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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.

Trial Registration: ClinicalTrials.gov Identifier: NCT02527486.

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.

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]

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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 [FEV_1]/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 FEV_1/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 $>$15% in FEV_1). The minor criteria included an elevated IgE level ($>$100 IU/mL) or a history of atopy, positive BDR ($>$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 FEV_1/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 FEV_1. 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 $\geq$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 FEV_1/FVC ratio <0.70) and for asthma (subjective wheezing in the last 12 months plus postbronchodilator increase in FEV_1 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, FEV_1 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).