

Different prevalence and clinical characteristics of asthma–chronic obstructive pulmonary disease overlap syndrome according to accepted criteria

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ABSTRACT

Background: A unified definition of asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS) is not available, which makes it difficult to evaluate the prevalence and clinical features of patients with ACOS.

Objective: To investigate the prevalence and clinical characteristics of ACOS according to the updated widely accepted diagnostic criteria.

Methods: Participants were enrolled from a prospective cohort study conducted between April 2013 and November 2016 in South Korea. We adopted 4 criteria of ACOS: modified Spanish, American Thoracic Society (ATS) Roundtable criteria, the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO), and the Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease (GINA/GOLD) criteria. The prevalence, clinical characteristics, and exacerbations of ACOS were investigated.

Results: Among 301 patients with chronic obstructive pulmonary disease, 31.3%, 11.9%, 48.3%, and 46.15% were diagnosed with ACOS according to the modified Spanish, ATS Roundtable criteria, PLATINO, and GINA/GOLD criteria, respectively. Compared with other criteria, patients with ACOS diagnosed according to the modified Spanish criteria had better exercise capacity and lung function at baseline but higher risk of moderate to severe (adjusted hazard ratio, 1.97; 95% confidence interval, 1.14–3.41; $P = .01$) and total (adjusted odds ratio, 2.10; 95% confidence interval, 1.33–3.31; $P < .01$) exacerbations during at least a 1-year follow-up period than patients without ACOS.

Conclusion: The prevalence of ACOS varied according to the diagnostic criteria. Among the different criteria, the modified Spanish criteria could identify patients with more asthmatic features and higher risk of exacerbation.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) have been regarded as 2 distinguishable disease entities. However, the cases of patients with features of both asthma and COPD, termed as asthma-COPD overlap syndrome (ACOS), have been highlighted recently.

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The Global Initiative for Asthma (GINA)/Global Initiative for Chronic Obstructive Lung Disease (GOLD) has dedicated an independent chapter for ACOS,^{1,2} and studies have found that approximately 15% of patients with COPD diagnosed using spirometry may have ACOS.^{1–5} However, whether ACOS is a single distinct disease entity has been widely debated.^{6,7} Therefore, more research is necessary to verify the pathophysiologic findings, clinical characteristics, treatment response, and prognosis of ACOS to distinguish it from asthma or COPD. In fact, several studies have documented the contradictory results of the use of inhaled corticosteroids (ICSs) in ACOS on clinical outcome,^{8,9} as well as the effect of ACOS itself on prognosis, including exacerbation and mortality.^{4,10–12}

The absence of a standard definition of ACOS is a fundamental issue. To date, several definitions of ACOS have been suggested by incorporating some clinical features of asthma and COPD simultaneously.^{1,4,12–14} However, no comparative study has attempted to provide a definition for identifying and representing ACOS in practice. This lack of studies makes it difficult for clinicians to understand the pathophysiology and unique clinical manifestations of ACOS, which might differ according to the criteria used. Thus, we aimed to compare the prevalence, clinical characteristics, and exacerbation risk of ACOS according to the several diagnostic criteria of ACOS.

Methods

Study Design and Participants

The Seoul National University Airway Registry is an ongoing, prospective, observational, multicenter cohort study that enrolls patients with chronic airway disease, including COPD. Among the participants in the cohort, patients 40 years or older with COPD defined by persistent airflow limitation (postbronchodilator forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] ratio <0.7) between April 2013 and November 2016 were included in this study. Patients who did not agree to the cohort study or without available post-BD spirometry data were excluded from the analyses. Patients were followed up every 3 months, and the present study analyzed baseline data for all included patients and evaluated the risk of exacerbation in those who were followed up at least 1 year from enrollment.

All patients signed the informed consent form to participate in this observational cohort. This study was approved by the institutional review board of Seoul National University Hospital.

Clinical Data Measurements

Demographic and clinical data evaluated at baseline included anthropometric data (age, sex, and body mass index [BMI]); previous history of physician-diagnosed or self-reported asthma, atopy, and allergic rhinitis; other comorbidities; family history of respiratory disease, smoking status and pack-years and biomass exposure history; symptom questionnaires (modified Medical Research Council [mMRC] scale, COPD Assessment Test [CAT], and Clinical COPD Questionnaire [CCQ]); exercise capacity (6-minute walking distance [6MWD]); and airflow limitation on spirometry. A blood sample was collected to quantify total serum IgE, and both blood and sputum samples were collected to determine the percentage of blood and airway eosinophils.

Spirometry was performed using standardized equipment, and lung volume was measured following the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.^{15,16} Spirometry was performed at least 3 times to verify the reproducibility and validity, and assessments of pulmonary function test results were performed using computer programs and reviewed by highly qualified physicians. The spirometric reference value was calculated using Morris's predictive equation.^{17,18} Spirometry was performed before and after a 15-minute delay of the inhalation of 2 puffs of salbutamol to identify bronchodilator response (BDR) as recommended by ATS/ERS guidelines.

In this observational cohort study, treatment for individual patients depends on each attending physician's choice. Patients are followed up every 3 months, and we checked the treatment drugs and the experience of exacerbations at each visit. Exacerbations were assessed on the basis of self-reported aggravation of respiratory symptoms that required the modification of current treatment during the regular follow-up period in participants who were followed up for more than a year. Total exacerbations included mild, moderate, and severe exacerbations. Mild exacerbation was

defined as an exacerbation event spontaneously resolved without medication; moderate exacerbation was defined as an exacerbation that required a visit to an outpatient clinic and treatment with short-term systemic corticosteroids or antibiotics; and severe exacerbation was defined as an exacerbation event that required a visit to the emergency department or hospitalization.

Diagnostic Criteria for ACOS

We adopted 4 of the latest and well-known guidelines of ACOS. A multicenter COPD cohort defined by a smoking history of 10 pack-years or more and a postbronchodilator FEV₁/FVC ratio less than 0.7 after 400 µg of inhaled salbutamol in Spain suggested 6 diagnostic criteria to identify patients with ACOS. The major criteria included a previous history of asthma and very positive BDR (>400 mL and >15% in FEV₁). The minor criteria included an elevated IgE level (>100 IU/mL) or a history of atopy, positive BDR (>12% and 200 mL) on at least 2 occasions, and blood eosinophilia (eosinophil count >5%). Patients had to meet at least 1 major or 2 minor criteria to be diagnosed with ACOS. This criteria was named the modified Spanish criteria in this study.⁴

The recent diagnostic criteria for ACOS were established at a global expert panel discussion at the 2015 ATS conference, named the ATS Roundtable criteria in the present study.^{14,19} It included 6 criteria to diagnose ACOS. The major criteria included fixed airflow limitation (postbronchodilator FEV₁/FVC ratio <0.70) in patients older than 40 years, with a smoking amount of more than 10 pack-years or equivalent indoor or outdoor air pollution exposure, and a history of asthma diagnosis before 40 years or BDR greater than 400 mL in FEV₁. The minor criteria included a history of atopy, allergic rhinitis, positive BDR (>12% and 200 mL) on at least 2 occasions, and blood eosinophilia (eosinophil count ≥300 cells/µL).

A population-based survey cohort study in Latin America named the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) defined ACOS when the patients met both criteria for COPD (postbronchodilator FEV₁/FVC ratio <0.70) and for asthma (subjective wheezing in the last 12 months plus post-bronchodilator increase in FEV₁ or FVC of 200 mL and 12%; a history of diagnosed asthma could be an alternative) simultaneously.¹²

The GINA/GOLD criteria suggest a tick-box approach to ACOS diagnosis and included clinical characteristics (eg, diagnosis of asthma by a physician) and spirometric feature (eg, a significant BDR). If more than 3 boxes were checked for asthma or COPD, the patients were considered to have that disease, but if the number of checked boxes was similar in both columns, a diagnosis of ACOS was considered.¹ In our study, ACOS was diagnosed in patients who satisfied at least 3 items in both the asthma and COPD categories simultaneously.

Statistical Analysis

We evaluated the prevalence of ACOS according to these criteria. The clinical characteristics of patients with and without ACOS were compared according to these criteria. The Pearson χ^2 test for categorical variables and the *t* test for continuous variables were applied. The risks of exacerbation during the follow-up period were investigated. The time to first exacerbation was analyzed by using Kaplan-Meier methods and Cox proportional hazards regression analysis, and the incidence of exacerbations was analyzed using negative binomial regression models. Covariates, including age, sex, BMI, FEV₁ percentage predicted at baseline, history of total exacerbations in the past year before enrollment, and use of ICSs and long-acting β_2 -agonists (LABAs), were adjusted for in the multivariable analyses. All analyses were 2-sided and performed at a significance level of .05 unless otherwise noted. *P* < .05 was considered statistically significant. All analyses were performed using STATA software, version 14.2 (StataCorp, College Station, Texas).

Results

Prevalence of ACOS According to Different Criteria

In total, 301 patients were included in the analysis (Fig 1). The number of patients who were diagnosed with ACOS according to the modified Spanish, ATS Roundtable, PLATINO, and GINA/GOLD criteria were 31.3%, 11.9%, 48.3%, and 46.15%, respectively (Table 1 and Fig 2). The features that favored asthma, as suggested by the GINA/GOLD guidelines, are presented in eTable 1.

Comparison of Clinical Characteristics Between ACOS Group and Non-ACOS Group According to Different Criteria

Patients with ACOS diagnosed according to the modified Spanish criteria were younger and had higher BMIs than did patients without ACOS. A history of physician-diagnosed or self-reported asthma was more prevalent among patients with ACOS diagnosed according to the modified Spanish, PLATINO, and GINA/GOLD criteria, and those who diagnosed as having ACOS according to PLATINO and GINA/GOLD criteria were more likely to have a family history of allergic disease, including asthma. In addition, patients with ACOS defined by modified Spanish and GINA/GOLD criteria tended to have more asthmatic symptoms than did patients without ACOS. Patients with ACOS across 4 adopted criteria tend to be treated with ICSs and LABAs more frequently than non-ACOS group, but this finding was not statistically significant. Long-acting muscarinic receptor agonist and/or LABA use was significantly observed in those without ACOS based on modified Spanish criteria ($P < .01$) (Table 2).

Patients with ACOS according to the modified Spanish, PLATINO, and GINA/GOLD criteria were apt to experience worse symptoms, even though patients with ACOS diagnosed according to the modified Spanish criteria had a lower mMRC grade and better exercise capacity (Table 3). Patients with ACOS diagnosed according to the modified Spanish and PLATINO criteria had experienced more exacerbations in the past year than did patients without ACOS (Table 3).

However, the patients with ACOS diagnosed according to the modified Spanish criteria had better pulmonary function at

Table 1

Prevalence of ACOS Based on Different Criteria

Criterion	No. (%) of Patients	
	Meet the Criteria	Do Not Meet the Criteria
Modified Spanish criteria		
Major		
Previous history of asthma	80 (27.5)	211 (72.5)
BDR to salbutamol >15% and 400 mL	8 (2.7)	293 (97.3)
Minor		
IgE >100 IU/mL or history of atopy	53 (37.9)	87 (62.1)
2 Separate BDRs >12% and 200 mL	3 (2.0)	102 (97.1)
Blood eosinophil count >5%	46 (19.6)	189 (80.4)
ACOS (1 major or 2 minor)	91 (31.3)	200 (68.7)
ATS Roundtable criteria		
Major		
Postbronchodilator FEV ₁ /FVC ratio <0.7 and age ≥40 y	279 (93.0)	21 (7.0)
Smoking ≥10 pack-year or exposure to air pollution ≥10year	239 (81.3)	55 (18.7)
History of asthma before 40 years or BDR >400 mL in FEV ₁	16 (36.4)	28 (63.6)
Minor		
History of atopy or allergic rhinitis	40 (13.5)	257 (86.5)
2 Separate BDRs ≥12% and 200 mL	3 (2.9)	102 (97.1)
Blood eosinophil count ≥300 cells/μL	43 (18.4)	192 (81.7)
ACOS (all 3 major and at least 1 minor)	5 (11.9)	37 (88.1)
PLATINO study criteria		
Postbronchodilator FEV ₁ /FVC ratio <0.7	279 (92.7)	22 (7.3)
Subjective wheezing and BDR positivity ^a or prior diagnosis of asthma	156 (53.8)	134 (46.2)
ACOS (combination of above 2 items)	140 (48.3)	150 (51.7)
GINA/GOLD document^b		
ACOS (≥3 asthma and ≥3 COPD features)	42 (46.1)	49 (53.8)

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; BDR, bronchodilator response; COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aPositive bronchodilator response implies elevated FEV₁ greater than 12% and greater than 200 mL from baseline FEV₁ after the inhalation of 200 μg of salbutamol.

^bGOLD/GINA criteria–based ACOS was defined if the patients met at least 3 items in both the asthma and COPD categories.

baseline (Table 4). A positive BDR was identified across the criteria except for the GINA/GOLD criteria and 2 separated positive BDRs to salbutamol observed only in patients with ACOS diagnosed according to the modified Spanish criteria (Table 4).

Risk of Exacerbation During Follow-up Period in Patients With ACOS According to Different Criteria

Among the 301 patients included in the analysis, 194 patients were followed up at least 1 year. Patients with ACOS diagnosed according to the modified Spanish criteria had significantly shorter time to the first moderate to severe exacerbation (adjusted hazard ratio [aHR], 1.97; 95% confidence interval [CI], 1.14–3.41) (Table 5 and Table 6) and first total exacerbation (aHR, 2.10; 95% CI, 1.33–3.31) (eTable 2 and eTable 3). Patients diagnosed according to the GINA/GOLD criteria had significantly shorter time to the first total exacerbation (aHR, 1.90; 95% CI, 1.02–3.55) during the follow-up period. Although the finding was not statistically significant, the patients with ACOS diagnosed according to all criteria, except the ATS Roundtable criteria, tended to have a higher exacerbation risk (Table 5, Table 6, eTable 2, eTable 3, and Fig 3).

Discussion

Our study found that the prevalence of ACOS varied according to different criteria and that the patients with ACOS diagnosed according to the modified Spanish criteria had not only more

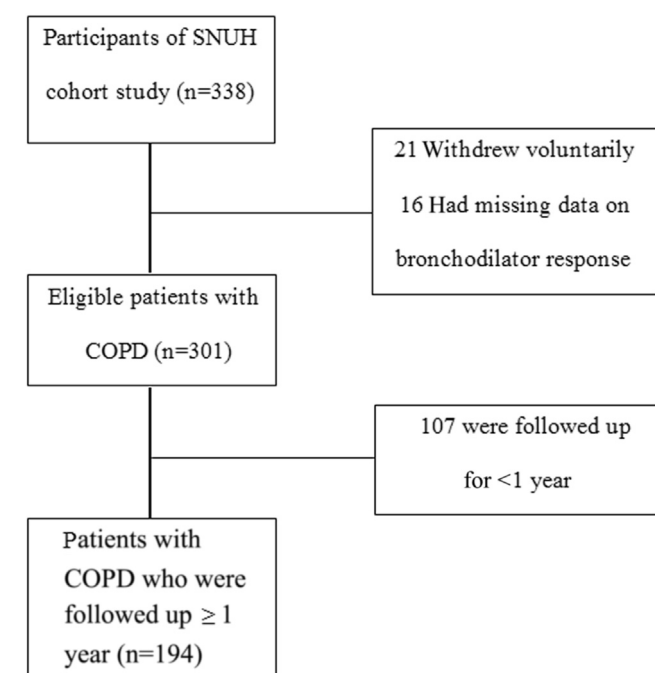


Figure 1. Flowchart showing participant inclusion. COPD indicates chronic obstructive pulmonary disease; SNUH, Seoul National University Hospital.

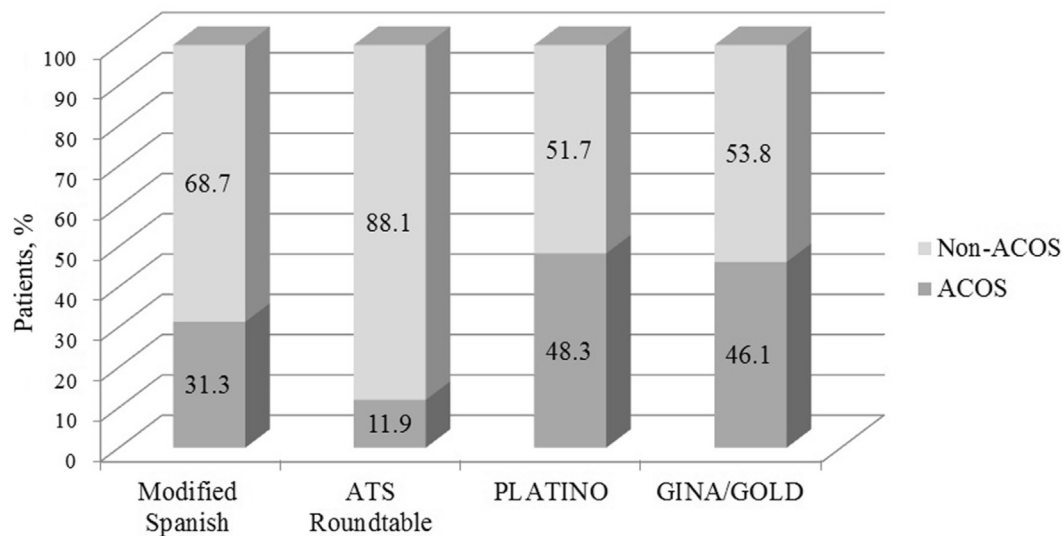


Figure 2. Prevalence of asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS) diagnosed according to different criteria. ATS indicates American Thoracic Society; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

asthmatic features but also higher exacerbation risk than did patients without ACOS.

Previous studies have found that patients with ACOS more commonly experience respiratory symptoms and frequent exacerbation and have limited physical activity with lower lung function and poor quality of life than do patients without ACOS.^{10,12,20–22} Although some of our study results were similar, some differed from the results of previous studies. Compared with the patients with ACOS diagnosed according to the other criteria, those diagnosed using the modified Spanish and PLATINO criteria had worse scores in the symptom questionnaires SGRQ, CAT, and CCQ in the context of COPD and in the ACT and Mini Asthma Quality of Life Questionnaire in the context of asthma and more previous exacerbation history in the past year. However, the patients with ACOS diagnosed using the modified Spanish criteria were less dyspneic (lower mMRC grade) and had better lung function than did the patients diagnosed using the other criteria.

Old age,²³ higher mMRC grade,²⁴ lower lung function,^{24,25} weight loss,²⁶ and shorter 6MWD^{27,28} are related to an increased risk of exacerbation of COPD. Interestingly, although the patients diagnosed using the modified Spanish criteria were younger, weighed more, were less dyspneic and less restricted in physical activity, and had more favorable lung function, they had a higher risk of exacerbation during the follow-up period. This paradox could be explained by the hypothesis that the patients with ACOS diagnosed using the modified Spanish criteria had close-to-pure asthma, characterized by variable clinical features and baseline characteristics that indicated a stable status. This finding also suggests that many exacerbations in the modified Spanish criteria-defined ACOS were asthma-related events. In fact, the patients with ACOS diagnosed using the modified Spanish criteria had more asthma-like clinical features, including variable symptoms and symptoms with diurnal variation. In addition, more than 80% of them reported asthma history. It suggests that a self-reported previous history of asthma might be a key of the possibility of ACOS in patients with COPD.

Whether ACOS is a unique disease distinguishable from asthma or COPD is questionable, and more studies are needed to confirm this.^{5–7} However, in the present study, the patients with ACOS diagnosed using the modified Spanish criteria had different, but consistent, clinical features from the patients without ACOS and

from patients with ACOS defined by criteria itself as a predictor of exacerbation. In this context, the modified Spanish criteria—defined ACOS might be a unique phenotype. In fact, the phenotype-based classification and approach to COPD have highlighted ACOS as a distinct phenotype in the modified Spanish guidelines for COPD.^{13,29} Although a study using data from the COPD History Assessment in Spain cohort found a better survival among patients with ACOS,⁴ 1 year may be a short observation time for evaluating the alteration of disease progression or mortality.³⁰ In that study, exacerbation was not compared between patients with and without ACOS.

The prevalence of ACOS defined by the ATS Roundtable criteria was 11.9%, which was the lowest among the applied criteria. This finding might be attributed to the small number of cases diagnosed using these criteria, which imposes strict conditions for distinguishing ACOS from COPD or asthma. In our study, the patients with ACOS diagnosed using the ATS Roundtable criteria did not have any differences in clinical characteristics and the risk of exacerbations than did patients without ACOS.

Among the asthmatic features used for defining ACOS, BDR positivity and eosinophilic airway inflammation are considered critical,^{4,5,10,11,14,31} but a previous history of asthma has been considered representative of asthma as well. In the PLATINO criteria, the asthmatic component of ACOS was characterized by subjective wheezing along with BDR positivity, but these factors could be substituted by prior diagnosis of asthma. Considering the vague reliability of a self-reported history of previously diagnosed asthma, the asthmatic component of ACOS might be overestimated despite the fact that the patients with ACOS diagnosed using the PLATINO criteria had a similar pattern of clinical features and exacerbations to the patients with ACOS diagnosed using the other criteria.

To our knowledge, this study is the first to investigate the prevalence, clinical characteristics, and outcomes of GINA/GOLD criteria-defined ACOS. However, using the GINA/GOLD criteria for defining ACOS may be impractical because of the complex guidelines that involve many subjectively reported items. We diagnosed ACOS if patients met at least 3 criteria related to asthma and COPD simultaneously, but this definition was ambiguous and did not yield clear results. Complexity and lack of clear definition of ACOS in GINA/GOLD criteria might make clinicians seldom use that

Table 2
Comparisons of Demographic and Clinical Characteristics Between Patients With and Without ACOS^a

Variable	Total (N = 301)	Modified Spanish		P Value	ATS Roundtable		P Value	PLATINO		P Value	GINA/GOLD		P Value
		ACOS (n = 91)	Non-ACOS (n = 200)		ACOS (n = 5)	Non-ACOS (n = 37)		ACOS (n = 140)	Non-ACOS (n = 150)		ACOS (n = 42)	Non-ACOS (n = 49)	
Age, mean (SD), y	70.9 (8.7)	69.4 (9.1)	71.8 (8.2)	.03	66.2 (9.5)	69.4 (8.8)	.45	70.6 (7.6)	71.2 (9.5)	.53	70.1 (7.6)	71.7 (9.5)	.40
Male sex	276 (91.7)	80 (87.9)	187 (93.5)	.11	5 (100)	32 (86.5)	.38	128 (91.4)	138 (92.0)	.86	40 (95.2)	46 (93.9)	.78
BMI, mean (SD)	23.1 (3.4)	23.9 (3.3)	22.7 (3.4)	.01	25.9 (3.4)	24.4 (3.6)	.40	22.9 (3.3)	23.3 (3.4)	.34	23.7 (2.9)	23.4 (3.7)	.69
Smoking, mean (SD), pack-year	44.5 (25.4)	44.2 (25.5)	44.3 (25.5)	.97	47.1 (39.3)	40.5 (22.6)	.59	46.9 (24.1)	42.0 (26.6)	.12	43.6 (27.0)	48.4 (24.6)	.40
History of asthma													
Yes (%)	80 (27.5)	80 (87.9)	0 (0)	<.01	4 (80.0)	25 (67.6)	.57	67 (48.5)	13 (8.7)	<.01	24 (57.5)	9 (18.7)	<.01
Before 40 years	8 (20.5)	7 (24.1)	1 (10.0)	.34	1 (25.0)	7 (21.2)	.86	4 (14.3)	4 (36.4)	.12	4 (16.7)	1 (12.5)	.78
History of atopy	10 (3.4)	5 (5.5)	5 (2.5)	.20	0 (0)	2 (5.4)	.59	6 (4.3)	4 (2.7)	.44	2 (4.8)	1 (2.0)	.47
Family history of asthma or allergy	47 (15.6)	17 (18.7)	29 (14.5)	.36	2 (40.0)	9 (24.3)	.45	30 (21.4)	17 (11.3)	.02	17 (40.5)	3 (6.1)	<.01
Symptoms suggestive of asthma													
Variable symptom	32 (35.2)	19 (47.5)	13 (26.5)	.04	3 (75.0)	15 (55.6)	.46	19 (34.5)	13 (37.1)	.80	24 (57.1)	8 (16.7)	<.01
Diurnal variation	26 (28.9)	16 (40.0)	9 (18.7)	.03	1 (25.0)	13 (48.1)	.38	20 (36.4)	6 (17.6)	.06	20 (47.6)	6 (12.5)	<.01
Initial treatment													
ICS and LABA	119 (39.5)	41 (45.0)	76 (38.0)	.25	4 (80.0)	19 (51.3)	.23	61 (43.6)	56 (37.3)	.28	25 (59.5)	22 (44.9)	.16
LAMA and/or LABA	160 (53.2)	31 (34.1)	126 (63.0)	<.01	0 (0)	13 (35.1)	.11	70 (50.0)	85 (56.7)	.25	18 (42.9)	28 (57.1)	.17

Abbreviations: ACOS, asthma-COPD overlap syndrome; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic receptor agonist; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aData are presented as number (percentage) of patients unless otherwise indicated.

Table 3
Comparisons of Symptom, Exercise Capacity, and Exacerbation History Between Patients With and Without ACOS^a

Variable	Total (N = 301)	Modified Spanish		P Value	ATS Roundtable		P Value	PLATINO		P Value	GINA/GOLD		P Value
		ACOS (n = 91)	Non-ACOS (n = 200)		ACOS (n = 5)	Non-ACOS (n = 37)		ACOS (n = 140)	Non-ACOS (n = 150)		ACOS (n = 42)	Non-ACOS (n = 49)	
Indexes of dyspnea and quality of life, mean (SD)													
SGRQ	34.3 (17.6)	37.4 (18.6)	33.1 (17.1)	.07	34.9 (18.5)	39.0 (18.5)	.64	39.4 (17.7)	29.5 (16.3)	<.01	37.1 (16.7)	36.3 (18.0)	.82
CAT	15.4 (7.3)	17.2 (7.9)	14.7 (7.0)	.01	18 (7.2)	17.5 (7.1)	.89	17.8 (7.7)	13.1 (6.2)	<.01	17.3 (6.6)	17.2 (7.5)	.93
CCQ	18.8 (9.2)	19.0 (9.4)	18.7 (9.3)	.86	13.2 (5.6)	19.5 (9.4)	.20	20.6 (9.1)	16.5 (9.0)	<.01	19.7 (9.0)	18.5 (8.7)	.54
6MWD, m	437.6 (109.4)	461.0 (97.3)	427.9 (111.8)	.02	527.6 (50.4)	438.6 (98.0)	.06	441.6 (109.4)	436.3 (107.4)	.70	433.2 (92.6)	437.6 (113.6)	.85
mMRC	1.5 (0.9)	1.4 (0.8)	1.6 (0.9)	.03	1.0 (0.7)	1.4 (0.7)	.29	1.5 (0.8)	1.5 (0.9)	.67	1.2 (0.7)	1.4 (0.6)	.20
ACT	18.3 (4.4)	17.0 (4.6)	20.1 (3.4)	<.01	16.2 (4.8)	17.5 (4.2)	.58	17.4 (4.5)	20.1 (3.5)	<.01	17.7 (3.9)	19.2 (4.0)	.16
Mini-AQLQ	74.2 (17.0)	69.7 (18.4)	80.6 (12.9)	<.01	67.0 (17.3)	72.0 (19.4)	.63	70.4 (17.0)	82.3 (14.2)	<.01	70.9 (16.8)	80.1 (12.5)	.02
History of exacerbation during past 1 year													
Total No. (%)	87 (28.9)	46 (50.5)	39 (19.5)	<.01	2 (40)	21 (56.8)	.48	57 (40.7)	30 (20.0)	<.01	21 (50)	18 (36.7)	.20
Frequency, mean (SD) No. per years	0.7 (1.8)	1.3 (2.4)	0.4 (1.4)	<.01	1.6 (3.0)	1.6 (2.7)	.98	1.1 (2.4)	0.3 (0.8)	<.01	1.1 (2.1)	1.1 (2.6)	.92
Moderate to severe, No. (%)	71 (23.6)	42 (46.1)	28 (14.0)	<.01	2 (40)	19 (51.3)	.63	48 (34.3)	23 (15.3)	<.01	17 (40.5)	16 (32.6)	.44
Frequency, mean (SD) No. per year	0.4 (1.2)	1.0 (1.8)	0.2 (0.7)	<.01	0.8 (1.3)	1.3 (2.4)	.62	0.7 (1.5)	0.2 (0.8)	<.01	0.9 (2.1)	0.7 (1.4)	.56

Abbreviations: ACOS, asthma-COPD overlap syndrome; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease; SGRQ, St. George's Respiratory Disease Questionnaire; 6MWD, 6-minute walk distance.

^aData are presented as number (percentage) of patients unless otherwise indicated.

Table 4
Comparisons of Pulmonary Function and Laboratory Results of Patients With and Without ACOS^a

Variable	Total (N = 301)	Modified Spanish		P Value	ATS Roundtable		P Value	PLATINO		P Value	GINA/GOLD		P Value
		ACOS (n = 91)	Non-ACOS (n = 200)		ACOS (n = 5)	Non-ACOS (n = 37)		ACOS (n = 140)	Non-ACOS (n = 150)		ACOS (n = 42)	Non-ACOS (n = 49)	
FVC, mean (SD), L	3.3 (0.7)	3.5 (0.8)	3.2 (0.7)	<.01	4.0 (0.8)	3.5 (0.7)	.13	3.4 (0.7)	3.2 (0.7)	0.06	3.6 (0.8)	3.3 (0.7)	.07
FVC, mean (SD), % predicted	92.1 (17.1)	96.6 (18.7)	90.1 (16.1)	<.01	100.8 (24.4)	96.1 (15.2)	.55	93.5 (17.8)	90.5 (16.3)	.13	95.0 (17.1)	93.0 (19.3)	.61
FEV ₁ , mean (SD), L	1.6 (0.6)	1.8 (0.6)	1.5 (0.5)	<.01	2.3 (0.5)	1.8 (0.5)	.05	1.6 (0.5)	1.7 (0.6)	.44	1.8 (0.5)	1.6 (0.6)	.15
FEV ₁ , mean (SD), % predicted	66.7 (20.4)	73.8 (19.3)	63.2 (20.3)	<.01	81.4 (14.5)	71.4 (17.5)	.23	65.3 (18.6)	67.7 (22.3)	.32	68.5 (16.1)	65.9 (21.8)	.53
FEV ₁ /FVC, mean (SD)	49.5 (13.4)	53.2 (14.4)	47.4 (12.6)	<.01	57.2 (7.3)	52.2 (13.1)	.41	47.8 (12.0)	50.8 (14.7)	.06	50.2 (11.8)	48.1 (12.4)	.41
BDR, mean (SD), mL	107.9 (135.1)	170.0 (168.3)	81.3 (105.4)	<.01	538 (116.5)	170.3 (185.7)	<.01	146.3 (152.0)	78.5 (107.5)	<.01	163.8 (161.4)	118.2 (155.7)	.17
BDR, mean (SD), %	4.2 (5.9)	6.7 (6.8)	3.0 (5.1)	<.01	19.2 (4.8)	6.9 (8.0)	<.01	5.8 (6.2)	2.9 (5.4)	<.01	6.3 (6.2)	4.7 (6.2)	.23
BDR positivity, No. (%) ^b													
Yes	20 (6.6)	14 (15.4)	6 (3.0)	<.01	4 (80.0)	7 (18.9)	<.01	19 (13.6)	1 (0.7)	<.01	7 (16.7)	4 (8.2)	.21
≥2	3 (2.9)	3 (7.0)	0 (0)	.04	3 (33.3)	1 (5.6)	.13	3 (5.6)	0 (0)	.10	1 (5.0)	0 (0)	.31
BDR >400 mL, No. (%)	9 (3.0)	9 (9.9)	0 (0)	<.01	5 (100)	4 (10.8)	<.01	9 (6.4)	0 (0)	<.01	4 (9.5)	1 (2.0)	.12
Total IgE >100 IU/mL, No. (%)	45 (32.8)	31 (43.1)	13 (21.0)	.01	3 (100)	8 (25.8)	.01	27 (32.1)	18 (34.6)	.77	15 (40.5)	10 (28.6)	.29
Blood eosinophil count >2%, No. (%)	155 (66.0)	65 (74.7)	87 (62.1)	.05	4 (100)	27 (75.0)	.26	76 (62.3)	76 (72.4)	.11	28 (70.0)	34 (73.9)	.69
Blood eosinophil count >5%, No. (%)	46 (19.6)	28 (32.2)	16 (11.4)	<.01	3 (75.0)	7 (19.4)	.01	22 (18.0)	23 (21.9)	.47	10 (25.0)	11 (23.9)	.91

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; BDR, bronchodilator response; COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bPositive bronchodilator response implies elevated FEV₁ greater than 12% and greater than 200 mL from baseline FEV₁ after the inhalation of 200 µg OF salbutamol.

Table 5

Risk of Moderate to Severe Exacerbation Within 1 Year in Patients With and Without ACOS

Criterion	Crude HR (95% CI)	P Value	Adjusted HR ^a (95% CI)	P Value
ACOS by Modified Spanish criteria	2.09 (1.28–3.40)	<.01	1.97 (1.14–3.41)	.01
ACOS by ATS Roundtable criteria	1.22 (0.28–5.36)	.79	1.07 (0.20–5.82)	.93
ACOS by PLATINO criteria	1.75 (1.10–2.78)	.02	1.35 (0.81–2.25)	.25
ACOS by GINA/GOLD criteria	1.60 (0.83–3.07)	.16	2.01 (0.97–4.15)	.06

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; CI, confidence interval; ATS, American Thoracic Society; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aAdjusted by age, sex, body mass index, initial FEV₁, use of ICSs or LABAs, and frequency of total exacerbations in the past year before enrollment.

criteria in clinical research to identify ACOS. Furthermore, the patients with ACOS diagnosed using the GINA/GOLD criteria did not have significant clinical differences from the patients without ACOS, which further obscures the practical value of the GINA/GOLD criteria.

Although this could be the first study comparing the prevalence and clinical features of ACOS by using the updated, widely acceptable 4 diagnostic criteria, ranging from the GINA/GOLD criteria to the ATS Roundtable criteria based on ATS consensus, this study has several limitations. First, there was a considerable amount of missing data on laboratory results, including IgE and blood eosinophil concentration, and subjectively reported symptomatic questionnaires, which affected the applicability of the ATS Roundtable criteria and GINA/GOLD criteria. Second, the small number of patients with ACOS based on the ATS Roundtable criteria and GINA/GOLD criteria might lead to imprecise estimation. Third, because we analyzed data collected only at the 1-year follow-up, any alteration in disease progression, including mortality and lung function decline, was not investigated. Fourth, the relatively small number of participants might have resulted in a lack of statistical power. Fifth, it remains unclear whether the concept of ACOS actually helps physicians manage patients with airway diseases.^{32–35} Although we found an increased risk of exacerbation, it does not directly mean that ACOS defined by modified Spanish criteria is a real unique disease entity. Further studies are needed.

Table 6

Incidence Rates of Moderate to Severe Exacerbation Within 1 Year in Patients With and Without ACOS

Criterion	Crude IRR (95% CI)	P Value	Adjusted IRR ^a (95% CI)	P Value
ACOS by Modified Spanish criteria	1.25 (0.66–2.36)	.49	0.95 (0.46–1.96)	.89
ACOS by ATS Roundtable criteria	0.37 (0.06–2.29)	.28	0.35 (0.06–2.10)	.25
ACOS by PLATINO criteria	1.58 (0.88–2.81)	.12	1.18 (0.65–2.13)	.59
ACOS by GINA/GOLD criteria	1.17 (0.55–2.45)	.68	1.92 (0.89–4.11)	.09

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; CI, confidence interval; ATS, American Thoracic Society; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IRR, incident rate ratio; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aAdjusted by age, sex, body mass index, initial FEV₁, use of ICSs or LABAs, and frequency of total exacerbations in the past year before enrollment.

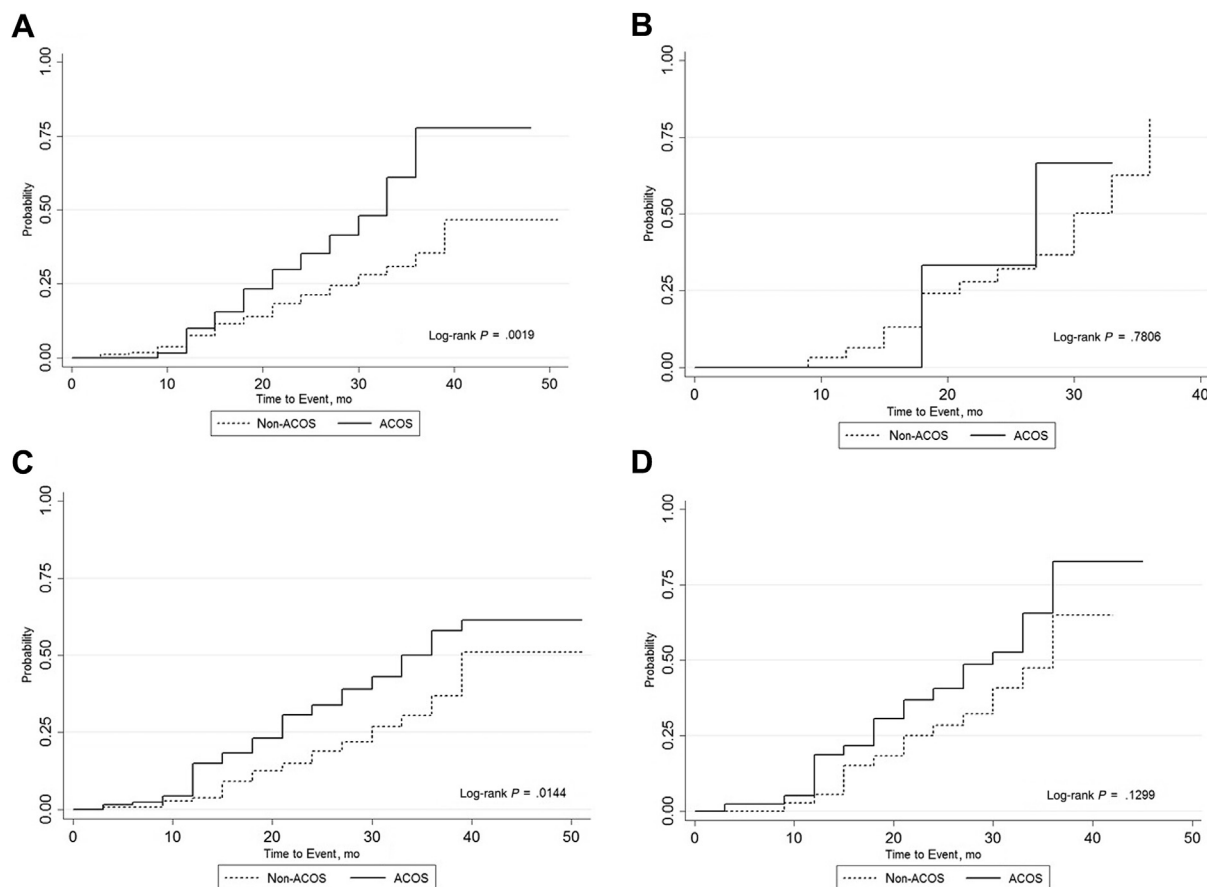


Figure 3. Kaplan-Meier estimates of moderate to severe exacerbation according to the following diagnostic criteria: modified Spanish (A), American Thoracic Society Roundtable criteria (B), Latin American Project for the Investigation of Obstructive Lung Disease (C), and Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease (D) criteria. ACOS indicates asthma–chronic obstructive pulmonary disease overlap syndrome.

In conclusion, the prevalence of ACOS varied according to the diagnostic criteria used. The patients with ACOS diagnosed using the modified Spanish criteria had different clinical features and an increased risk of exacerbation than did patients without ACOS, thereby suggesting that the modified Spanish criteria could be more useful than the other criteria in defining ACOS.

Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2017.04.010>.

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Supplementary Data

eTable 1Patients Classified According to the GINA/GOLD Criteria^a

Clinical Feature	ACOS (n = 42)	Non-ACOS (n = 49) ^b
Onset age ^c	3 (7.5)	2 (6.1)
Variation or persistent of symptom	24 (57.1)	8 (16.7)
Diurnal variation	20 (47.62)	6 (12.5)
Presence of aggravating factors	32 (76.2)	10 (20.8)
Persistent airflow limitation	40 (95.2)	46 (93.9)
Lung function between symptoms	NA	NA
Heavy exposure to smoke or biomass fuels	10 (24.4)	12 (26.1)
Previous physician diagnosis of asthma or COPD	24 (58.5)	9 (18.7)
Family history of asthma or other allergic disease	17 (40.5)	3 (6.1)
Progressive in symptom	22 (52.4)	16 (33.3)
Response to bronchodilator or ICS	13 (33.3)	7 (17.1)

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; COPD, chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid.

^aData are presented as number and percentage and indicate the asthmatic component.

^bPatients in the non-ACOS group were classified according to the GINA/GOLD criteria and included 3 patients with asthma (each patient satisfied 5 of the 7 asthmatic features) and 46 patients with COPD.

^cOnset before the age of 20 years and after 40 years was relevant to asthma and COPD, respectively.

eTable 2

Risk of Total Exacerbation Within 1 Year in Patients With and Without ACOS

Criterion	Crude HR (95% CI)	P Value	Adjusted HR ^a (95% CI)	P Value
ACOS by modified Spanish criteria	2.15 (1.42–3.23)	<.001	2.10 (1.33–3.31)	<.01
ACOS by <i>ERJ</i> criteria	1.55 (0.45–5.29)	.48	1.43 (0.36–5.76)	.61
ACOS by PLATINO criteria	1.84 (1.24–2.73)	<.001	1.49 (0.97–2.29)	.07
ACOS by GINA/GOLD criteria	1.59 (0.90–2.80)	.11	1.90 (1.02–3.55)	.04

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; *ERJ*, *European Respiratory Journal*; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazards ratio; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aAdjusted for age, sex, body mass index, initial forced expiratory volume in 1 second, use of inhaled corticosteroid or long-acting β_2 -agonist, and frequency of total exacerbation in the past year before enrollment.

eTable 3

Incidence Rates of Total Exacerbation Within 1 Year in Patients With and Without ACOS

Criterion	Crude IRR (95% CI)	P Value	Adjusted IRR ^a (95% CI)	P Value
ACOS by modified Spanish criteria	1.54 (0.92–2.57)	.10	1.40 (0.79–2.50)	.25
ACOS by <i>ERJ</i> criteria	0.48 (0.11–2.18)	.35	0.55 (0.12–2.39)	.42
ACOS by PLATINO criteria	1.63 (1.01–2.61)	.04	1.19 (0.73–1.95)	.49
ACOS by GINA/GOLD criteria	1.20 (0.66–2.17)	.54	1.58 (0.89–2.80)	.12

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; *ERJ*, *European Respiratory Journal*; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazards ratio; PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease.

^aAdjusted for age, sex, body mass index, initial forced expiratory volume in 1 second, use of inhaled corticosteroid or long-acting β_2 -agonist, and frequency of total exacerbation in the past year before enrollment.