. Innate and adaptive immune responses in asthma. Nat Med 2012; 18: 673-83.
4. Jeffery PK. Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004; 1: 176-83.
5. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report).
6. Eapen M, Myers S, Walters E, Sohal S. Airway inflammation in chronic obstructive pulmonary disease (COPD): a true paradox. Expert Rev Respir Med 2017; 11: 827-39.
7. Jones RL, Noble PB, Elliot JG, James AL. Airway remodeling in COPD: it's not asthma! Respirology 2016; 21: 1347-56.
8. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features, and how important are they? Thorax 2009; 64:728-35.
9. Woodruff PG, Van Den Berge M, Boucher RC, et al. American Thoracic Society/National Heart, lung, and blood institute asthma-chronic obstructive pulmonary disease overlap workshop report. Am J Respir Crit Care Med 2017; 196: 375-81.
10. Global Initiative for Asthma. Global Strategy for Asthma management and Prevention (Online). www.ginasthma.org 2021.
11. Uchida A, Sakaue K, Inoue H. Epidemiology of asthma-chronic obstructive pulmonary disease overlap (ACO). Allergol Int 2018; 67: 165-71.
12. Şen E, Oğuzülgen IK, Bavbek S, et al. Asthma-COPD overlap syndrome. Tuberk Toraks 2015; 63: 265-77.
13. Albertson ET, Chenoweth JA, Pearson SJ, Murin S. The pharmacological management of asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). Expert Opin Pharmacother 2020; 21: 213-31.
14. Alshabanat A, Zafari Z, Albanyan O, et al. Asthma and COPD overlap syndrome (ACOS): a systemic review and meta-analysis. PLoS One 2015; 10: e013065.
15. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. Eur Respir J 2016; 48: 664-73.
16. Özden Ş. Astım-KOAH Overlap. Güncel Göğüs Hastalıkları Serisi. 2020.
17. Lainez S, Court-Fortune I, Vercherin P, et al. Clinical ACO phenotypes: description of a heterogeneous entity. Respir Med Case Rep 2019; 28: 100929.
18. Joo H, Han D, Lee JH, Rhee CK. Heterogeneity of asthma-COPD overlap syndrome. Int J Chron Obstruct Pulmon Dis 2017; 12: 697-703.
19. Kim MH, Rhee CK, Kim K, et al. Heterogeneity of asthma and COPD overlap. Int J Chron Obstruct Pulmon Dis 2018; 13: 1251-60.
20. Mekov E, Nuńez A, Sin DD, et al. Update on asthma-COPD overlap (ACO): a narrative review. Int J Chron Obstruct Pulmon Dis 2021; 16: 1783-99.
21. Rhee CK. Phenotype of asthma–chronic obstructive pulmonary disease overlap syndrome. Korean J Intern Med 2015; 30: 443-9.
22. Joo H, Park SY, Park SY, et al. Phenotype of asthma-COPD overlap in COPD and severe asthma cohorts. J Korean Med Sci 2022; 37: e236.
23. Plaza V, Álvarez F, Calle M, et al. Consensus on the asthma-COPD overlap syndrome (ACOS) between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the

Management of Asthma (GEMA). Arch Bronconeumol 2017; 53: 443-9.
24. Cosio BG, Soriano JB, Lopez-Campos JL, et al. Distribution and outcomes of a phenotype-based approach to guide COPD management: results from the CHAIN cohort. PLoS One 2016; 11: e0160770.
25. Wurst KE, Kelly-Reif K, Bushnell GA, et al. Understanding asthma-chronic obstructive pulmonary disease overlap syndrome. Respir Med 2016; 110: 1-11.
26. Guerriero M, Caminati M, Viegi G, et al. Prevalence and features of asthma-chronic obstructive pulmonary disease overlap in Northern Italy general population. J Asthma 2019; 56: 27-33.
27. Krishnan JA, Nibber A, Chisholm A, et al. Prevalence and characteristics of asthma-chronic obstructive pulmonary disease overlap in routine primary care practices. Ann Am Thorac Soc 2019; 16: 1143-50.
28. Kumbhare S, Pleasants R, Ohar JA, Strange C. Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. Ann Am Thorac Soc 2016; 13: 803-10.
29. Mendy A, Forno E, Niyonsenga T, et al. Prevalence and features of asthma-COPD overlap in the United States 2007-2012. Clin Respir J 2018; 12: 2369-77.
30. Gould HJ, Sutton BJ, Beavil AJ, et al. The biology of IGE and the basis of allergic disease. Annu Rev Immunol 2003; 21: 579-628.
31. Wickman M. Experience with quantitative IgE antibody analysis in relation to allergic disease within the BAMSE birth cohort--towards an improved diagnostic process. Allergy 2004; 59 (Suppl 78): 30-1.
32. Jones R, Noble P, Elliot J. James A. Airway remodeling in COPD: it's not asthma! Respirology 2016; 21: 1347-56.
33. Karakioulaki M, Papakonstantinou E, Goulas A, Stolz D. The role of atopy in COPD and asthma. Front Med (Lausanne) 2021; 8: 674742.
34. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178: 218-24.
35. Global Initiative for Asthma Scientific C. Global Strategy for Asthma Management and Prevention. 2022. Available from: http://ginasthma.org/.
36. Fortis S, Comellas A, Make BJ, et al. Gene Investigators – Core Units: Administrative Center, COPDGene Investigators– Clinical Centers: Ann Arbor. Combined forced expiratory volume in 1 second and forced vital capacity bronchodilator response, exacerbations, and mortality in chronic obstructive pulmonary disease. Ann Am Thorac Soc 2019; 16: 826-35.
37. Chou KT, Su KC, Hsiao YH, et al. Post-bronchodilator reversibility of FEV1 and eosinophilic airway inflammation in COPD. Arch Bronconeumol 2017; 53: 547-53.
38. Naveed M, Khan MNA, Shah SU, et al. Association of absolute eosinophil count and postbronchodilator reversibility in the chronic obstructive pulmonary disease patients. Pak Armed Forces Med J 2023; 73: 361-4.
39. Loza MJ, Djukanovic R, Chung KF, et al. ADEPT (Airways Disease Endotyping for Personalized Therapeutics) and U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome Consortium) investigators. Validated and longitudinally stable asthma phenotypes based on cluster analysis of the ADEPT study. Respir Res 2016; 17: 165.
40. de Llano LP, Cosio BG, Iglesias A, et al. Mixed Th2 and non-Th2 inflammatory pattern in the asthma-COPD overlap: a network approach. Int J Chron Obstruct Pulmon Dis 2018; 13: 591-601.
41. Toledo-Pons N, van Boven JFM, Román-Rodríguez M, et al. ACO: time to move from the description of different phenotypes to the treatable traits. PLoS One 2019; 14: e0210915.