



Clinical, laboratory, and functional characteristics of asthma-COPD overlap in patients with a primary diagnosis of COPD

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ABSTRACT

Objective: To evaluate the frequency of asthma-COPD overlap (ACO) in patients with COPD and to compare, from a clinical, laboratory, and functional point of view, patients with and without ACO, according to different diagnostic criteria. **Methods:** The participants underwent evaluation by a pulmonologist, together with spirometry and blood tests. All of the patients were instructed to record their PEF twice a day. The diagnosis of ACO was based on the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease) criteria, the American Thoracic Society (ATS) Roundtable criteria, and the Spanish criteria. We investigated patient histories of exacerbations and hospitalizations, after which we applied the COPD Assessment Test and the modified Medical Research Council scale, to classify risk and symptoms in accordance with the GOLD criteria. **Results:** Of the 51 COPD patients, 14 (27.5%), 8 (12.2%), and 18 (40.0%) were diagnosed with ACO on the basis of the PLATINO, ATS Roundtable, and Spanish criteria, respectively. The values for pre-bronchodilator FVC, post-bronchodilator FVC, and pre-bronchodilator FEV₁ were significantly lower among the patients with ACO than among those with COPD only (1.9 ± 0.4 L vs. 2.4 ± 0.7 L, 2.1 ± 0.5 L vs. 2.5 ± 0.8 L, and 1.0 ± 0.3 L vs. 1.3 ± 0.5 L, respectively). When the Spanish criteria were applied, IgE levels were significantly higher among the patients with ACO than among those with COPD only (363.7 ± 525.9 kU/L vs. 58.2 ± 81.6 kU/L). A history of asthma was more common among the patients with ACO (p < 0.001 for all criteria). **Conclusions:** In our sample, patients with ACO were more likely to report previous episodes of asthma and had worse lung function than did those with COPD only. The ATS Roundtable criteria appear to be the most judicious, although concordance was greatest between the PLATINO and the Spanish criteria.

Keywords: Asthma/diagnosis; Pulmonary disease, chronic obstructive/diagnosis; Asthma-chronic obstructive pulmonary disease overlap syndrome/diagnosis.

INTRODUCTION

Asthma and COPD are diseases that are well understood scientifically and have particular features, determining their distinction. However, it can be difficult to reach an accurate diagnosis in patients with clinical findings consistent with both diseases. Therefore, GINA and GOLD have proposed the term asthma-COPD overlap (ACO).^(1,2) In brief, ACO may be used to describe patients with asthma who have features of COPD (specifically, incompletely reversible airflow obstruction) or to describe patients with COPD who have features of asthma (such as bronchodilator responsiveness and bronchial hyperresponsiveness).⁽³⁾

It is estimated that from 0.9% to 11.1% of the general population can be classified as having ACO.⁽⁴⁾ However, ACO is not a primary diagnosis, and patients with this condition are usually found among patients with asthma or COPD.⁽⁵⁾ Having that in mind, the prevalence of ACO among patients with a primary diagnosis of COPD is

estimated to range from 4.2% to 68.7%. This variation is due to the availability of various sets of criteria for the classification of patients with ACO.^(4,5)

Of the 35 studies reviewed by Uchida et al.,⁽⁴⁾ most defined ACO as a combination of asthma and COPD, on the basis of factors such as a history of asthma, symptoms of cough and wheezing, airflow limitation, bronchial hyperresponsiveness, and bronchodilator responsiveness. Those studies, however, differ greatly in terms of the characteristics used in the diagnosis and the way they are used.

Many of the studies that sought to evaluate the characteristics of patients with ACO found that these individuals have more severe symptoms, a greater number of exacerbations and hospitalizations, poorer quality of life, and poorer prognosis than do those without ACO.⁽⁶⁻⁸⁾ These characteristics translate to high health costs for these subjects.⁽⁹⁾

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The aforementioned findings may be due to a lack of concrete data to inform the appropriate therapeutic choice for each patient profile. Once the clinical features of patients have been identified, treatment can be personalized, optimizing outcomes in terms of both functional performance and quality of life. Therefore, the present study aimed to evaluate the frequency of ACO in a sample of patients with a primary diagnosis of COPD and to compare, from a clinical, laboratory, and functional standpoint, patients with ACO and those with COPD only.

METHODS

This cross-sectional observational study was conducted to evaluate the frequency of ACO in a sample of patients with a primary diagnosis of COPD and to compare those with and without ACO from a clinical, laboratory, and functional standpoint. This study is nested within the Follow-COPD Cohort Study, which is ongoing at the Center for Research on Asthma and Airway Inflammation of the Professor Polydoro Ernani de São Thiago University Hospital, located in the city of Florianópolis, Brazil, and was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (CAAE no. 85662718.5.0000.0121), located in that same city.

Our sample, which comprised participants from the Follow-COPD Cohort Study, was selected in an intentional and non-probabilistic manner. The inclusion criteria adopted in that study were as follows: having been diagnosed with COPD; being a former or current smoker; having been clinically stable for at least one month; having been on appropriate medical treatment for at least one month; and having agreed to participate in the study by giving written informed consent. The exclusion criteria adopted in that study was having a clinically significant oncological, cardiovascular, neurological, musculoskeletal, rheumatological, or cognitive comorbidity that limited one's understanding of and adherence to the proposed evaluation methods.

Patients had an appointment with a pulmonologist, in which sociodemographic and clinical data were collected. Blood tests for peripheral eosinophil count and IgE were also requested. The request for blood tests was sent to primary health care clinics so that the tests could be performed at third-party laboratories affiliated with the Brazilian Unified Health Care System.

The diagnosis of COPD was based on the GOLD criteria,⁽²⁾ which include the presence of symptoms (dyspnea, chronic cough, and production of secretion), exposure to risk factors, and a post-bronchodilator FEV₁/FVC ratio < 0.70 on spirometry, which was performed with the Koko Sx 1000 spirometer (PDS Instrumentation Inc., Louisville, CO, USA). In addition, patients completed the COPD Assessment Test and the modified Medical Research Council dyspnea scale, the scores of which, together with the history of exacerbations and hospitalizations, were used in order to classify risk and symptoms.⁽²⁾

For the diagnosis of ACO, three different sets of criteria were used. The first, established by the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease),⁽⁶⁾ defines COPD as a post-bronchodilator FEV₁/FVC ratio < 0.70 and defines asthma as wheezing in the previous 12 months and bronchodilator responsiveness in FEV₁ or FVC (≥ 200 mL and ≥ 12%), although a report of previous asthma diagnosis can also be used. ACO is defined as combined features of both COPD and asthma. The second set of criteria, established at the American Thoracic Society conference (ATS Roundtable),⁽¹⁰⁾ includes three major and three minor characteristics—all three major characteristics and at least one minor characteristic are required for the diagnosis of ACO. The major characteristics include non-reversible airflow limitation (a post-bronchodilator FEV₁/FVC < 0.70) in individuals over 40 years of age, a smoking history ≥ 10 pack-years, and either a history of asthma before age 40 or bronchodilator responsiveness in FEV₁ (> 400 mL). The minor characteristics include a history of atopy or allergic rhinitis, bronchodilator responsiveness in FEV₁ (≥ 200 mL and ≥ 12%) at two distinct time points, and a peripheral blood eosinophil count ≥ 300 cells/mm³. The third set of criteria, established by Cosio et al.⁽¹¹⁾ and designated the Spanish criteria, is based on a previous diagnosis of COPD (age > 40 years, a post-bronchodilator FEV₁/FVC < 0.7, and exposure to tobacco smoke) and comprises two major and three minor characteristics—at least one major characteristic or two minor characteristics are required for the diagnosis of ACO. The major characteristics include a history of asthma and bronchodilator responsiveness in FEV₁ (≥ 400 mL and ≥ 15%), whereas the minor characteristics include an IgE level > 100 kU/L, a history of atopy, bronchodilator responsiveness in FEV₁ (≥ 200 mL and ≥ 12%) at two time points, and a blood eosinophil count > 5%.

Patients were instructed to measure their PEF in the morning and in the evening for 30 days, with a portable PEF meter (Medicate; Dorja, Itu, Brazil), and to record their PEF values in a diary. The highest morning and evening PEF values for 7 consecutive days during which the diary was appropriately completed were used. Daily variation in PEF (Δ PEF) is the difference between the highest morning PEF value and the highest evening PEF value, whereas percent change in PEF is calculated as Δ PEF divided by the highest daily PEF value and multiplied by 100.

Statistical analysis

Continuous variables were expressed as means and standard deviations, and categorical variables were expressed as absolute and relative frequencies. The chi-square test was used to determine associations between nominal variables, and the Student's t-test was used to compare means between groups. The kappa statistic was used to assess concordance between the different diagnostic criteria for ACO. Values of $p < 0.05$

were considered significant. The data were analyzed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

All 51 patients who participated in the Follow-COPD Cohort Study between January of 2018 and July of 2019 were evaluated. Of those, 27 (52.9%) were men, 27 (52.9%) had had at least one COPD exacerbation in the previous year, and 6 (11.8%) had been hospitalized in the previous year. Other characteristics of the sample are described in Table 1.

Airflow limitation was classified as mild (grade 1), in 3 patients (5.9%); moderate (grade 2), in 18 (35.3%); severe (grade 3), in 19 (37.3%); and very severe (grade 4), in 11 (21.6%). With regard to risk and symptoms, 13 patients (25.0%) were classified as group A, 17 (33.3%) were classified as group B, and 21 (41.2%) were classified as group D, with no patients being classified as group C.

All 51 participants were evaluated using the PLATINO criteria, 49 were evaluated using the ATS Roundtable criteria, and only 45 were evaluated using the Spanish criteria, because 2 and 4 patients had no eosinophil count and no IgE level results, respectively. In this sample of COPD patients, the frequency of ACO was 27.5% ($n = 14$), 12.2% ($n = 6$), and 40.0% ($n = 18$) according to the PLATINO, ATS Roundtable, and Spanish criteria, respectively.

Patients with ACO, regardless of the diagnostic criteria used, were more likely to report previous episodes of

asthma than were those with COPD only (Table 2). In addition, patients with ACO were more likely to have bronchodilator responsiveness at two distinct time points than were those with COPD only. Patients with ACO according to the Spanish criteria were more likely to have an elevation in IgE than were those with COPD only, as well as having higher IgE values (Table 3).

There were no differences in spirometry results between patients with and without ACO when the Spanish criteria were applied; however, differences were found when the PLATINO and the ATS Roundtable criteria were applied. When the PLATINO criteria were used, there were differences between the two groups in pre- and post-bronchodilator FVC (in L) and in pre-bronchodilator FEV₁ (in L). When the ATS Roundtable criteria were used, differences also were found between the two groups in pre-bronchodilator FVC (in L) and in pre-bronchodilator FEV₁ (in L). Table 4 shows the spirometry results for patients with and without ACO, by diagnostic criteria.

An analysis of concordance between the three different sets of criteria for the diagnosis of ACO used in the present study showed moderate concordance between the PLATINO and the ATS Roundtable criteria and between the Spanish and the ATS Roundtable criteria, but strong concordance between the PLATINO and the Spanish criteria. Table 5 shows the assessment of concordance between the different diagnostic criteria.

DISCUSSION

In the present study, when the PLATINO criteria were applied to a cohort of patients with COPD, the frequency of ACO was 27.5%. Patients with ACO had worse pre- and post-bronchodilator FVC and worse pre-bronchodilator FEV₁ than did patients with COPD only. In addition, a history of asthma was more common among those with ACO than among those with COPD only.

When applying the PLATINO criteria to patients with a primary diagnosis of COPD, Jo et al.⁽⁵⁾ reported the presence of ACO in 48.3% of the participants, whereas in the studies by Mendy et al.⁽¹²⁾ and Menezes et al.,⁽⁶⁾ the frequency of ACO was 12.6% and 12.4%, respectively. The discrepancy between the studies can be partly explained by methodological characteristics. By including subjects with and without respiratory problems, population-based studies^(6,12) may find a reduced frequency of ACO in comparison with studies that exclusively include patients with COPD. In contrast, studies that include only patients with COPD⁽⁵⁾ are subject to the fact that COPD is an underdiagnosed disease and they therefore tend to include patients with more symptoms and greater airflow limitation,^(13,14) among whom are patients with ACO.

Patients classified as having ACO on the basis of the PLATINO and the ATS Roundtable criteria have worse lung function than do those with COPD only. This profile has been described in various studies that used different diagnostic criteria: patients with ACO

Table 1. Characteristics of the sample (N = 51).^a

Characteristic	Result
Age, years	64.1 ± 8.4
BMI, kg/m ²	25.5 ± 5.5
Smoking history, pack-years	47.3 ± 30.4
Eosinophils, cells/mm ³	286.2 ± 431.7
Eosinophils, %	3.2 ± 2.1
CAT score	18 (9-29)
mMRC dyspnea scale score	2 (1-4)
Pulmonary function	
Pre-BD FVC, L	2.2 ± 0.7
Pre-BD FVC, % pred	64.3 ± 18.2
Pre-BD FEV ₁ , L	1.2 ± 0.5
Pre-BD FEV ₁ , % pred	44.5 ± 17.6
Pre-BD FEV ₁ /FVC	0.5 ± 0.1
Post-BD FVC, L	2.4 ± 0.7
Post-BD FVC, % pred	67.7 ± 19.2
Post-BD FEV ₁ , L	1.3 ± 0.5
Post-BD FEV ₁ , % pred	47.5 ± 18.3
Post-BD FEV ₁ /FVC	0.5 ± 0.1
BD responsiveness: FVC, mL	118.6 ± 148.6
BD responsiveness: FEV ₁ , mL	83.7 ± 94.0

CAT: COPD Assessment Test; mMRC: modified Medical Research Council; BD: bronchodilator; and pred: predicted value. ^aValues expressed as mean ± SD or as median (IQR).

Table 2. Frequency of patients with asthma-COPD overlap or COPD only, by diagnostic criteria.^a

Characteristic	Criteria					
	PLATINO		ATS Roundtable		Spanish	
	ACO (n = 14)	COPD (n = 37)	ACO (n = 6)	COPD (n = 43)	ACO (n = 18)	COPD (n = 27)
Male gender	6 (42.9)	21 (56.8)	1 (16.7)	24 (55.8)	10 (55.6)	14 (51.9)
History of asthma	12 (85.7)	0 (0.0)**	6 (100.0)	4 (9.3)**	12 (66.7)	0 (0.0)**
History of atopy	8 (57.1)	17 (45.9)	5 (83.3)	20 (46.5)	11 (61.1)	11 (40.7)
Eosinophils ≥ 300 cells/mm ³	2 (20.0)	8 (25.0)	1 (16.7)	9 (20.9)	5 (27.8)	5 (18.5)
IgE > 100 kU/L	5 (41.7)	7 (22.6)	3 (50.0)	9 (20.9)	10 (55.6)	2 (7.4)**
CAT score ≥ 10	10 (71.4)	27 (73.0)	6 (100.0)	30 (69.8)	13 (72.2)	19 (70.4)
mMRC dyspnea scale score ≥ 2	8 (57.1)	20 (54.1)	5 (83.3)	23 (53.5)	9 (50.0)	14 (51.9)
BD responsiveness: FVC > 350 mL	1 (7.1)	1 (2.7)	0 (0.0)	2 (4.7)	1 (5.6)	1 (3.7)
BD responsiveness: FEV ₁ > 200 mL and 12%	2 (14.3)	2 (5.4)	0 (0.0)	4 (9.3)	1 (5.6)	3 (11.1)
BD responsiveness: FEV ₁ > 200 mL and 12% at two time points	2 (20.0)	2 (6.7)	2 (33.3)	2 (4.7)*	2 (11.1)	1 (3.7)
Airflow limitation						
Mild	0 (0.0)	3 (8.1)	0 (0.0)	3 (7.0)	0 (0.0)	2 (7.4)
Moderate	3 (21.4)	15 (40.5)	1 (16.7)	17 (39.5)	6 (33.3)	10 (37.0)
Severe	6 (42.9)	13 (35.1)	4 (66.7)	15 (34.9)	7 (38.9)	10 (37.0)
Very severe	5 (35.7)	6 (16.2)	1 (16.7)	8 (18.6)	5 (27.8)	5 (18.5)
Risk and symptom classification						
A	4 (28.6)	9 (24.3)	0 (0.0)	12 (27.9)	5 (27.8)	7 (25.9)
B	4 (28.6)	13 (35.1)	2 (33.3)	14 (32.6)	5 (27.8)	11 (40.7)
D	6 (42.9)	15 (40.5)	4 (66.7)	17 (39.5)	8 (44.4)	9 (33.3)

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); ATS: American Thoracic Society; ACO: asthma-COPD overlap; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; and BD: bronchodilator. ^aValues expressed as n (%). *p < 0.05. **p < 0.01.

Table 3. Comparison of clinical characteristics between patients with asthma-COPD overlap and those with COPD only, by diagnostic criteria.^a

Characteristic	Criteria					
	PLATINO		ATS Roundtable		Spanish	
	ACO (n = 14)	COPD (n = 37)	ACO (n = 6)	COPD (n = 14)	ACO (n = 37)	COPD (n = 6)
Age, years	62.1 \pm 9.2	64.9 \pm 8.0	60 \pm 10.8	64.2 \pm 7.8	62.1 \pm 9.6	65.9 \pm 6.3
BMI, kg/m ²	25 \pm 4.5	25.7 \pm 5.8	25.1 \pm 5.9	25.8 \pm 5.5	26.7 \pm 6.3	24.8 \pm 5.2
Smoking history, pack-years	39.5 \pm 27.2	50.2 \pm 31.4	46.9 \pm 35.8	48.0 \pm 30.5	47.6 \pm 33.3	44.1 \pm 26.3
Exacerbation in the previous year	1.5 \pm 1.5	1.2 \pm 1.5	2.3 \pm 1.6	1.2 \pm 1.5	1.4 \pm 1.4	1.0 \pm 1.4
Hospitalization in the previous year	0.14 \pm 0.4	0.14 \pm 0.4	0.0 \pm 0.0	0.2 \pm 0.4*	0.2 \pm 0.4	0.1 \pm 0.5
Eosinophils, cells/mm ³	200.1 \pm 129.1	315.7 \pm 493.5	187.6 \pm 101.3	299.1 \pm 457.1	281.5 \pm 174.5	293.6 \pm 532.8
Eosinophils, %	2.9 \pm 2.0	3.3 \pm 2.1	2.6 \pm 1.3	3.3 \pm 2.2	3.8 \pm 2.2	3.0 \pm 2.1
IgE, kU/L	305.05 \pm 601.6	122.3 \pm 182.6	482.3 \pm 916.3	134.8 \pm 195.2	363.7 \pm 525.9	58.2 \pm 81.6*
Daily variation in PEF, L/min	21.7 \pm 12.2	21.6 \pm 13.8	13.9 \pm 8.6	22.7 \pm 13.6	25.1 \pm 12.7	19.6 \pm 13.7
Daily variation in PEF, %	10.4 \pm 7	9.5 \pm 5.0	8.9 \pm 7.7	9.9 \pm 5.4	9.8 \pm 4.9	9.4 \pm 5.9

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); ATS: American Thoracic Society; and ACO: asthma-COPD overlap. ^aValues expressed as mean \pm SD. *p < 0.05.

had reduced FEV₁ (absolute and relative values), FVC (absolute and relative values), and FEV₁/FVC ratio when compared with those with COPD only,^(6,12,15-17) as well as when compared with those with asthma only.^(12,18) In contrast, two studies that used different diagnostic criteria reported better lung function in patients with ACO. Kauppi et al.⁽⁷⁾ reported that

pre- and post-bronchodilator FVC (as percent of predicted) and post-bronchodilator FEV₁ (as percent of predicted) were higher in the ACO group than in the COPD-only group, but they were lower in the ACO group than in the asthma-only group. In the study by Cosentino et al.,⁽¹⁹⁾ the FEV₁/FVC ratio was also higher in the ACO group.

Table 4. Comparison of pulmonary function between patients with asthma-COPD overlap and those with COPD only, by diagnostic criteria.^a

Characteristic	Criteria					
	PLATINO		ATS Roundtable		Spanish	
	ACO (n = 14)	COPD (n = 37)	ACO (n = 6)	COPD (n = 14)	ACO (n = 37)	COPD (n = 6)
Pre-BD FVC, L	1.9 ± 0.4	2.4 ± 0.7*	1.9 ± 0.4	2.3 ± 0.7*	2.3 ± 0.7	2.2 ± 0.6
Pre-BD FVC, % pred	58.2 ± 13.5	66.6 ± 19.4	59.9 ± 17.8	65.2 ± 18.7	63.2 ± 15.8	63.0 ± 18.9
Pre-BD FEV ₁ , L	1.0 ± 0.3	1.3 ± 0.5*	1.0 ± 0.2	1.2 ± 0.5*	1.2 ± 0.5	1.2 ± 0.4
Pre-BD FEV ₁ , % pred	38.3 ± 12.7	46.8 ± 18.8	40.3 ± 13.8	45.6 ± 18.3	42.7 ± 14.5	43.9 ± 18.0
Pre-BD FEV ₁ /FVC	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Post-BD FVC, L	2.1 ± 0.5	2.5 ± 0.8*	2.0 ± 0.4	2.4 ± 0.7	2.4 ± 0.8	2.3 ± 0.6
Post-BD FVC, % pred	62.1 ± 16.4	69.9 ± 20.0	63.8 ± 19.1	68.6 ± 19.7	66.3 ± 17.6	66.7 ± 19.6
Post-BD FEV ₁ , L	1.1 ± 0.4	1.3 ± 0.5	1.1 ± 0.2	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4
Post-BD FEV ₁ , % pred	42.0 ± 15.7	49.6 ± 18.9	43.9 ± 14.6	48.9 ± 18.8	45.6 ± 16.2	47.3 ± 18.5
Post-BD FEV ₁ /FVC	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
BD responsiveness: FVC, mL	132.9 ± 158.9	113.2 ± 146.4	136.7 ± 108.2	119.1 ± 153.8	113.3 ± 140.8	123.3 ± 159.4
BD responsiveness: FEV ₁ , mL	108.6 ± 108.3	74.3 ± 87.8	113.3 ± 49.3	85.6 ± 95.8	90.0 ± 99.9	87.0 ± 91.5

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); ATS: American Thoracic Society; ACO: asthma-COPD overlap; BD: bronchodilator; and pred: predicted value. ^aValues expressed as mean ± SD. *p < 0.05.

Table 5. Assessment of concordance between the diagnostic criteria used.

Criteria	PLATINO		Kappa	Spanish		
	With ACO	Without ACO		With ACO	Without ACO	Kappa
ATS Roundtable						
With ACO	6 (100%)	0 (0%)	0.60	6 (100%)	0 (0%)	0.43
Without ACO	37 (86%)	6 (14%)		10 (27%)	27 (73%)	
Spanish						
With ACO	13 (72.2)	5 (27.8%)	0.71			
Without ACO	1 (3.7%)	26 (96.3%)				

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); and ;ACO: asthma-COPD overlap.

Bronchodilator responsiveness, despite being a consensus among different diagnostic criteria,^(6,10,11) remains a source of debate and divergence among researchers.⁽²⁰⁻²²⁾ This divergence stems from the fact that positive bronchodilator responsiveness is common in patients with COPD⁽²³⁾ and that this is an inconstant finding, which may vary from one spirometry test to another.⁽²⁴⁾ Those results corroborate findings of the present study, in which only when the ATS Roundtable criteria were used did we find differences between the ACO and the COPD-only groups in terms of bronchodilator responsiveness on two or more spirometry tests. Therefore, bronchodilator responsiveness should not be used in isolation for the diagnosis of ACO, but rather in combination with other characteristics.⁽²⁵⁾ In addition to bronchodilator responsiveness, a history of asthma and blood levels of eosinophils and IgE are characteristics that are usually part of diagnostic criteria for ACO.^(6,10,11)

Patients with ACO are more likely to report previous episodes of asthma than are those with COPD only, regardless of the criteria used. This is easily explained by the fact that all criteria include this characteristic as a key factor in diagnosing ACO. A study by Barrecheguren

et al.⁽²⁶⁾ demonstrated that COPD patients who were diagnosed with ACO solely on the basis of a history of asthma had characteristics similar to those of COPD patients diagnosed with ACO on the basis of the Spanish criteria. A similar finding was reported in a study in which the addition of characteristics other than a history of asthma made no difference in the diagnosis of ACO.⁽²⁷⁾ Therefore, besides a diagnosis of COPD (FEV₁/FVC < 0.7), a history of asthma has been described as an important characteristic in identifying patients with ACO.

A common feature of asthma is ΔPEF, determined by using a peak flow meter, an important instrument in the management of asthma.⁽¹⁾ However, this instrument has also proven to be an ally to COPD patients in monitoring and preventing exacerbations.⁽²⁸⁾ Therefore, some studies have used ΔPEF as a feature of asthma that contributes to identifying ACO,^(4,25) and one population-based study even demonstrated that patients with ACO have lower PEF than do patients with either asthma or COPD only.⁽¹²⁾ However, there were no differences in PEF between the groups in the present study.

In our study, no differences were found in peripheral blood eosinophil counts between patients with ACO and those with COPD only. However, recent studies have highlighted the relationship between high blood eosinophil levels and asthma-related features, such as increased bronchodilator responsiveness and increased responsiveness to treatment with inhaled corticosteroids.⁽²¹⁾ Therefore, blood eosinophil counts in patients with COPD have been suggested as indicative of ACO⁽²²⁾ and as a predictor of treatment responsiveness.⁽²⁹⁾

Although total IgE levels do not provide information related to atopic etiology as do specific IgE levels, they appear to be related to atopy in asthma⁽³⁰⁾ and are therefore included in some criteria for the diagnosis of ACO.⁽⁴⁾ In the present study, only when the Spanish criteria were used did we find differences in IgE levels between patients with ACO and patients with COPD only, as in the study by Jo et al.⁽⁵⁾ However, the Spanish criteria are the only criteria that use IgE as a required characteristic for the diagnosis of ACO, which can generate debate about the veracity of this finding and about the role of IgE levels in the diagnosis of ACO.

As expected, different criteria resulted in different frequencies of ACO. This finding has been addressed in other studies,^(5,31) in which, when the ATS Roundtable criteria were applied, 1.9-11.9% of the participants were diagnosed with ACO, whereas, when the Spanish criteria were applied, 31.3-47.7% received this diagnosis. This confirms the findings of the present study: the ATS Roundtable criteria proved to be more rigorous than did the Spanish and the PLATINO criteria in discriminating between COPD and ACO.

Of the three sets of criteria analyzed in the present study, the PLATINO criteria appear to be the simplest and therefore the most appropriate for application in epidemiological studies and clinical practice, given that only two characteristics are required for the diagnosis of ACO. The need for testing bronchodilator responsiveness at least at two different time points and performing biochemical tests makes the application of the Spanish and the ATS Roundtable criteria more complex. However, spirometry and measurement of blood levels of eosinophils and total IgE are standardized and accessible, as well as being recommended by GOLD (respectively, for monitoring lung function and for estimating treatment efficacy and predicting

exacerbations),⁽²⁾ which enables the application of the Spanish and the ATS Roundtable criteria in clinical practice. In addition, although the Spanish criteria are similar in format to the ATS Roundtable criteria, they showed greater concordance with the PLATINO criteria, which leads one to question whether the ATS Roundtable criteria impose too strict conditions for the diagnosis of ACO. In contrast, an analysis of the conditions imposed by the PLATINO and the Spanish criteria shows that the characteristics of the former are included in the latter, that is, a diagnosis of COPD as defined by GOLD⁽²⁾ and a history of asthma, which results in strong concordance between these two sets of criteria.

The present study has some limitations. The fact that this was a small convenience sample consisting of patients followed at a public hospital outpatient clinic who had a primary diagnosis of COPD compromises the generalizability of the findings, as well as being able to affect those findings and even the frequency of ACO. Therefore, further studies are required for external validation of these findings. A self-reported history of asthma, despite being a variable that is widely accepted and valid in studies, is subject to patient subjectivity. With regard to laboratory findings, data on eosinophil and IgE levels were missing for some patients, which may have affected not only the application of the diagnostic criteria but also the comparisons between the groups. The measurement of PEF, despite instructions, was subject to errors in diary completion and patient subjectivity.

We therefore conclude that the frequency of ACO in this cohort of patients with COPD was 27.5%. Patients with ACO were more likely to report previous episodes of asthma and had worse lung function than did those with COPD only. Of the diagnostic criteria used in this study, the ATS Roundtable criteria appear to be the most judicious, although concordance was greatest between the PLATINO and the Spanish criteria.

Further studies are needed to determine the importance, as well as the specificity and sensitivity, of the different characteristics that comprise the diagnostic criteria for ACO. In addition, longitudinal studies should be considered to follow patients with ACO from a clinical, laboratory, and functional standpoint, as well as in terms of important outcomes, such as hospitalizations and mortality.

REFERENCES

1. Global Initiative for Asthma [homepage on the Internet]. Bethesda: Global Initiative for Asthma; c2019 [cited 2020 May 1]. Global Strategy for Asthma Management and Prevention (2019 update). Available from: <https://ginasthma.org/>
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD [cited 2020 May 1]. Global Strategy for the Diagnosis, Management, and Prevention of COPD 2019 Report. Available from: <https://goldcopd.org>
3. Woodruff PG, van den Berge M, Boucher RC, Brightling C, Burchard EG, Christenson SA, 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(3):375-381. <https://doi.org/10.1164/rccm.201705-0973WS>
4. Uchida A, Sakaue K, Inoue H. Epidemiology of asthma-chronic obstructive pulmonary disease overlap (ACO). *Allergol Int.* 2018;67(2):165-171. <https://doi.org/10.1016/j.alit.2018.02.002>
5. Jo YS, Lee J, Yoon HI, Kim DK, Yoo CG, Lee CH. Different prevalence and clinical characteristics of asthma-chronic obstructive pulmonary disease overlap syndrome according to accepted criteria. *Ann Allergy Asthma Immunol.* 2017;118(6):696-703.e1. <https://doi.org/10.1016/j.anai.2017.04.010>
6. Menezes AMB, Montes de Oca M, Pérez-Padilla R, Nadeau

- G, Wehrmeister FC, Lopez-Varela MV, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest*. 2014;145(2):297-304. <https://doi.org/10.1378/chest.13-0622>
7. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpeläinen M, Kinnula VL, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma*. 2011;48(3):279-285. <https://doi.org/10.3109/02770903.2011.555576>
 8. Brzostek D, Kokot M. Asthma-chronic obstructive pulmonary disease overlap syndrome in Poland. Findings of an epidemiological study. *Postepy Dermatol Alergol*. 2014;31(6):372-379. <https://doi.org/10.5114/pdia.2014.47120>
 9. Kim J, Kim YS, Kim K, Oh YM, Yoo KH, Rhee CK, et al. Socioeconomic impact of asthma, chronic obstructive pulmonary disease and asthma-COPD overlap syndrome. *J Thorac Dis*. 2017;9(6):1547-1556. <https://doi.org/10.21037/jtd.2017.05.07>
 10. Sin DD, Miravittles M, Mannino DM, Soriano JB, Price D, Celli BR, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. *Eur Respir J*. 2016;48(3):664-673. <https://doi.org/10.1183/13993003.00436-2016>
 11. Cosio BG, Soriano JB, López-Campos JL, Calle-Rubio M, Soler-Cataluna JJ, de-Torres JP, et al. Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort. *Chest*. 2016;149(1):45-52. <https://doi.org/10.1378/chest.15-1055>
 12. Mendy A, Forno E, Niyonsenga T, Carnahan R, Gasana J. Prevalence and features of asthma-COPD overlap in the United States 2007-2012. *Clin Respir J*. 2018;12(8):2369-2377. <https://doi.org/10.1111/crj.12917>
 13. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest*. 2015;148(4):971-985. <https://doi.org/10.1378/chest.14-2535>
 14. Queiroz MC, Moreira MA, Rabahi MF. Underdiagnosis of COPD at primary health care clinics in the city of Aparecida de Goiânia, Brazil. *J Bras Pneumol*. 2012;38(6):692-699. <https://doi.org/10.1590/S1806-37132012000600003>
 15. Chung JW, Kong KA, Lee JH, Lee SJ, Ryu YJ, Chang JH. Characteristics and self-rated health of overlap syndrome. *Int J Chron Obstruct Pulmon Dis*. 2014;9:795-804. <https://doi.org/10.2147/COPD.S61093>
 16. Kim MH, Rhee CK, Kim K, Kim SH, Lee JY, Kim YH, et al. Heterogeneity of asthma and COPD overlap. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1251-1260. <https://doi.org/10.2147/COPD.S152916>
 17. Montes de Oca M, Victorina Lopez Varela M, Laucho-Contreras ME, Casas A, Schiavi E, Mora JC. Asthma-COPD overlap syndrome (ACOS) in primary care of four Latin America countries: the PUMA study. *BMC Pulm Med*. 2017;17(1):69. <https://doi.org/10.1186/s12890-017-0414-6>
 18. Milanese M, Di Marco F, Corsico AG, Rolla G, Sposato B, Chieco-Bianchi F, et al. Asthma control in elderly asthmatics. An Italian observational study. *Respir Med*. 2014;108(8):1091-1099. <https://doi.org/10.1016/j.rmed.2014.05.016>
 19. Cosentino J, Zhao H, Hardin M, Hersh CP, Crapo J, Kim V, et al. Analysis of Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome Defined on the Basis of Bronchodilator Response and Degree of Emphysema. *Ann Am Thorac Soc*. 2016;13(9):1483-1489. <https://doi.org/10.1513/AnnalsATS.201511-761OC>
 20. Izbicki G, Teo V, Liang J, Russell GM, Holland AE, Zwar NA, et al. Characteristics Of Patients With Asthma COPD Overlap (ACO) In Australian Primary Care. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2745-2752. <https://doi.org/10.2147/COPD.S220346>
 21. Nuñez A, Sarasate M, Loeb E, Esquinas C, Miravittles M, Barrecheguren M. Practical Guide to the Identification and Diagnosis of Asthma-COPD Overlap (ACO). *COPD*. 2019;16(1):1-7. <https://doi.org/10.1080/15412555.2019.1575802>
 22. Yanagisawa S, Ichinose M. Definition and diagnosis of asthma-COPD overlap (ACO). *Allergol Int*. 2018;67(2):172-178. <https://doi.org/10.1016/j.alit.2018.01.002>
 23. Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. *Eur Respir J*. 2008;31(4):742-750. <https://doi.org/10.1183/09031936.00129607>
 24. Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax*. 2003;58(8):659-664. <https://doi.org/10.1136/thorax.58.8.659>
 25. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. *PLoS One*. 2015;10(9):e0136065. <https://doi.org/10.1371/journal.pone.0136065>
 26. Barrecheguren M, Román-Rodríguez M, Miravittles M. Is a previous diagnosis of asthma a reliable criterion for asthma-COPD overlap syndrome in a patient with COPD?. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1745-1752. <https://doi.org/10.2147/COPD.S87025>
 27. Wurst KE, Rheault TR, Edwards L, Tal-Singer R, Agusti A, Vestbo J. A comparison of COPD patients with and without ACOS in the ECLIPSE study. *Eur Respir J*. 2016;47(5):1559-1562. <https://doi.org/10.1183/13993003.02045-2015>
 28. So JY, Lastra AC, Zhao H, Marchetti N, Criner GJ. Daily Peak Expiratory Flow Rate and Disease Instability in Chronic Obstructive Pulmonary Disease. *Chronic Obstr Pulm Dis*. 2015;3(1):398-405. <https://doi.org/10.15326/jcopdf.3.1.2015.0142>
 29. Agusti A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2019;381(13):1248-1256. <https://doi.org/10.1056/NEJMra1900475>
 30. Ahlstedt S, Murray CS. In vitro diagnosis of allergy: how to interpret IgE antibody results in clinical practice. *Prim Care Respir J*. 2006;15(4):228-236. <https://doi.org/10.1016/j.pcrj.2006.05.004>
 31. Song JH, Lee CH, Kim DK, Yoon H, Byun MK, Rhee CK, et al. Differences in prevalence of asthma-COPD overlap according to different criteria. *Medicine (Baltimore)*. 2018;97(36):e12049. <https://doi.org/10.1097/MD.00000000000012049>