ORIGINAL ARTICLE
https://doi.org/10.4046/trd.2017.0064
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2018;81:289-298

Increased Risk of Exacerbation in Asthma Predominant Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome

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Background: Obstructive airway disease patients with increased variability of airflow and incompletely reversible airflow obstruction are often categorized as having asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS). ACOS is heterogeneous with two sub-phenotypes: asthma-ACOS and COPD-ACOS. The objective of this study was to determine the difference in risk of exacerbation between the two sub-phenotypes of ACOS.
Methods: A total of 223 patients exhibiting incompletely reversible airflow obstruction with increased variability (spirometrically defined ACOS) were enrolled. These patients were divided into asthma-ACOS and COPD-ACOS according to their physician's diagnosis and smoking history of 10 pack-years. Within-group comparisons were made for asthma-ACOS versus COPD-ACOS and light smokers versus heavy smokers.
Results: Compared to patients with COPD-ACOS, patients with asthma-ACOS experienced exacerbation more often despite their younger age, history of light smoking, and better lung function. While the light-smoking group showed better lung function, they made unscheduled outpatient clinic visits more frequently. On multivariate analysis, asthma-ACOS and poor inhaler compliance were significantly associated with more than two unscheduled clinic visits during the previous year.
Conclusion: Spirometrically defined ACOS includes heterogeneous subgroups with different clinical features. Phenotyping of ACOS by physician's diagnosis could be significant in predicting future risk of exacerbation.

Keywords: Asthma; Pulmonary Disease, Chronic Obstructive; Phenotype

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Received: May. 23, 2017, **Revised:** Oct. 23, 2017, **Accepted:** Jan. 2, 2018, **Published online:** Mar. 7, 2018

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common among the general population, and a significant proportion of patients present with characteristics of both[1,2]. However, the estimated prevalence of asthma–COPD overlap syndrome (ACOS) varies depending on how it is defined. There is no general consensus regarding the definition, although several have been suggested. The main context for any definition is recognition of the coexistence of increased variability of airflow and incompletely reversible airway obstruction[1-5].

Patients with ACOS have more rapid disease progression[6], worse health-related quality of life[7], more frequent exacerbations[7-10], and more comorbidities and healthcare utilization than do patients with either disease alone[10-13]. However, recommendations for the management of ACOS are vague and extrapolated from the guidelines for either asthma or COPD alone[5,6,14,15].

ACOS is considered heterogeneous but can be divided into two clinical phenotypes[2,5]: asthma with fixed airflow limitation and COPD accompanied by reversible airway obstruction. Either phenotype may have distinct clinical features.

Characterization of different phenotypes in ACOS must be addressed to individualize and optimize phenotype-guided treatment and thus achieve the best outcome with the fewest side effects for the patient. Therefore, distinguishing the different ACOS phenotypes and their respective characteristics is clinically worthwhile.

We investigated the difference in risk of exacerbation between clinical phenotypes of ACOS.

Materials and Methods

1. Study subjects

This was a multicenter (seven institutes), cross-sectional study in which clinical data were collected by physicians via patient interviews and reviews of their medical records. Patients with ACOS were enrolled on a day-to-day basis when they met the following criteria: age ≥40 years, >1 year of in-clinic follow-up, and demonstrable incompletely reversible airflow obstruction with increased variability on spirometry during the previous year as suggested by Gibson and Simpson[1]. Incompletely reversible airflow obstruction was defined as a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) of <70% and an FEV_1 of <80% after inhalation of a bronchodilator, while increased airflow variability was established if patients met at least one of the following criteria: increased diurnal variability in peak expiratory flow rates (PEFRs; maximum-minimum/average >10%), increased response to a bronchodilator (>200 mL and >12% improvement in FEV_1 from baseline after immediate bronchodilator inhalation or >20% increase in FEV_1 from baseline after treatment), or increased airway responsiveness (methacholine provocation concentration [PC_{20}] of <8 mg/mL). Patients were excluded if they experienced acute exacerbations or respiratory infections within 4 weeks or other comorbid obstructive airway diseases, such as bronchiectasis and sequelae of tuberculosis. Patients with terminal cancer or other severe diseases that would affect the clinical manifestation or prognosis were also excluded.

2. Measurements of clinical parameters

Patients were asked about the following parameters: age at onset of respiratory symptoms, diagnosis of asthma before the age of 40 years, history of other allergic diseases, comorbidities, smoking history, duration of respiratory disease treatment, compliance with medication, and history of acute exacerbations (unscheduled visits to the outpatient clinic, emergency room attendance, hospitalization, and intensive care unit [ICU] admission). Each patient's medication history and the total amount of inhalers or systemic corticosteroids prescribed over the previous 6 months were also checked. Inhaler compliance of patient was indirectly calculated according to the amount of inhalers. In addition, we used the Korean version of the Asthma Control Test (ACT), COPD Assessment Test (CAT), and Patient Health Questionnaire (PHQ-9). The best spirometry result was selected for patients who had undergone pulmonary function testing several times during the previous year.

3. Categorization and determination of ACOS phenotype

The physicians who enrolled patients in the study also made the final diagnosis for each patient according to the weight of evidence and their experience. The final diagnosis comprised five categories: asthma, COPD, asthma-dominant ACOS (A-ACOS), COPD-dominant ACOS (C-ACOS), and asthma=COPD ACOS. After categorization, the ACOS phenotypes were determined based on the physicians' diagnoses. There were two phenotypes: the asthma predominant ACOS, which included asthma or A-ACOS, and the COPD predominant ACOS, which included COPD or C-ACOS. The asthma=COPD ACOS category was excluded. We compared the clinical characteristics and frequency of exacerbations between the two phenotypes.

We then divided the patients with ACOS into two groups in terms of their smoking history (in pack-years): light smokers (<10 pack-years) versus heavy smokers (≥10 pack-years). We also compared the clinical parameters and frequency of exacerbations between the two groups.

4. Statistics

Descriptive statistics are presented as mean and standard deviation for continuous variables and number and percentage for categorical variables. To compare the two groups in terms of demographic and baseline characteristics, Student's t test and the chi-square test were used for continuous and categorical variables, respectively. The parameters associated with exacerbations leading to more than two unscheduled outpatient clinic visits during the previous year were compared by calculating the odds ratios and their 95% confidence intervals. Univariate and multivariate linear regression analyses were also performed. All statistical analyses were undertaken by a two-sided test at the conventional 5% significance level using the statistical software SPSS version 11 (SPSS Inc., Chicago, IL, USA).

Table 1. Baseline characteristics of study population

Characteristic	Value
Age, yr	66.4±9.5
Male sex	174 (78.0)
Smoking status	
Pack-years	34.2±35.4
Current/Ex-/Never smoker	72 (32.3)/107 (48.0)/44 (19.7)
Age at symptom onset, yr	52.9±15.0
Duration of treatment, yr	7.7±6.8
Asthma diagnosis before age 40	40 (17.9)
Other allergic diseases	54 (24.2)
Post-bronchodilator FEV_1, % predicted	59.6±13.7
Diagnosis of airflow variability	
Immediate BDR	184 (82.5)
>20% FEV_1 after treatment	41 (18.4)
PEFR variability	45 (20.2)
Methacholine provocation test	10 (4.5)
Comorbidity	
Rhinosinusitis	23 (10.3)
Gastroesophageal reflux	28 (12.6)
Hypertension	86 (38.6)
Ischemic heart disease	23 (10.3)
Heart failure	13 (5.8)
Arrhythmia	11 (4.9)
Diabetes mellitus	33 (14.8)
Osteoporosis	27 (12.1)
Aspirin sensitivity	8 (3.6)
Depression	24 (10.8)
Physician's diagnosis	
Asthma	22 (9.9)
COPD	45 (20.2)
Asthma-dominant ACOS	72 (32.3)
COPD-dominant ACOS	84 (37.7)

Values are presented as mean±SD or number (%) unless otherwise indicated.
FEV_1: forced expiratory volume in 1 second; BDR: bronchodilator response; PEFR: peak expiratory flow rate; COPD: chronic obstructive pulmonary disease; ACOS: asthma-COPD overlap syndrome.

5. Ethics

This study was approved by the institutional review board of each individual hospital. Informed consent was obtained from each patient prior to enrollment.

Results

1. Baseline characteristics

In total, 223 patients were enrolled in the study between May 2013 and April 2014. The demographic profiles of all patients are presented in Table 1. Overall mean age was 66 years, and 19.7% had never smoked. Average age of symptom onset was 53 years, and mean treatment duration was 8 years. Approximately 17.9% had been diagnosed with asthma before age 40 years, and 24.2% had a history of other allergic diseases. The most common comorbidity was hypertension (38.6%).

The mean post-bronchodilator FEV_1 was 59.6% of the predicted value. More than 80.0% had an immediate response to bronchodilation. Some patients showed an increase of >20% in the FEV_1 from baseline after treatment (18.4%), PEFR variability (20.2%), or positive methacholine provocation test (4.5%).

According to the physicians' diagnoses, 22 patients (9.9%) were diagnosed with asthma, 45 (20.2%) with COPD, 72 (32.3%) with A-ACOS, and 84 (37.7%) with C-ACOS. Only one patient was diagnosed with asthma=COPD ACOS. After the patient with asthma=COPD ACOS was excluded, asthma predominant phenotype (94 patients, 42.1%) and COPD predominant phenotype (129 patients, 57.8%) were divided.

2. Comparisons of clinical characteristics between the asthma and COPD predominant ACOS

Patients with the asthma predominant ACOS were younger, more likely to be female, and had a history of light smoking. They were also younger at the onset of respiratory symptoms, had more accompanying allergic diseases, and better lung function compared with patients with the COPD predominant ACOS. However, the proportion of patients diagnosed

Table 2. Demographic and baseline characteristics of asthma and COPD phenotype groups

	Asthma predominant ACOS (n=94)	COPD predominant ACOS (n=129)	p-value
Age, yr	63.8±10.1	68.2±8.6	0.001
Male sex	57 (59.6)	118 (91.5)	<0.001
Smoking status			
Pack-years	19.1±25.1	45.1±37.8	<0.001
Current/Ex-/Never smoker	23 (24.5)/37 (39.4)/34 (36.2)	49 (38.0)/70 (54.3)/10 (7.8)	<0.001
Age at symptom onset, yr	48.7±14.7	56.0±14.6	<0.001
Duration of treatment, yr	8.0±6.3	7.4±7.2	0.518
Asthma diagnosis before age 40	17 (18.1)	23 (17.8)	1.000
Other allergic disease	30 (31.9)	24 (18.6)	0.027
Post-bronchodilator FEV_1, % predicted	64.1±11.2	56.2±14.4	<0.001
Post-bronchodilator FEV_1/FVC, %	56.3±9.5	47.9±11.2	<0.001
Change in FEV_1, mL	386.0±240.4	347.3±165.9	0.198
Change in FEV_1, %	25.8±15.8	26.3±16.7	0.850
Diagnosis of airflow variability			
Immediate BDR	75 (79.8)	109 (84.5)	0.071
>20% FEV_1 after treatment	24 (27.0)	17 (13.5)	0.046
PEFR variability	14 (14.9)	31 (24.0)	0.114
Methacholine provocation test	8 (8.5)	2 (1.6)	0.019
Patient reported outcome			
ACT score	17.9±6.4	19.3±5.0	0.080
CAT score	12.4±8.2	13.5±9.2	0.374
PHQ-9 score	3.7±4.9	3.6±4.4	0.888
Comorbidity			
Rhinosinusitis	14 (14.9)	9 (7.0)	0.074
Gastroesophageal reflux	11 (11.7)	17 (13.2)	0.839
Hypertension	32 (34.0)	54 (41.9)	0.266
Ischemic heart disease	5 (5.3)	18 (14.0)	0.045
Heart failure	3 (3.2)	10 (7.8)	0.246
Arrhythmia	3 (3.2)	8 (6.2)	0.364
Diabetes mellitus	9 (9.6)	24 (18.6)	0.085
Osteoporosis	16 (17.0)	11 (8.5)	0.063
Aspirin sensitivity	5 (5.3)	3 (2.3)	0.286
Depression	11 (11.7)	13 (10.1)	0.827
Medication			
ICS inhaler	7 (7.4)	2 (1.6)	0.039
ICS+LABA combination inhaler	87 (91.6)	87 (68)	<0.001
LAMA inhaler	27 (28.7)	93 (72.1)	<0.001
LABA inhaler	1 (1.1)	13 (10.1)	0.005
Triple therapy (LAMA+ICS+LABA)	26 (27.7)	62 (48.1)	0.002
Leukotriene receptor antagonist	55 (58.5)	17 (13.2)	<0.001
Oral theophylline	22 (23.4)	47 (36.4)	0.040
Oral steroid	8 (8.5)	10 (7.8)	0.489
Inhaler compliance >75%	83 (87.4)	114 (89.1)	0.833
Total systemic steroid/6 mo*	233.3±511.9	70.4±207.0	0.004

Values are presented as mean±SD or number (%) unless otherwise indicated.
*The amount of total systemic steroid used for the last 6 months is described as the equivalent dose of prednisolone.
COPD: chronic obstructive pulmonary disease; ACOS: asthma-COPD overlap syndrome; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; BDR: bronchodilator response; PEFR: peak expiratory flow rate; ACT: asthma control test; CAT: COPD Assessment Test; PHQ-9: Patient Health Questionnaire; ICS: inhaled corticosteroid; LABA: long acting β2 agonist; LAMA: long acting muscarinic antagonist.

Table 3. Demographic and baseline characteristics of the less-smoking and the more-smoking groups

	Less-smoking* (n=60)	More-smoking* (n=163)	p-value
Age, yr	64.6±11.8	67.0±8.4	0.141
Male sex	20 (33.3)	154 (94.5)	<0.001
Smoking status			
Pack-year	1.7±3.5	46.1±34.3	<0.001
Current/Ex-/Never smoker	7 (11.7)/9 (15.0)/44 (73.3)	65 (39.9)/98 (60.1)/0 (0)	<0.001
Age at symptom onset, yr	51.5±14.3	53.4±15.3	0.407
Duration of treatment, yr	6.9±5.5	8.0±7.2	0.233
Asthma diagnosis before age 40	11 (18.3)	29 (17.8)	1.000
Other allergic disease	21 (35.0)	33 (20.2)	0.033
Post-bronchodilator FEV_1, % predicted	62.0±12.5	58.7±14.0	0.103
Post-bronchodilator FEV_1/FVC, %	57.9±11.0	49.1±10.4	<0.001
Change in FEV_1, mL	327.9±194.3	376.6±203.6	0.127
Change in FEV_1, %	23.7±12.2	26.9±17.4	0.146
Patient reported outcome			
ACT score	20.0±4.4	18.3±6.0	0.026
CAT score	13.2±9.2	13.0±8.6	0.882
PHQ-9 score	3.9±5.2	3.5±4.4	0.610
Comorbidity			
Rhinosinusitis	10 (16.7)	13 (8.0)	0.080
Gastroesophageal reflux	8 (13.3)	20 (12.3)	0.822
Hypertension	20 (33.3)	66 (40.5)	0.356
Ischemic heart disease	4 (6.7)	19 (11.7)	0.331
Heart failure	1 (1.7)	12 (7.4)	0.193
Arrhythmia	4 (6.7)	7 (4.3)	0.492
Diabetes mellitus	5 (8.3)	28 (17.2)	0.136
Osteoporosis	17 (28.3)	10 (6.1)	<0.001
Aspirin sensitivity	4 (6.7)	4 (2.5)	0.216
Depression	7 (11.7)	17 (10.4)	0.809
Medication			
ICS inhaler	4 (6.7)	5 (3.1)	0.255
ICS+LABA combination inhaler	49 (81.7)	125 (76.7)	0.471
LAMA inhaler	18 (30.0)	102 (62.6)	<0.001
LABA inhaler	3 (5.0)	11 (6.7)	0.764
Triple therapy (LAMA+ICS+LABA)	12 (20.0)	76 (46.6)	<0.001
Leukotriene receptor antagonist	28 (46.7)	44 (27.0)	0.006
Oral theophyllin	14 (23.3)	55 (33.7)	0.145
Oral steroid	2 (3.3)	16 (9.8)	0.078
Inhaler compliance >75%	55 (91.7)	154 (94.5)	0.443
Total systemic steroid/6 mo†	241.3±582.0	101.6±254.3	0.077

Values are presented as mean±SD or number (%) unless otherwise indicated.
*The less-smoking group represents the patients group with a smoking history of less than 10 pack-years and the more-smoking group represents the patients group with a smoking history of equal or more than 10 pack-years. †The amount of total systemic steroid used for the last 6 months is described as the equivalent dose of prednisolone.
FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ACT: Asthma Control Test; CAT: COPD Assessment Test; PHQ-9: Patient Health Questionnaire; ICS: inhaled corticosteroid; LABA: long acting β2 agonist; LAMA: long acting muscarinic antagonist.

with asthma before 40 years of age did not differ significantly between the two phenotypes, nor did ACT, CAT, or PHQ-9 scores. Ischemic heart disease was more frequent in patients with the COPD predominant ACOS.

As expected, patients with the asthma predominant ACOS underwent more frequent treatment with inhaled corticosteroids (ICS) or a combination of ICS+long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA), while patients with the COPD predominant ACOS were more commonly treated with long-acting muscarinic antagonists (LAMA), inhaled LABA, oral theophylline, or triple inhaler therapy (LAMA+ICS+LABA).

The total amount of systemic steroids prescribed over the previous 6 months was much higher in the asthma predominant ACOS than in the COPD predominant ACOS (233.3±511.9 vs. 70.4±207.0 mg of an equivalent dose of prednisolone, respectively; p=0.004) (Table 2).

3. Comparisons of clinical characteristics between the light- and heavy-smoking groups

The heavy-smoking group was predominantly male and had a mean smoking history of 46 pack-years. The light-smoking group had more incidences of other allergic diseases and showed a higher post-bronchodilator FEV_1/FVC percentage and ACT score. Osteoporosis was more common in the light-smoking group.

Patients in the light-smoking group were more frequently treated with LTRA, while patients in the heavy-smoking group were more frequently treated with LAMA or triple inhaler therapy (LAMA+ICS+LABA) (Table 3).

Approximately three-quarters (73.3%) of the patients in the light-smoking group were categorized as the asthma predominant ACOS and 69.3% of those in the heavy-smoking group were categorized as the COPD predominant ACOS.

4. Comparison of exacerbation between the asthma and COPD predominant ACOS

During the previous year, 52.1% of patients with the asthma predominant ACOS and 70.5% of those with the COPD predominant ACOS had no unscheduled clinic visits, while 30.9% of the patients with the asthma predominant ACOS and 12.4% of those with the COPD predominant ACOS had more than two unscheduled clinic visits (p=0.002). Additionally, patients with the asthma predominant ACOS had approximately twice the number of unscheduled outpatient clinic visits, emergency room visits, and hospitalizations during the previous

Table 4. Exacerbation history of asthma phenotype and COPD phenotype groups

	Asthma predominant ACOS (n=94)	COPD predominant ACOS (n=129)	p-value
Exacerbations per patient			
Unscheduled clinic visit			0.002
None	49 (52.1)	91 (70.5)	
1	16 (17.0)	22 (17.1)	
≥2	29 (30.9)	16 (12.4)	
Emergency room visit			0.197
None	75 (79.8)	112 (86.8)	
≥1	19 (20.2)	17 (13.2)	
Hospital admission			0.189
None	76 (80.9)	113 (87.6)	
≥1	18 (19.1)	16 (12.4)	
ICU admission			0.652
None	91 (96.8)	127 (98.4)	
≥1	3 (3.2)	2 (1.6)	
Rate of exacerbation per year			
Unscheduled clinic visit	1.30±2.21	0.53±1.11	0.003
Emergency room visit	0.36±0.85	0.16±0.42	0.032
Hospitalization	0.29±0.68	0.13±0.36	0.046
ICU admission	0.04±0.25	0.02±0.12	0.337

Values are presented as number (%) or mean±SD.
COPD: chronic obstructive pulmonary disease; ACOS: asthma-COPD overlap syndrome; ICU: intensive care unit.

Table 5. Exacerbation history of the less-smoking and the more-smoking groups

	Less-smoking* (n=60)	More-smoking* (n=163)	p-value
Exacerbations per patient			
Unscheduled clinic visit			0.007
None	29 (48.3)	111 (68.1)	
1	11 (18.3)	27 (16.6)	
≥2	20 (33.3)	25 (15.3)	
Emergency room visit			0.412
None	48 (80.0)	139 (85.3)	
≥1	12 (20.0)	24 (14.7)	
Hospital admission			0.529
None	49 (81.7)	140 (85.9)	
≥1	11 (18.3)	23 (14.1)	
ICU admission			0.327
None	60 (100)	158 (96.9)	
≥1	0 (0)	5 (3.1)	
Rate of exacerbation per year			
Unscheduled clinic visit	1.37±1.91	0.67±1.58	0.013
Emergency room visit	0.38±0.92	0.19±0.50	0.128
Hospitalization	0.27±0.66	0.17±0.47	0.309
ICU admission	0.00±0.00	0.04±0.22	0.033

Values are presented as number (%) or mean±SD.
*The less-smoking group represents the patients group with a smoking history of less than 10 pack-years and the more-smoking group represents the patients group with a smoking history of equal or more than 10 pack-years.
ICU: intensive care unit.

Table 6. Association of clinical parameters with exacerbation (≥2 unscheduled outpatient clinic visits last year)

	Univariate		Multivariate	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	0.911 (0.948–1.015)	0.939		
Female sex	3.605 (1.773–7.332)	<0.001	2.423 (0.929–6.315)	0.070
Less-smoking group (smoking <10 pack-years)	2.760 (1.386–5.490)	0.003	1.029 (0.390–2.715)	0.954
Post-bronchodilator FEV_1, % predicted	0.972 (0.951–0.994)	0.158		
Poor inhaler adherence (<75%)	6.198 (2.029–18.930)	<0.001	4.321 (1.746–10.695)	0.002
ACOS phenotype (asthma phenotype)	3.151 (1.593–6.234)	0.001	2.433 (1.117–5.302)	0.025

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; ACOS: asthma-chronic obstructive pulmonary disease overlap syndrome.

year compared with the COPD predominant ACOS group, with only the rate of ICU admission having no statistical significance (Table 4).

5. Comparison of exacerbation between the light- and heavy-smoking groups

The proportion of patients with more than two unscheduled outpatient clinic visits, as well as the rate of unscheduled outpatient clinic visits during the previous year, was significantly higher in the light than heavy-smoking group. However, ICU admission was more common in the heavy-smoking group (Table 5).

6. Parameters associated with more than two unscheduled clinic visits during the last year

On univariate analysis, female sex, light smoking, a poor inhaler compliance of <75%, and a diagnosis of the asthma predominant ACOS were all significantly associated with exacerbation (i.e., more than two unscheduled clinic visits). However, only poor inhaler compliance and the asthma predominant ACOS were found to be significant on multivariate analysis. In particular, the risk of exacerbation for patients with the asthma predominant ACOS was 2.4 times higher than that for patients with the COPD predominant ACOS. The post-bronchodilator FEV_1 was not associated with exacerbation (Table 6).

Discussion

This study is meaningful to support the clinical heterogeneity of patients with ACOS with increased airflow variability and incompletely reversible airway obstruction on spirometry.

The clinical characteristics of physician-diagnosed asthma and COPD predominant ACOS among patients with ACOS differed: patients with the asthma predominant ACOS were younger, more likely to be female, more commonly had never smoked, had a smoking history of fewer pack-years, and had better lung function. More importantly, patients with the asthma predominant ACOS of ACOS experienced more exacerbations than did those with the COPD predominant ACOS.

Although some patients were clinically diagnosed with pure asthma or pure COPD rather than ACOS, they could be regarded as having asthma with fixed airflow limitation or COPD with airflow variability, respectively, and could therefore have a distinct clinical phenotype of asthma or COPD. We included these patients in the analysis because we were attempting to identify clinical heterogeneity among the group of patients who showed fixed airflow limitation with airflow variability.

Asthmatics who smoke frequently show fixed airway obstruction and have more severe symptoms of asthma[16,17], an accelerated decline in lung function[6,18], an increased risk of frequent exacerbations[19], and an increased risk of death[20].

In this study, phenotyping using smoking history proved less definitive than the physician's diagnosis. Interestingly, when patients with ACOS were divided according to smoking history, patients in the light-smoking group had more frequent unscheduled clinic visits despite having better lung function and higher ACT scores. The more frequent occurrence of exacerbation in the light-smoking group may be related to the larger number of patients with the asthma predominant ACOS in this group, because the light-smoking group was associated with frequent exacerbation only on univariate analysis and not on multivariate analysis. However, smoking history is easily obtainable from patients and would be a straightforward guide for choosing the initial treatment, particularly in primary-care clinics when physicians are confronted with complex cases of ACOS.

Exacerbation of asthma and COPD is associated with poor health status and accelerated lung-function decline[21-23], and patients with ACOS experience exacerbations more frequently than do those with either disease alone[11-13]. A major target in managing patients with obstructive airway disease is reduction of acute exacerbation. Therefore, it is important to know which patients with ACOS are susceptible to exacerbation.

In our patient population, other parameters related to frequent exacerbation in obstructive lung disease, such as poor lung function[24] and female sex[25-27], were not significantly associated with exacerbation. However, poor inhaler compliance was strongly related to frequent exacerbation, as in other studies[28,29]. In asthmatic patients in particular, inadequate use of ICS is the primary risk factor for frequent and fatal exacerbation[30,31]. However, in our study almost all patients with the asthma predominant ACOS used ICS, and inhaler compliance did not differ between the asthma and COPD predominant ACOS.

It is important to note that the asthma predominant ACOS, rather than the degree of airflow limitation, was related to frequent exacerbation. Airflow variability and symptom variability are the most important characteristics of asthma. Airway hyperresponsiveness in patients with COPD is also an independent predictor of exacerbation and mortality[32,33]. Symptom variability is also associated with increased frequency of COPD exacerbation[34]. Given the above, the variability of either airflow or symptoms may partly explain the high frequency of exacerbation in patients with ACOS.

This study has several limitations. First, we defined ACOS using only spirometry results. Although several criteria for the definition of ACOS exist, no definite ACOS criteria have been established, and most suggested criteria are relatively complex. In this situation, simplicity may offer the best solution. Second, we used the criteria of a positive bronchodilator response of >12% and a 200-mL improvement in FEV_1 after inhalation of a bronchodilator when we enrolled patients, although a higher positive bronchodilator response has been suggested by some recently published ACOS criteria[4,5]. However, due to the retrospective observational nature of this study, we could not control bronchodilator use during the bronchial reversibility test, and most of the hospitals used 200 g of salbutamol, a smaller dose than used in Western studies. Therefore, we considered that the criterion of an increase in FEV_1 would be sufficient to observe a bronchodilator response. Third, the criteria for diagnosis used by our physicians appeared to be arbitrary. However, considering that each patient had been treated by their physician for several years, the physicians' diagnosis based on the weight of evidence that the physicians encountered in each patient was likely relatively accurate. In

the situation where neither biomarkers nor spirometry has any value in distinguishing between asthma and COPD predominant ACOS, the physician's diagnosis would be important. In addition, a physician's diagnosis is a widely accepted diagnostic criterion in clinical studies of ACOS or asthma. It is also important to note that only one of 223 patients was diagnosed with asthma=COPD ACOS. Lastly, we could not evaluate the relationship between the two phenotypes and blood eosinophil counts. In a recent study, phenotypes of ACOS, classified according to blood eosinophil counts and smoking history of the patients, showed difference in the proportion of patients free of severe exacerbation[35]. It could be confounding bias.

In conclusion, we found that patients who met the spirometric ACOS criteria could be divided into two clinically distinct groups: those with the asthma predominant ACOS and those with the COPD predominant ACOS. The most striking result was that the asthma predominant ACOS group showed more frequent exacerbation despite their history of light smoking and better lung function. Smoking history could, therefore, be another diagnostic criterion when differentiation between the asthma and COPD predominant ACOS proves difficult. Future studies are needed to further our understanding of the heterogeneity of ACOS and to establish an appropriate therapeutic intervention.

Authors' Contributions

Conceptualization: Park J, Lee JH. Methodology: Park J, Kim EK, Kim MA, Lee JH. Formal analysis: Park J, Lee JH. Data curation: all authors. Investigation: all authors. Writing - original draft preparation: Park J, Lee JH. Writing - review and editing: Park J, Lee JH. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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