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Characteristics of Specialist-Diagnosed Asthma-COPD Overlap in Severe Asthma: Observations from the Korean Severe Asthma Registry (KoSAR)

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Abbreviations: ACO, Asthma-COPD overlap; BMI, body mass index COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in 1 second; FVC, Forced expiratory volume ; GINA, Global Initiative for Asthma; KAAACI, The Korean Academy of Asthma, Allergy, and Clinical Immunology; KoSAR, The Korean Severe Asthma Registry; SWAG, The Working group on Severe Asthma.

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Abstract

Background: While the clinical characteristics and outcomes of asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) have been frequently compared with those of COPD or asthma, the prevalence and features of ACO in patients with severe asthma are unclear.

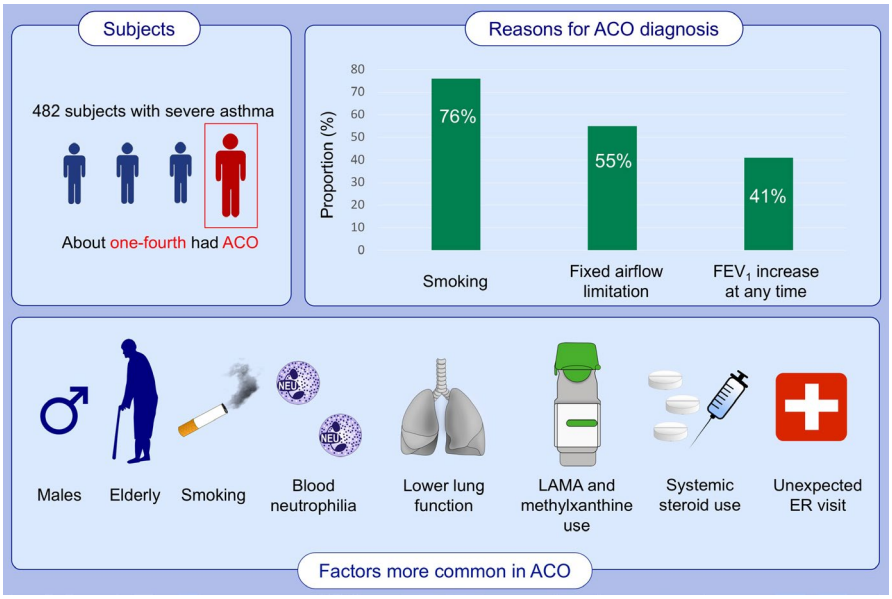
Objectives: Evaluation of the prevalence and clinical features of ACO using the Korean severe asthma registry.

Methods: At the time of registration, ACO was determined in patients with severe asthma by attending specialists. Patients were classified into ACO and non-ACO groups, and the demographic and clinical characteristics of these two groups were compared.

Results: Of 482 patients with severe asthma, 23.7% had ACO. Patients in the ACO group were more likely to be male ($P < .001$), older ($P < .001$), and ex- or current smokers ($P < .001$) compared with those in the non-ACO group. Patients in the ACO group had lower mean forced expiratory volume in 1 second ($P < .001$) and blood eosinophil percentage ($P = .006$), but higher blood neutrophil percentage ($P = .027$) than those in the non-ACO group. The ACO group used more inhaled long-acting muscarinic antagonist ($P < .001$), methylxanthine ($P = .001$), or sustained systemic corticosteroid ($P = .002$). In addition, unscheduled emergency department visits due to exacerbation were more frequent in the ACO group ($P = .006$).

Conclusion: Among patients with severe asthma, those with ACO were older, predominantly male, and were more likely to have a smoking history than those with asthma only. Patients with ACO used more systemic corticosteroid and had more frequent exacerbations related to emergency department visits than those with severe asthma only.

KEYWORDS
asthma-COPD overlap, registry, severe asthma



GRAPHICAL ABSTRACT

We found that about one-fourth of patients with severe asthma was diagnosed with ACO by specialists. The most common reason for ACO diagnosis was smoking history. ACO patients were predominantly male, older, and had more smoking history compared with non-ACO patients. ACO patients had higher blood neutrophil count, but lower lung function. ACO patients used more LAMA, methylxanthine, and systemic corticosteroid and had more frequent exacerbations related to ER visits compared with those with severe asthma only.
Abbreviations: ACO, asthma-COPD overlap; ER, emergency room; FEV1, forced expiratory volume in one second

1 | INTRODUCTION

Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is a condition in which the clinical features of asthma and COPD coexist.[1] Despite considerable effort to define ACO, there is currently no consensus on the definite diagnostic criteria. Despite this limitation, numerous studies have shown that the prevalence of ACO is substantial, occurring in 3% to 51% of patients with asthma.[2] It is also well recognized that ACO patients are more symptomatic, have more frequent exacerbations, more severely reduced quality of life, higher mortality, and increased health care use than patients with asthma only.[3-6]

Severe asthma is defined as that requiring a high dose of inhaled corticosteroid (ICS) to maintain asthma control or that remains uncontrolled despite this therapy.[7] The reported prevalence of severe asthma is about 5%-10%[7-9]; however, the disease burden associated with severe asthma is substantial, with the consumption of more healthcare resources than non-severe asthma patients.[10-13] In addition, compared with patients with milder asthma, those with severe asthma have worse symptoms with frequent exacerbation, lower quality of life, and airflow limitations, which are also characteristic of ACO patients.[14] Thus, the main challenge in real-world practice is to distinguish patients with ACO from those with severe asthma only. However, there have been few studies that have revealed the clinical characteristics of ACO in the context of severe asthma. Accordingly, there is not enough evidence to identify a method to differentiate ACO from severe asthma in real-world clinics.

The Korean Severe Asthma Registry (KoSAR) of the Korean Academy of Asthma, Allergy, and Clinical Immunology (KAAACI), the Working Group on Severe Asthma (SAWG) is a prospective multicenter observational study for adult severe refractory asthma from 15 institutions in Korea.[15] At the time of registration, the presence of ACO and the reasons for the diagnosis of ACO were determined by attending specialists. Thus, we aimed to investigate the prevalence, clinical characteristics, quality of life, and exacerbations between patients with ACO and those with severe asthma using the KoSAR Registry. We also evaluated the factors used by specialists to recognize ACO.

2 | MATERIALS AND METHODS

2.1 | Study design

The Korean SAWG was established in 2009 by the members of the KAAACI to evaluate severe asthma to develop a better treatment strategy for severe asthma. We have been running KoSAR (https://severeasthmawg.com), an ongoing prospective multicenter observational study for adult severe refractory asthma, from 2010. The objectives of KoSAR are 1) to define clinical characteristics and phenotypes of severe asthma in Korea in multicenter, prospective observational study design, 2) to estimate the burden of severe asthma and estimate treatment status of severe asthma in Korea, and 3) to develop a better strategy for management of severe asthma.

A total of 482 patients with severe asthma enrolled between January 2010 and December 2016 were included in this study. The inclusion criteria were patients with severe asthma, which is defined as follows. 1) Patients who are treated by asthma specialists under regular follow-up for at least one year or who could not consistently achieve a well-controlled status after Global Initiative for Asthma (GINA) treatment step 4 or 5; 2) patients who achieved a well-controlled status after GINA treatment step 4 or 5 but had visited an emergency room more than once a year, received steroid burst treatment more than three times per year, experienced worsening of asthma on tapering of oral CS or ICS, or experienced a near-fatal asthma attack anytime in the past.[15] The exclusion criteria were patients with a primary diagnosis of bronchiectasis, those with pulmonary diseases such as tuberculosis-destroyed lung disease, active infectious pulmonary disease (eg, active pulmonary tuberculosis), or interstitial lung disease, those with severe congestive heart failure, or those with a severe psychotic disorder. The detailed study protocol was described in our previous report.[15]

2.2 | Definition

At the time of registration, patients with severe asthma were determined to be ACO or not by attending specialists. Using questionnaires, we collected data regarding the reasons for diagnosis of ACO based on the following: 1) history of smoking, 2) presence of fixed airflow limitation, or 3) presence of an at least 12% and 200 mL increase in forced expiratory volume in 1 second (FEV_1) at any time (bronchodilator response or after CS treatment; hereafter, FEV_1 increase at any time) in patients with airflow limitation. Body mass index (BMI) was categorized as follows: 1) obesity as BMI ≥25 kg/m^2, 2) overweight as BMI ≥23 kg/m^2 and < 25 kg/m^2, 3) normal as BMI ≥18.5 kg/m^2 and <23 kg/m^2, and 4) underweight as BMI <18.5 kg/m^2.[16] As there are no severity criteria for ACO, ACO patients included in this study have been categorized as severe according to asthma criteria solely. Atopy was determined based on the results of skin prick test to common aeroallergens, which include house dust mite, pollen, ragweed, mugwort, hop, birch, cockroach, fungi such as Alternaria and Aspergillus, and animal dander such as cat and dog. The tests were regarded as positive when the wheel diameter was 3 mm or larger. Sustained systemic CS use was defined as systemic CS use once daily or every other day in the previous 6 months.

2.3 | Aim of this study

The primary objective of this study was to evaluate the clinical characteristics of patients with ACO using the severe asthma registry. The secondary outcomes of this study were to evaluate the prevalence of ACO and reasons for the diagnosis of ACO by asthma specialists among patients with severe asthma.

TABLE 1 Demographic and clinical characteristics in patients with severe asthma according to the presence or absence of ACO

	Non-ACO group (n = 368)	ACO group (n = 114)	*P* value
Age, years	60.2 ± 14.3	69.0 ± 10.6	<.001
Male, n (%)	125 (34.0)	95 (83.3)	<.001
BMI, kg/m^2 (n = 476)*	24.0 ± 3.8	23.9 ± 3.4	.716
Underweight	22 (6.0)	7 (6.3)	.656
Normal	128 (35.1)	41 (36.9)	
Overweight	81 (22.2)	29 (26.1)	
Obesity	134 (36.7)	34 (30.6)	
Smoking history (n = 476)			<.001
Never	239 (66.0)	17 (14.9)	
Ex-smoker	83 (22.9)	78 (68.4)	
Current smoker	40 (11.1)	19 (16.7)	
Asthma history			
Age at symptom onset, years (n = 455)	39.5 ± 16.9	45.4 ± 17.2	.001
Age at asthma diagnosis, years (n = 452)	43.3 ± 16.1	50.1 ± 15.2	<.001
Age at treatment initiation (n = 426)	44.6 ± 15.5	52.1 ± 15.4	<.001
Duration of treatment (n = 340)	10.3 ± 8.7	11.2 ± 12.3	.467
Comorbidities			
Allergic rhinitis (n = 459)	224 (63.8)	45 (41.7)	<.001
Allergic conjunctivitis (n = 476)	26 (7.2)	5 (4.4)	.291
Atopic dermatitis (n = 474)	32 (8.9)	7 (6.1)	.352
Aspirin intolerant asthma (n = 448)	58 (17.1)	4 (3.7)	<.001
Chronic sinusitis (n = 478)	98 (26.8)	18 (16.1)	.021
History of pulmonary tuberculosis (n = 473)	10 (2.8)	11 (9.8)	.002
History of pneumonia (n = 470)	33 (9.2)	11 (9.9)	.821
Sleep apnea (n = 474)	6 (1.7)	2 (1.8)	>.999
Gastroesophageal reflux (n = 474)	46 (12.7)	15 (13.4)	.850
Hypertension (n = 476)	102 (28.2)	45 (39.5)	.023
Heart failure (n = 473)	4 (1.1)	4 (3.5)	.097
Arrhythmia (n = 473)	5 (1.4)	1 (0.9)	.676
Osteoporosis (n = 474)	29 (8.0)	15 (13.3)	.094
Anxiety disorder (n = 474)	7 (1.9)	1 (0.9)	.686
Depression (n = 477)	16 (4.4)	2 (1.8)	.265

Note: Continuous values are presented as mean ± SD, and categorical variables are presented as number (%).

Abbreviations: ACO, asthma-chronic obstructive pulmonary disease overlap; BMI, body mass index.

*BMI was categorized as follows: 1) obesity as BMI ≥ 25 kg/m^2, 2) overweight as BMI ≥ 23 kg/m^2 and < 25 kg/m^2, 3) normal as BMI ≥ 18.5 kg/m^2 and < 23 kg/m^2, and 4) underweight as BMI < 18.5 kg/m^2.

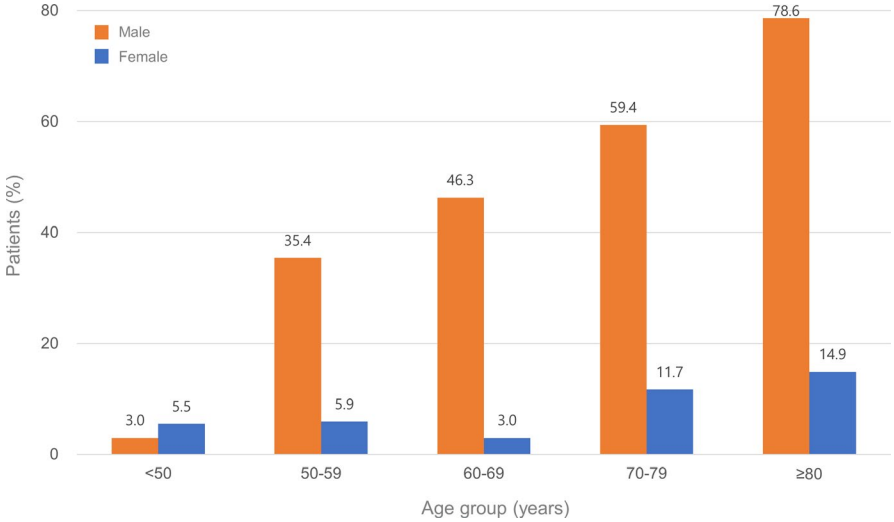


FIGURE 1 The proportion of ACO by age group and sex. Abbreviation: ACO, asthma-chronic obstructive pulmonary disease overlap.

2.4 | Statistical analyses

Continuous data with normal distribution are presented as mean with standard deviation (SD), and those with non-normal distribution are presented as median with interquartile range (IQR). The former was compared using the t test, and the latter were compared using Mann-Whitney U tests. Categorical data are presented as number (%) and compared using Pearson's chi-square test or Fisher's exact test, as appropriate. A two-sided $P < .05$ was considered to show statistical significance in this study. All analyses were performed using SPSS version 24.0 (IBM Corp.) and STATA version 15.0 (Stata Corporation).

3 | RESULTS

3.1 | Patients

Of 482 patients with severe asthma, there were 368 (76.3%) in the non-ACO group and 114 (23.7%) in the ACO group (Table 1). Compared with the non-ACO group, the ACO group were more likely to be older (69.0 ± 10.6 years vs. 60.2 ± 14.3 years, $P < .001$) and male (83.3% vs. 33.7%, $P < .001$) (Figure 1). The proportion of ACO was different by smoking history (Figure S1). The prevalence of ACO was 6.6% (17/256) in never-smokers and 44.1% (97/220) among current or ex-smokers. The ACO group had a higher proportion of ex- or current smokers (85.1% vs. 34.0%, $P < .001$) than the non-ACO group. Age of symptom onset (45.4 ± 17.2 years vs. 39.5 ± 16.9 years, $P = .001$), asthma diagnosis (50.1 ± 15.2 years vs. 43.3 ± 16.1 years, $P < .001$), and treatment initiation (52.1 ± 15.4 years vs. 44.6 ± 15.5 years, $P < .001$) were higher in the ACO group than in the non-ACO group.

As shown in Table 1, there were no differences in the proportion of most comorbidities between the two groups. However, allergic rhinitis ($P < .001$), chronic sinusitis ($P = .021$), and aspirin intolerant asthma ($P < .001$) were more common in the non-ACO group than in the ACO group. In contrast, the proportion of hypertension ($P = .023$) was higher in patients of the ACO group than those of the non-ACO group.

3.2 | Reasons for diagnosis of ACO

Figure 2 shows the conditions for the determination of ACO by attending specialists. Of the 100 patients who received a diagnosis of ACO, 76, 55, and 41 were diagnosed based on smoking history, fixed airflow limitation, and FEV_1 increase at any time in the presence of airflow limitation, respectively. Thirty-three patients had both smoking history and FEV_1 increase at any time, 37 had both fixed airflow limitation and smoking history, and 20 had both fixed airflow limitation and FEV_1 increase at any time. All three criteria were shown in 18 patients.

3.3 | Pulmonary function and laboratory findings

As shown in Table 2, the ACO group had lower mean FVC, L ($P < .001$), FVC, %predicted ($P < .001$), FEV_1, L ($P < .001$), FEV_1, %predicted ($P < .001$), and FEV_1/FVC ($P < .001$) than the non-ACO group.

Regarding laboratory findings, the ACO group had a higher neutrophil percentage ($P = .027$) and lower blood eosinophil percentage ($P = .006$) and lower blood eosinophil count ($P = .016$) than the non-ACO group. However, there were no differences in the proportion of patients with blood eosinophil ≥300, total immunoglobulin E level, sputum cell counts, and fractional exhaled nitric oxide level between the two groups.

3.4 | Medications

As shown in Figure 3, there were no differences in use of ICS/long-acting β_2 agonist (95.7% vs. 95.6%, $P > .999$), leukotriene receptor antagonist (71.4% vs. 75.7%, $P = .377$), and omalizumab (2.0% vs. 1.8%, $P > .999$) as controlling treatment between the two groups. However, long-acting muscarinic antagonist (64.5%

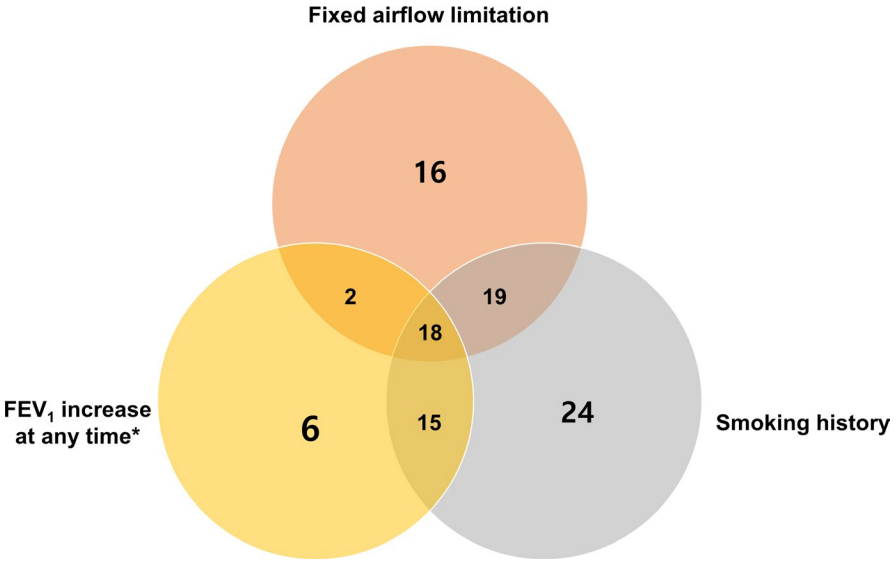


FIGURE 2 Reasons for diagnosis of ACO by specialists. Abbreviations: ACO, asthma-chronic obstructive pulmonary disease overlap. FEV_1, forcxed expiratory volume in 1 second. *indicates the presence of at least 12% and 200 mL increase in the FEV_1 at any time (bronchodilator response or after corticosteroid treatment) in patients with airflow limitation.

TABLE 2 Lung function and laboratory findings

	Non-ACO group (n = 367)	ACO group (n = 114)	*P*-value
Mean values of pulmonary function in the previous year			
FVC, L (n = 453)	2.6 ± 0.8	2.4 ± 0.8	<.001
FVC, %predicted (n = 449)	80.8 ± 13.3	70.4 ± 18.5	<.001
FEV1, L (n = 456)	1.9 ± 0.7	1.4 ± 0.6	<.001
FEV1, %predicted (n = 450)	72.2 ± 12.3	54.3 ± 16.6	<.001
FEV1/FVC (n = 451)	70.7 ± 13.6	61.0 ± 13.0	<.001
Laboratory findings			
WBC (n = 426)	8,920 ± 6,723	9,145 ± 2,885	.745
Neutrophil (%) (n = 336)	59.3 ± 13.5	63.2 ± 14.3	.027
Blood eosinophil (%) (n = 423)*	3.4 (1.5-7.1)	2.1 (0.8-5.9)	.006
Blood eosinophil (/μL) (n = 423)*	258 (112-543)	183 (76-383)	.016
Blood eosinophil ≥ 300/μL (n = 422)	141 (43.7)	33 (33.3)	.080
Total IgE (IU/mL) (n = 246)*	181.0 (72.0-525.0)	189.5 (39.0-386.0)	.360
Positive skin prick test (n = 270)	85 (38.5)	19 (38.8)	.967
Sputum cell counts at the stable status			
Macrophage (n = 118)*	15.1 (5.0-50.1)	24.2 (4.0-67.7)	.286
Neutrophil (n = 132)*	64.2 (25.5-88.0)	36.5 (19.2-70.5)	.089
Lymphocyte (n = 71)*	2.0 (0-5.0)	2.0 (1.0-3.0)	.718
Eosinophil (n = 119)*	6.0 (1.0-37.3)	5.6 (1.0-14.3)	.729
FENO (ppb) (n = 78)*	40.0 (24.0-60.0)	32.0 (14.0-45.0)	.315

Note: Values are presented as number (%) and mean ± SD or median with interquartile range.
Abbreviations: ACO, asthma-chronic obstructive pulmonary disease overlap; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; FENO, fractional exhaled nitric oxide.
*Mann-Whitney U test.

vs. 22.2%, $P < .001$) and methylxanthine (73.0% vs. 54.6%, $P = .001$) were more frequently used in the ACO group than in the non-ACO group. Regarding systemic CS use in the previous 6 months, the proportion of patients who used sustained systemic CS was more frequent in patients of the ACO group (29.8% vs. 16.3%, $P = .001$) than in those of the non-ACO group. The total mean dose of annual oral CS (prednisolone equivalent dose) per patient was also higher in patients of the ACO group

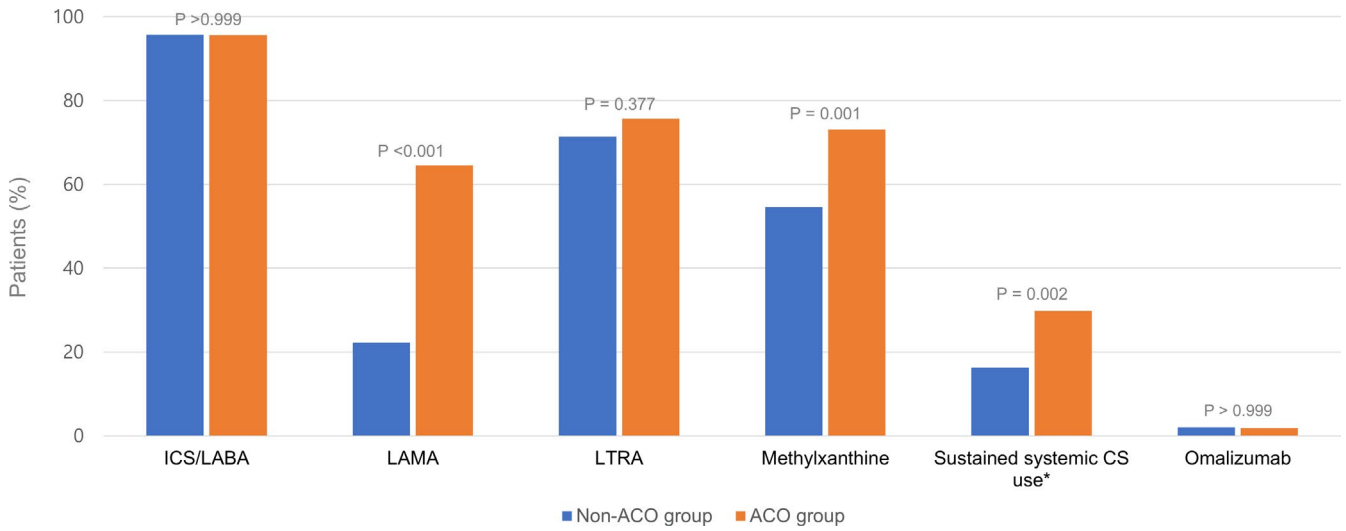


FIGURE 3 Use of asthma-related medications. Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; CS, corticosteroid. Sustained systemic CS use was defined as systemic CS use once daily or every other day in the previous 6 months.

than in those of the non-ACO group (1153.9 ± 1326.6 mg vs. 693.9 ± 1254.2 mg, $P < .001$).

3.5 | Quality of life

Regarding the quality of life, there was no difference in the quality of life questionnaire in adult Korean asthmatics[17] between the patients of the ACO group and non-ACO group (62.0 [IQR, 46.0-73.0] vs 62.0 [IQR, 52.0-70.0], $P = .987$) (Figure 4).

3.6 | Acute exacerbation

Table 3 shows that the proportion of patients who received steroid burst treatment for at least three days was higher in patients of the ACO group than in those of the non-ACO group (52.7% vs. 38.2%, $P = .012$). The number of steroid bursts of five or more times was significantly more frequent in ACO patients than in asthma patients (22.6% vs. 11.5%, $P = .005$). Whereas the presence of unscheduled visits to the outpatient department ($P = .148$), hospitalization ($P = .134$), and intensive care unit admission ($P = .139$) in the previous year were not different between the groups, the presence of an unscheduled emergency department visit ($P = .006$) was more common in ACO patients than in asthma patients. However, the number of unscheduled visits per patient to the outpatient department or emergency department or hospitalization was not different between the two groups.

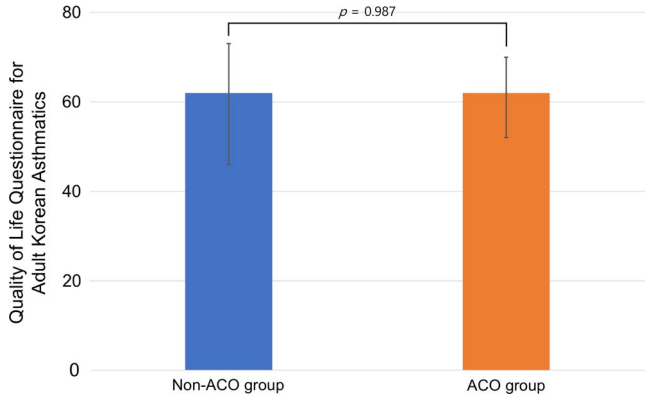


FIGURE 4 Quality of life. Abbreviation: ACO, asthma-chronic obstructive pulmonary disease overlap.

4 | DISCUSSION

In our study, about one-fourth of severe asthma patients had ACO. The rate of ACO was significantly different by smoking history, about 7% in never-smokers, and 45% in current or ex-smokers. Accordingly, smoking history was the most common reason for a specialist's diagnosis of ACO. ACO patients are older, predominantly male, and had more smoking history; however, the onset of asthma-related symptoms and age at the time of asthma diagnosis and treatment was later than non-ACO patients. Allergic rhinitis, chronic sinusitis, allergic conjunctivitis, and aspirin intolerant asthma were more frequent in the non-ACO group compared with the ACO group. Compared with non-ACO patients, ACO patients had lower lung function and blood eosinophil counts, but higher blood neutrophil counts. ACO patients received more sustained systemic CS, long-acting muscarinic antagonist, and methylxanthine than non-ACO patients. Regarding exacerbations, ACO patients received more frequent steroid burst treatment and performed more unscheduled emergency department visits than non-ACO patients.

ACO is defined as persistent airflow limitation with several features associated with asthma and several features associated with

TABLE 3 Exacerbations in the previous year

	Non-ACO group (n = 362)	ACO group (n = 112)	*P*-value
Steroid burst treatment for at least 3 days (n = 423)	126 (38.2)	49 (52.7)	.012
Number of steroid bursts over at least 3 days (n = 423)			.005
0	204 (61.8)	44 (47.3)	
1	31 (9.4)	12 (12.9)	
2	23 (7.0)	4 (4.3)	
3-4	34 (10.3)	12 (12.9)	
≥5	38 (11.5)	21 (22.6)	
Presence of unscheduled visit in the previous year			
Outpatient department visit (n = 474)	59 (16.3)	12 (10.7)	.148
Emergency department visit (n = 472)	38 (10.6)	23 (20.5)	.006
Hospitalization (n = 471)	60 (16.8)	26 (23.0)	.134
Intensive care unit admission (n = 469)	1 (0.3)	2 (1.8)	.139

Note: Values are presented as number (%).

Abbreviation: ACO, asthma-chronic obstructive pulmonary disease overlap.

COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA).[1] As this approach does not indicate the number of elements necessary to define ACO, it is imprecise. Accordingly, the diagnosis of ACO is usually made at the discretion of attending physicians, resulting in uncertainty in the features used in the diagnosis of ACO in real-world clinics. Our study, for the first time, revealed the proportion of ACO among severe asthma patients and provided the reasons for the diagnosis of ACO in the real-world clinic.

According to a questionnaire survey of specialists in asthma and airway diseases, the estimated proportion of ACO by specialists was 38% among severe asthma patients, and specialists responded that smoking history, persistently low FEV_1, and low FEV_1 variation are major components for diagnosis of ACO among asthma patients.[18] In agreement with the survey results, approximately 24% of patients with severe asthma were diagnosed with ACO by specialists based on smoking history, persistent airflow limitation, and significant increase of FEV_1 at any time during follow-up. An observational study in Sweden also revealed that COPD was present in 22% of severe asthma patients.[9] The clinical characteristics of specialist-diagnosed ACO in this study are also in keeping with the previous studies. Several studies have revealed that patients with ACO are older and have male predominance, smoking history, lower pulmonary function, poor quality of life, and more exacerbations.[3-6] However, there has been a lack of data that comprehensively compare clinical characteristics, quality of life, and exacerbations at baseline. Considering that it is complicated to distinguish ACO from severe asthma since the two diseases have similar features, data regarding this issue are essential. From this perspective, our study presents valuable information on prevalence, baseline demographics, the predominance of eosinophilic or neutrophilic inflammation, lung function, and exacerbations in patients with ACO in the severe asthma registry. These real-world data will be very informative to clinicians who manage chronic obstructive airway diseases.

Interestingly, according to ACO diagnosis by specialists, there were several differences in clinical characteristics and laboratory findings. Whereas non-ACO patients had more comorbidities, including allergic rhinitis, chronic sinusitis, allergic conjunctivitis, and aspirin intolerant asthma than non-ACO patients, previous tuberculosis was more common in ACO patients than in non-ACO patients. However, there was no intergroup difference in obesity. This finding is interesting because we would expect severe asthma patients to have a higher prevalence of obesity. Further studies using other registries are needed to determine the relationship between BMI and ACO among severe asthma patients. In this study, sputum neutrophil counts tended to be higher (not statistically significant) in non-ACO patients than ACO patients. In contrast to our findings, previous studies with a small number of patients showed that sputum neutrophils are higher in ACO patients than asthma patients.[19,20] However, the number of patients who measured sputum cell counts is relatively small in our study, and there have been no well-designed studies that compared sputum cell counts in patients with severe asthma and ACO. Thus, further studies are needed for this issue.

In this study, ACO patients used more medications, including long-acting muscarinic antagonist, methylxanthine, and systemic CS than non-ACO patients. The focus of the medication burden is the chronic use of systemic corticosteroid because it is associated with severe complications[12,21-25] and increased mortality.[26] Interestingly, despite a substantial burden of chronic systemic CS use and exacerbations related to emergency department visits, the use of biologic agents was very low, probably due to their high cost, which is not covered by Korean insurance. Evidence indicates that patients with ACO might benefit from the use of biologic agents and enable them

to use a minimum dose of systemic CS.[27-29] Biologic agents could also be useful in reducing the frequency of exacerbations in ACO patients.

The major strength of our study is that our severe asthma registry is a multicenter observational cohort study of severe asthma patients, which might represent our national data. However, there are also several limitations to our study. First, this study was performed in one country. As there is no consensus for the diagnosis of ACO in severe asthma patients, there is likely global heterogeneity in this issue.[30] Thus, the findings of our study should be interpreted cautiously. Regarding the criteria used by specialists to define ACO, smoking history, especially alone, can exist in smoking asthmatic, without necessarily involving COPD (a smoking patient with positive bronchodilator response and without fixed airflow obstruction). On the other hand, fixed airflow obstruction may be seen in pure asthma in asthmatics with fixed airflow obstruction. Also, the presence of at least 12% and 200 mL increase may be present in patients with COPD alone or bronchiectasis. So all three criteria—especially when used alone—and not all three together are not safe enough to define ACO, especially in the context of severe asthma. However, despite these limitations, we suggest that providing information on how specialists determine ACO is important to recognize real-world clinical practice for the diagnosis of ACO in the context of severe asthma. Second, all patients were enrolled from the specialists' centers. Therefore, the patients may have had more severe disease, conferring a selection bias. Third, due to the observational design reflecting real-world clinical practice, laboratory tests, such as total immunoglobulin E, blood, or sputum eosinophil counts, were not performed in all patients. There were also some missing values for comorbidities. Fourth, regarding comorbidity profiles were substantial differences in our study results compared with previous findings. For example, the prevalences of some comorbidities such as gastroesophageal reflux,[31-33] chronic sinusitis,[31-33] and history of pneumonia[9,32] in this study were substantially lower compared with those in other studies. Also, the mean BMI was lower in Korean patients than those reported in the previous studies.[9,31-33] However, the proportion of obese patients (about 35% calculated using obesity definition for Asians [BMI >25 kg/m^2]) in this study was similar to previous findings (most are Western patients) ranging from about 26% to 46%.[31-33] The reasons why the prevalences of these comorbidities are different between Korean severe asthma patients and Western severe asthma patients are not well known. However, as shown in COPD and bronchiectasis, racial and ethnic differences might have a role.[34,35] Accordingly, it should be emphasized that comorbidity profiles of ACO patients in severe asthma registry in other counties (especially in Western countries) might be different from our findings.

To conclude, the prevalence of ACO in the severe asthma registry was 23.7%. Patients with ACO determined by specialists were more likely to be older, predominantly male, and current or ex-smokers than those with severe asthma only. Patients with ACO used more medication, including systemic CS, and had more frequent exacerbations related to emergency department visits. Treatment strategies are urgently needed to reduce systemic CS use and exacerbations in this patient group.

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CONFLICT OF INTEREST

None to disclose.

AUTHOR CONTRIBUTIONS

H. Lee, S-H. Kim, HJ. Yoon involved in study design. H. Lee, S-H. Kim involved in data analysis. H. Lee, S-H. Kim, HJ. Yoon involved in writing the manuscript. All authors involved in data collection and reviewing and revising the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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