



Perceptions of Severe Asthma and Asthma-COPD Overlap Syndrome Among Specialists: A Questionnaire Survey

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Purpose: Severe asthma and asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) are difficult to control and are often associated with poor clinical outcomes. However, much is not understood regarding the diagnosis and treatment of severe asthma and ACOS. To evaluate the current perceptions of severe asthma and COPD among asthma and COPD specialists, we designed an e-mail and internet-based questionnaire survey. **Methods:** Subjects were selected based on clinical specialty from among the members of the Korean Academy of Asthma, Allergy and Clinical Immunology and the Korean Academy of Tuberculosis and Respiratory Diseases. Of 432 subjects who received an e-mail invitation to the survey, 95 subjects, including 58 allergists and 37 pulmonologists, responded and submitted their answers online. **Results:** The specialists estimated that the percentage of severe cases among total asthma patients in their practice was $13.9\% \pm 11.0\%$. Asthma aggravation by stepping down treatment was the most common subtype, followed by frequent exacerbation, uncontrolled asthma despite higher treatment steps, and serious exacerbation. ACOS was estimated to account for 20.7% of asthma, 38.0% of severe asthma, and 30.1% of COPD cases. A history of smoking, persistently low forced expiratory volume in 1 second (FEV1), and low FEV1 variation were most frequently classified as the major criteria for the diagnosis of ACOS among asthma patients. Among COPD patients, the highly selected major criteria for ACOS were high FEV1 variation, positive bronchodilator response, a personal history of allergies and positive airway hyperresponsiveness. Allergists and pulmonologists showed different assessments and opinions on asthma phenotyping, percentage, and diagnostic criteria for ACOS. **Conclusions:** Specialists had diverse perceptions and clinical practices regarding severe asthma and ACOS patients. This heterogeneity must be considered in future studies and strategy development for severe asthma and ACOS.

Key Words: Severe asthma; asthma-chronic obstructive pulmonary disease overlap syndrome; perception

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INTRODUCTION

Some patients with asthma fail to achieve acceptable control of their symptoms despite active treatment and modification of comorbidities. Severe asthma is often defined as asthma requiring a high level of treatment to prevent it from becoming or remaining uncontrolled.^{1,2} Poor control of severe asthma is associated with frequent exacerbation, high medical costs, and mortality.^{3,4} Even with vigorous research to understand severe asthma, neither an effective nor a comprehensive strategy has been determined to diagnose and treat severe asthma in clinical practice.

Some patients with asthma or chronic obstructive pulmonary disease (COPD) show features of both diseases, which are often determined to be asthma-COPD overlap syndrome (ACOS).⁵ Many patients with previously diagnosed asthma or COPD alone are now recognized to have ACOS, particularly elderly patients.⁶ Furthermore, ACOS has been found to have worse health outcomes than asthma or COPD alone in terms of comorbidities, exacerbation frequencies, lung function decline, medication costs, and mortality.⁷⁻¹⁰ Like severe asthma, ACOS is hard to manage due to the lack of sound evidence for proper management. To date, prospective randomized controlled trials have not determined uniform diagnostic criteria¹¹ or an effective therapeutic strategy for ACOS.¹²

Despite increased interest and research, there is a grey zone in clinical practices concerning severe asthma and ACOS that has not been well addressed in the guidelines of the Global Initiative for Asthma (GINA)¹³ or the Global Initiative for Chronic Obstructive Lung Disease (GOLD).¹⁴ While a majority of the patients with severe asthma or ACOS are frequently referred to specialists, even the specialists' practices for those patients have not been standardized. The purpose of this study was to investigate the current perceptions and practices of severe asthma and ACOS among asthma and COPD specialists. Using a questionnaire, we asked specialists how they diagnose and treat patients with severe asthma or ACOS.

MATERIALS AND METHODS

Subjects

We conducted a questionnaire survey of specialists in asthma and airway diseases from among the members of the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI) of the Korean Board of Internal Medicine, and members of the Study Group for Asthma, the Study Group for COPD, and the Study Group for Smoking Cessation of the Korean Academy of Tuberculosis and Respiratory Diseases (KATRD) using e-mail and a web-based questionnaire. The e-mail for the questionnaire survey was sent to 432 study subjects whose e-mail addresses were confirmed to be valid.

Questionnaire

The questionnaire on severe asthma and ACOS was developed by the Severe Asthma Work Group (SAWG) of the KAAACI. The draft questionnaire for the survey was written and reviewed by all members of the SAWG. A pilot study was performed to test the questionnaire and included 15 members of the SAWG. Based on the feedback, the questionnaire was modified to provide more objective results. In the final questionnaire, written in the Korean language, the subjects were asked to include their age, gender, specialty, and primary field of clinical practice. The survey was comprised of three domains: 1) the diagnosis of severe asthma, 2) the treatment of severe asthma, and 3) the perception and diagnostic criteria for ACOS. To summarize the understanding and perceptions of the respondents, the subjects were instructed to answer the questions based on personal experiences with severe asthma and ACOS in clinical practice, not on the published literature or general consensus. Various types of questions were used, including dichotomous, rating scale, multiple choice, and open-ended questions. Questions were developed to assess the clinical characteristics or subtypes of patients with severe asthma in each subject's practice. In addition, the subjects were requested to provide the percentages (%) of patients with severe asthma among patients with asthma in their practices. We also assessed the diagnostic tests usually performed to phenotype severe asthma in clinical practice. Next, in the treatment of severe asthma, we asked the subjects to provide the percentage of patients who used each controller for asthma, as an open-ended question. For the questions on ACOS, we asked the subjects what percentage of all patients with asthma had ACOS. The same questions were also asked to assess the percentage of ACOS patients among all patients with severe asthma and COPD, respectively. We also asked the subjects to classify each clinical feature as major, minor, or no criteria for ACOS. We assessed the diagnostic criteria of ACOS among patients with COPD using similar questions. The complete survey is provided in Supplementary date 1.

E-mail and online survey

We sent e-mails to 432 subjects containing an invitation to the online questionnaire. The subjects who agreed to participate accessed the questionnaire via the website link provided in the e-mail. The subjects were informed that their answers would be gathered anonymously. Usually, it took approximately 10 to 15 minutes to answer all of the questions. Invitation e-mails were sent up to three times. Of the 432 subjects who received the invitation e-mail, 95 (22.0%) submitted answers to the questionnaire.

Statistical analysis

We used SPSS Statistics for Windows (Version 21.0, IBM Corp., Armonk, NY, USA) for statistical analysis. For each multiple-choice question, the number and percentage of the respondents are shown as number (%). May of the questions with numerical answers asked for percentages of patients; those data are presented as the mean \pm standard deviation. Comparisons between allergists and pulmonologists were performed using a χ^2 test (for nominal variables) or a Student's *t*-test (for continuous variables). *P* values <0.05 were considered significant.

RESULTS

Characteristics of the respondents

The demographics and patterns of the clinical practices of the subjects ($n=95$) are presented in Table 1. All specialists were Korean and were certified internists. By subspecialty, there were 58 allergists (61.1%) and 37 pulmonologists (38.9%). Most respondents worked in university hospitals ($n=77$, 81.1%); others were in clinical practice in general hospitals ($n=9$, 9.5%) or private clinics ($n=9$, 9.5%). Most specialists ($n=85$, 89.5%) accepted adult patients only; others ($n=10$, 10.5%) accepted both adults and children. There were significant differences in age, gender, and institution of employment between the allergists and pul-

Table 1. Characteristics of the respondents

Characteristic	Total (n=95)	Allergists (n=58)	Pulmonologists (n=37)	<i>P</i> value*
Age (year)	44.3 \pm 7.7	42.8 \pm 7.5	46.5 \pm 7.6	0.020
Male	59 (62.1)	31 (53.4)	28 (75.7)	0.033
Institution				0.035
University hospital	77 (81.1)	51 (87.9)	26 (70.3)	
General hospital	9 (9.5)	5 (8.6)	4 (10.8)	
Clinic	9 (9.5)	2 (3.4)	7 (18.9)	
Patient population				0.418
Adults	85 (89.5)	53 (91.4)	32 (86.5)	
Adults and children	10 (10.5)	5 (8.6)	5 (13.5)	

Values are presented as mean \pm standard deviation or number of patients (%). Bolded values denote statistical significance.

*Comparison between allergists and pulmonologists.

monologists.

Diagnosis of severe asthma

First, we attempted to assess the percentage of patients with severe asthma among all patients with asthma. To this purpose, we asked the specialists to provide the approximate percentage of severe asthma patients among total asthma patients in their clinical practice using an open-ended question. The mean percentage of severe asthma was $13.9\% \pm 11.0\%$, with a wide variance of estimation (range, 1%–70%; interquartile range [IQR], 5–20). There was no difference between allergist and pulmonologist responses (Fig. 1). As severe asthma is highly heterogeneous and includes different subtypes, we attempted to assess the variety of clinical features of severe asthma. We asked the subjects to estimate the percentage of patients with each subtype listed in the American Thoracic Society (ATS) guidelines¹⁵ among their patients with severe asthma. The most commonly reported subtype was aggravation of symptoms due to stepping down to GINA asthma management step 3 or lower ($22.4\% \pm 20.9\%$), followed by frequent exacerbation (2 or more occasions of oral corticosteroid bursts per year; $20.9\% \pm 17.8\%$), uncontrolled asthma even at GINA step 4 or 5 ($13.5\% \pm 12.6\%$), and serious exacerbation (one or more hospitalizations per year;

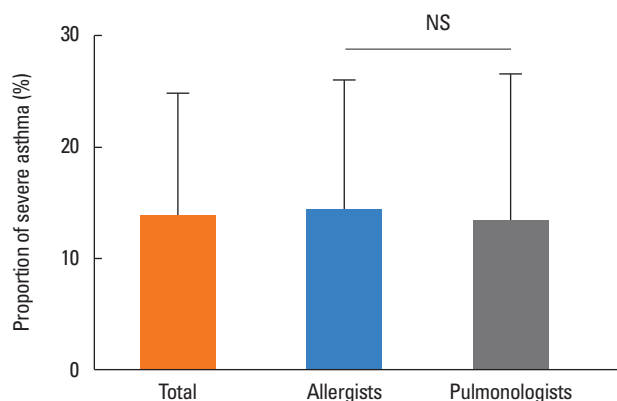


Fig. 1. Estimated percentage of asthma patients who had severe asthma.

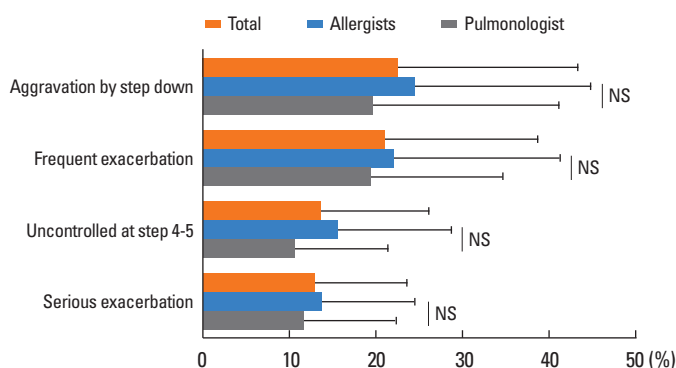


Fig. 2. Estimated percentage of asthma patients who had specific features of the disease.

12.8% ± 10.8%) (Fig. 2). There were no significant differences in the estimated percentages of each subtype of severe asthma between the allergists and pulmonologists.

Next, we attempted to assess how frequently different diagnostic tests were used to determine asthma phenotypes in clinical practice. The subjects were requested to select the tests that were usually performed at their practice to determine the phenotype of severe asthma. The most frequently used tests for asthma phenotyping were peripheral blood counts (93.7%), skin prick tests (SPTs), serum specific immunoglobulin E (IgE) (93.7%), and the measurement of serum total IgE (93.7%) (Table 2). Other tests included chest computed tomography (CT) (65.3%), induced sputum analysis (45.3%), measurement of exhaled nitric oxide (26.3%), and the aspirin provocation test (16.8%). Allergists used induced sputum analysis, exhaled nitric oxide, and the aspirin provocation test more frequently than pulmonologists, while pulmonologists tended to use peripheral blood cell counts more frequently than allergists.

Treatment of severe asthma

In the management of patients with severe asthma, poor response to medication is challenging. These patients fail to achieve

or maintain asthma control even at a higher level of asthma management, including high dose inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA). Thus, we attempted to assess what medications are used for pharmacologic treatment of severe asthma. The subjects were asked to estimate the percentage of patients using each medication added to high-dose ICS/LABA and leukotriene receptor antagonists. The most frequently used add-on medications were theophylline (46.0% ± 32.7%)

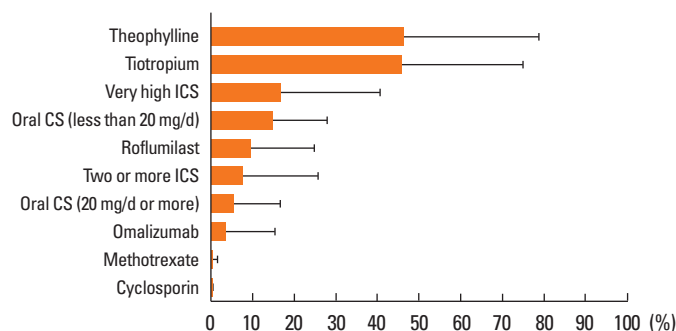


Fig. 3. Estimated percentage of patients with severe asthma who were prescribed add-on asthma controllers.

Table 2. Diagnostic tests used to determine the phenotypes of severe asthma

Test	Total (n=95)	Allergists (n=58)	Pulmonologists (n=37)	Pvalue*
Peripheral blood cell counts	89 (93.7)	52 (89.7)	37 (100.0)	0.043
SPT or serum specific IgE	89 (93.7)	55 (94.8)	34 (91.9)	0.566
Serum total IgE	89 (93.7)	54 (93.1)	35 (94.6)	0.771
Chest CT	62 (65.3)	42 (72.4)	20 (54.1)	0.067
Induced sputum eosinophil count	43 (45.3)	32 (55.2)	11 (29.7)	0.015
Exhaled nitric oxide	25 (26.3)	21 (36.2)	4 (10.8)	0.006
Aspirin provocation test	16 (16.8)	15 (25.9)	1 (2.7)	0.003

Values are presented as number of patients (%). Bolded values denote statistical significance.

SPT, skin prick test; IgE, immunoglobulin E; CT, computed tomography.

*Comparison between allergists and pulmonologists.

Table 3. Difficulties in the management of severe asthma

Factor	Total (n=95)	Allergists (n=58)	Pulmonologists (n=37)	Pvalue*
Lack of effective medication	83 (87.4)	53 (91.4)	30 (81.1)	0.141
Concern over adverse reactions to medication	45 (47.4)	24 (41.4)	21 (56.8)	0.143
Concern over insurance cuts	24 (25.3)	16 (27.6)	8 (21.6)	0.514
Fear of misdiagnosis	23 (24.2)	17 (29.3)	6 (16.2)	0.146
Poor patient compliance	23 (24.2)	16 (27.6)	7 (18.9)	0.336
Lack of severe asthma guideline	18 (18.9)	12 (20.7)	6 (16.2)	0.587
Difficulty with the patient relationship	13 (13.7)	6 (10.3)	7 (18.9)	0.236
High medical costs	12 (12.6)	8 (13.8)	4 (10.8)	0.670

Values are presented as number of patients (%). Lack of effective drugs (87.4%), concern over adverse reactions to medications (47.4%), concern over insurance cuts (25.3%), fear of misdiagnosis (24.2%), poor patient compliance (24.2%), lack of severe asthma guidelines (18.9%), difficulty with the patient relationship (13.7%), and high medical costs (12.6%).

*Comparison between allergists and pulmonologists.

and tiotropium ($45.5\% \pm 29.4\%$) (Fig. 3). The specialists responded that patients with severe asthma were prescribed very high dose ICS (more than the approved dose) ($16.6\% \pm 24.1\%$), regular use of oral corticosteroids (less than 20 mg/day of prednisolone) ($14.7\% \pm 13.3\%$), roflumilast ($9.3\% \pm 15.7\%$), two or more different types of ICS ($7.5\% \pm 18.4\%$), regular use of oral corticosteroids (20 mg/day or more of prednisolone) ($5.2\% \pm 11.6\%$), omalizumab ($3.3\% \pm 12.2\%$), methotrexate ($0.3\% \pm 1.4\%$), and cyclosporine ($0.1\% \pm 0.6\%$) for treatment of severe asthma. There was no difference in the prescription of add-on medications between allergists and pulmonologists.

Next, we assessed the difficulties specialists encountered when treating severe asthma. The subjects reported the following factors as major difficulties of severe asthma management: lack of effective drugs (87.4%), concern over adverse reactions to medications (47.4%), concern over insurance cuts (25.3%), fear of misdiagnosis (24.2%), poor patient compliance (24.2%), lack of severe asthma guidelines (18.9%), difficulty with the patient relationship (13.7%), and high medical costs (12.6%). No difference was found between allergists and pulmonologists in their experience of difficulties in the management of severe asthma (Table 3).

Perception and diagnostic criteria of ACOS

The second topic of this survey was the perception of ACOS among specialists. First, we asked the subjects to provide the estimated percentage of ACOS patients among patients with asthma in their clinical practice. Similar questions requested the percentage of ACOS patients among severe asthma cases and among COPD cases. The results of these three questions are illustrated in Fig. 4. The specialists estimated that the percentage of ACOS of asthma was $20.7\% \pm 10.7\%$. The estimated percentage of ACOS among patients with severe asthma was $38.0\% \pm 20.9\%$, and that of ACOS among patients with COPD

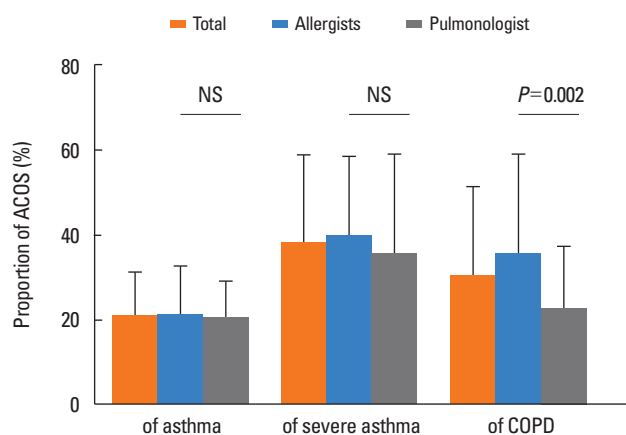


Fig. 4. Estimated proportion of patients with asthma, severe asthma, and COPD who had ACOS. COPD, chronic obstructive pulmonary disease; ACOS, asthma-chronic obstructive pulmonary disease overlap syndrome.

was $30.1\% \pm 21.3\%$. The mean values of the percentages of ACOS in overall asthma and severe asthma patients from the allergists' perspective were not different from those of pulmonologists. However, the estimated percentage of ACOS in patients with COPD was higher according to allergists than pulmonologists ($35.5\% \pm 23.6\%$ vs. $22.6\% \pm 14.8\%$; $P=0.002$).

Next, we attempted to identify the most important features in ACOS diagnosis. As ACOS is accepted as a subgroup of both asthma and COPD, we assumed that diagnosis of ACOS in patients with asthma would be different than diagnosis in patients with COPD. Thus, we asked the subjects two questions regarding the diagnosis of ACOS. First, we asked the specialists to classify each feature as a major or a minor criterion for the diagnosis of ACOS. The features most often classified as major criteria ($>70\%$ of the subjects) included a history of smoking (83.2%), persistently low forced expiratory volume in 1 second (FEV1 $<80\%$ of the predicted value, 81.1%), and low variation of FEV1 over time (71.6%). The features not consistently classified as major criteria ($<70\%$) included emphysema on chest images (67.4%), negative bronchodilator response (BDR) (54.7%), older age at onset of symptoms (≥ 40 years) (52.6%), no personal history of allergic diseases (27.4%), negative SPTs (14.7%), no family history of allergic diseases (11.6%), no sputum eosinophilia (9.5%), low serum total IgE (7.4%), and low exhaled nitric oxide concentration (3.2%) (Table 4). Allergists selected emphysema on chest images as a major criterion more frequently than pulmonologists (75.9% vs. 54.1%; $P=0.039$), while pulmonologists more commonly selected older age at onset of symptoms (70.3% vs. 41.4%; $P=0.010$) and low serum total IgE (13.5% vs. 3.4%; $P=0.010$).

The second question asked about the diagnosis of ACOS in patients with COPD. Most specialists responded that high FEV1 variation over time (86.3%), positive BDR (79.0%), a personal history of allergic disease (73.7%) and positive airway hyper-responsiveness (AHR) (71.6%) were major criteria for the diagnosis of ACOS in patients with COPD. The features less often classified as major criteria were no history of smoking (57.3%), young age of onset (<40 years) (63.2%), no history of smoking (56.8%), positive SPT (54.7%), high serum total IgE (50.5%), sputum eosinophilia (45.3%), family history of allergic diseases (40.0%), wheeze (35.8%), high exhaled nitric oxide concentration (31.6%), and lack of emphysema on chest images (23.2%) (Table 5). Of these features, the allergists tended to favour exhaled nitric oxide concentration in the determination of ACOS among COPD patients compared to pulmonologists (41.4% vs. 16.2%; $P=0.008$). However, the pulmonologists selected high serum total IgE as the diagnostic criterion for ACOS more frequently than allergists (54.1% vs. 48.3%; $P=0.040$).

Finally, we asked if ACOS in asthma and ACOS in COPD were the same disease. Overall, 37.9% of the specialists agreed that the two diseases are the same. More allergists tended to agree with this suggestion than pulmonologists (44.8% vs. 27.0%; $P=$

Table 4. Major and minor criteria for the diagnosis of ACOS in patients with asthma

Characteristic*	Criterion classification	Total (n=95)	Allergists (n=58)	Pulmonologists (n=37)	Pvalue [†]
History of smoking	Major	79 (83.2)	46 (79.3)	33 (89.2)	0.210
	Minor	16 (16.8)	12 (20.7)	4 (10.8)	
	No	0 (0.0)	0 (0.0)	0 (0.0)	
Persistently low FEV1 (<80% predicted)	Major	77 (81.1)	45 (77.6)	32 (86.5)	0.527
	Minor	12 (12.6)	9 (15.5)	3 (8.1)	
	No	6 (6.3)	4 (6.9)	2 (5.4)	
Low FEV1 variation over time	Major	68 (71.6)	41 (70.7)	27 (73.0)	0.251
	Minor	23 (24.2)	13 (22.4)	10 (27.0)	
	No	4 (4.2)	4 (6.9)	0 (0.0)	
Emphysema on chest images	Major	64 (67.4)	44 (75.9)	20 (54.1)	0.039
	Minor	26 (27.4)	13 (22.4)	13 (35.1)	
	No	5 (5.3)	1 (1.7)	4 (10.8)	
Negative BDR	Major	52 (54.7)	30 (51.7)	22 (59.5)	0.710
	Minor	36 (37.9)	23 (39.7)	13 (35.1)	
	No	7 (7.4)	5 (8.6)	2 (5.4)	
Age of onset ≥ 40 years	Major	50 (52.6)	24 (41.4)	26 (70.3)	0.010
	Minor	39 (41.1)	28 (48.3)	11 (29.7)	
	No	6 (6.3)	6 (10.3)	0 (0.0)	
No personal history of allergic disease	Major	26 (27.4)	14 (24.1)	12 (32.4)	0.117
	Minor	53 (55.8)	31 (53.4)	22 (59.5)	
	No	16 (16.8)	13 (22.4)	3 (8.1)	
Negative SPT	Major	14 (14.7)	10 (17.2)	4 (10.8)	0.095
	Minor	51 (53.7)	26 (44.8)	25 (67.6)	
	No	30 (31.6)	22 (37.9)	8 (21.6)	
No family history of allergic disease	Major	11 (11.6)	6 (10.3)	5 (13.5)	0.267
	Minor	60 (63.2)	34 (58.6)	26 (70.3)	
	No	24 (25.3)	18 (31.0)	6 (16.2)	
No sputum eosinophilia (<3%)	Major	9 (9.5)	4 (6.9)	5 (13.5)	0.396
	Minor	57 (60.0)	34 (58.6)	23 (62.2)	
	No	29 (30.5)	20 (34.5)	9 (24.3)	
Low serum total IgE	Major	7 (7.4)	2 (3.4)	5 (13.5)	0.010
	Minor	51 (53.7)	27 (46.6)	24 (64.9)	
	No	37 (39.0)	29 (50.0)	8 (21.6)	
Low exhaled nitric oxide (<25 ppb)	Major	3 (3.2)	2 (3.4)	1 (2.7)	0.732
	Minor	44 (46.3)	25 (43.1)	19 (51.4)	
	No	48 (50.5)	31 (53.4)	17 (45.9)	

Values are presented as number of patients (%). Bolded values denote statistical significance.

ACOS, asthma-chronic obstructive pulmonary disease overlap syndrome; FEV1, forced expiratory volume in 1 second; BDR, bronchodilator response; SPT, skin prick test; IgE, immunoglobulin E.

*Characteristics are listed in descending order in terms of % response of major criteria; [†]comparison between allergists and pulmonologists.

0.062). These findings suggest that the specialists consider different criteria for the diagnosis of ACOS in patients with asthma compared to patients with COPD. Moreover, the diagnostic criteria for ACOS perceived by the allergists were somewhat dissimilar to those perceived by the pulmonologists.

DISCUSSION

Severe asthma and ACOS are receiving more attention due to serious morbidity and poor clinical outcomes. However, ambiguity and uncertainty still exist in the understanding of severe asthma and ACOS, even among specialists. In this study, we es-

Table 5. Major and minor criteria for the diagnosis of ACOS in patients with COPD

Characteristic*	Criterion classification	Total (n=95)	Allergists (n=58)	Pulmonologists (n=37)	Pvalue [†]
High FEV1 variation over time	Major	82 (86.3)	50 (86.2)	32 (86.5)	0.479
	Minor	11 (11.6)	6 (10.3)	5 (13.5)	
	No	2 (2.1)	2 (3.4)	0 (0.0)	
Positive BDR	Major	75 (79.0)	50 (86.2)	25 (67.6)	0.094
	Minor	15 (15.8)	6 (10.3)	9 (24.3)	
	No	5 (5.3)	2 (3.4)	3 (8.1)	
Personal history of allergic diseases	Major	70 (73.7)	41 (70.7)	29 (78.4)	0.708
	Minor	22 (23.2)	15 (25.9)	7 (18.9)	
	No	3 (3.2)	2 (3.4)	1 (2.7)	
Positive AHR test	Major	68 (71.6)	40 (69.0)	28 (75.7)	0.496
	Minor	21 (22.1)	13 (22.4)	8 (21.6)	
	No	6 (6.3)	5 (8.6)	1 (2.7)	
Age of onset < 40 years	Major	60 (63.2)	28 (48.3)	32 (64.9)	0.256
	Minor	30 (31.6)	25 (43.1)	5 (27.0)	
	No	5 (5.3)	5 (8.6)	0 (8.1)	
No history of smoking	Major	54 (56.8)	31 (53.4)	23 (62.2)	0.555
	Minor	36 (37.9)	23 (39.7)	13 (35.1)	
	No	5 (5.3)	4 (6.9)	1 (2.7)	
Positive SPT	Major	52 (54.7)	32 (55.2)	20 (54.1)	0.091
	Minor	33 (34.7)	17 (29.3)	16 (43.2)	
	No	10 (10.5)	9 (15.5)	1 (2.7)	
High serum total IgE	Major	48 (50.5)	28 (48.3)	20 (54.1)	0.040
	Minor	34 (35.8)	18 (31.0)	16 (43.2)	
	No	13 (13.7)	12 (20.7)	1 (2.7)	
Sputum eosinophilia (>3%)	Major	43 (45.3)	31 (53.4)	12 (32.4)	0.118
	Minor	41 (43.2)	22 (37.9)	19 (51.4)	
	No	11 (11.6)	5 (8.6)	6 (16.2)	
Family history of allergic diseases	Major	38 (40.0)	20 (34.5)	18 (48.6)	0.072
	Minor	46 (48.4)	28 (48.3)	18 (48.6)	
	No	11 (11.6)	10 (17.2)	1 (2.7)	
Wheeze	Major	34 (35.8)	19 (32.8)	15 (40.5)	0.742
	Minor	50 (52.6)	32 (55.2)	18 (48.6)	
	No	11 (11.6)	7 (12.1)	4 (10.8)	
High exhaled nitric oxide (>50 ppb)	Major	30 (31.6)	24 (41.4)	6 (16.2)	0.008
	Minor	39 (41.1)	17 (29.3)	22 (59.5)	
	No	26 (27.4)	17 (29.3)	9 (24.3)	
Lack of emphysema on chest images	Major	22 (23.2)	15 (25.9)	7 (18.9)	0.720
	Minor	60 (63.2)	35 (60.3)	25 (67.6)	
	No	13 (13.7)	8 (13.8)	5 (13.5)	

Values are presented as number of patients (%). Bolded values denote statistical significance.

ACOS, asthma-chronic obstructive pulmonary disease overlap syndrome; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; BDR, bronchodilator response; AHR, airway hyper-responsiveness; SPT, skin prick test; IgE, immunoglobulin E.

*Characteristics are listed in descending order in terms of % response of major criteria; [†]comparison between allergists and pulmonologists.

timated the percentages and phenotypes of severe asthma and ACOS in the clinical practices of specialists. We also evaluated the patterns of diagnosis and treatment of severe asthma in clin-

ical practice. Thus, we assessed the current perceptions of severe asthma and ACOS among specialists in airway diseases using a questionnaire-based survey.

It is frequently said that 5%-10% of patients with asthma have severe asthma. However, this estimation varies depending on the diagnostic criteria and population. Studies so far have shown that approximately 3%-10% of patients with asthma in the general population suffer from severe asthma.¹⁶⁻¹⁸ However, the proportion of patients with severe asthma was determined to be 10%-25% of asthma patients in a specialty clinic.¹⁹ In our survey, the specialists' estimation of severe asthma prevalence was high, although estimates varied widely. As most respondents of this survey worked in university hospitals or general hospitals, these percentages reflect the population of severe asthma in specialist clinics, not in the general population. The reasons for the diversity of estimated prevalence could be due to the lack of a given definition of severe asthma, heterogeneity of the institutions, and patient populations.

Definitions of severe or refractory asthma have changed over time,^{1,2,15,20} and there is currently no universally accepted definition. However, it is acknowledged that severe asthma is heterogeneous and has many phenotypes and endotypes.²¹ Therefore, we asked specialists how frequently they observed each clinical subtype or characteristic of severe asthma, based on the diagnostic criteria of refractory asthma used by the ATS.¹⁵ Interestingly, the most common clinical features of severe asthma were aggravation of symptoms by stepping down treatment and frequent exacerbations, while the proportion of uncontrolled symptoms at GINA treatment steps 4-5 was not so high. These findings suggest that many patients with severe asthma require prolonged and higher medications to maintain control even though their symptoms are controlled.

Phenotypes are defined as composite and observable characteristics resulting from the interaction of genetic and environmental effects.¹ Phenotype-based asthma management has not been well emphasized to date, with the exception of the identification of allergic asthma for the use of anti-IgE. More than 90% of the specialists in this study measured peripheral blood cell eosinophil count and allergic status using total and serum specific IgE and a SPT for aeroallergens. Approximately 65% used a chest CT, usually to manage severe asthma. The chest CT is useful for the differential diagnosis of other respiratory diseases that mimic asthma, and for identification of emphysema, a feature of COPD. Measurement of sputum eosinophils, exhaled nitric oxide, and the aspirin provocation test were more frequently used by allergists than pulmonologists, suggesting that phenotyping of asthma has been more widely accepted by allergy specialists. In the near future, asthma phenotyping will be more important in cases of severe asthma, with introduction of new biological agents targeting type 2 inflammation, such as interleukin (IL)-5, IL-4, and IL-13.²² Problems in the treatment of severe asthma include the lack of guidance in the determination of asthma phenotypes and difficulty in the measurement and integration of various biomarkers.²³ Accurate, informative, and easy-to-measure biomarkers are needed to phenotype asthma.

One of the primary difficulties in the management of severe asthma is that there is no effective add-on treatment when asthma is uncontrolled, despite the use of high dose ICS and LABA. Lack of effective medication leads to the use of multiple medications to achieve and maintain asthma control. Moreover, polypharmacy in severe asthma is associated with increased direct medical costs and risk of adverse reactions.²⁴ Thus, we asked how many patients used add-on medications in addition to high-dose ICS/LABA and leukotriene receptor antagonists. As shown in Figure 3, the most frequently prescribed medications were theophylline and tiotropium, as recommended in the GINA guidelines.¹³ Oral corticosteroids were more commonly prescribed at low doses (<20 mg/day) than at high doses (\geq 20 mg/day). Omalizumab, which was the only available biological agent approved for use in severe allergic asthma at the time of this survey, was used in a small number of patients with severe asthma. Despite its proven efficacy in clinical trials and clinical practice,²⁵ the low use of omalizumab might be associated with one or more disadvantages, including high cost, complexity of administration, risk of serious adverse reactions, lack of efficacy, and relatively narrow indication in severe asthma.²⁶ In the survey regarding the difficulties of management of severe asthma, the lack of effective medications and concern over adverse reactions were most commonly selected (Table 3). The results of this study showed that the off-label use of medications, such as very high dose ICS, multiple ICSs, roflumilast, methotrexate, and cyclosporin, was also being tried in some patients with severe asthma. While these medications have failed to show significant overall efficacy in patients with severe asthma, some patients with specific phenotypes or endotypes might benefit from specific treatment that is not currently approved. As a future medication, personalized precision medicine targeting a treatable phenotype or pathophysiology is expected to be available soon for the management of severe asthma.²⁷ In addition to the sophisticated use of available medications, we must develop new effective therapeutic agents for severe asthma with fewer adverse effects.

ACOS is currently receiving a great deal of attention. Studies to date have shown that its clinical outcome is poorer than asthma or COPD alone, with a higher rate of exacerbations and greater mortality.^{7,8} While the prevalence of ACOS among chronic airway diseases has been reported to be approximately 20%,²⁸ it varies depending on the study design, population, and definition of ACOS. In our survey, the percentage of ACOS patients was estimated to be 20.7% in patients with asthma, 38.0% in patients with severe asthma, and 30.1% in patients with COPD. This estimate is based on patient populations of each subject, not the general population, reflecting actual experience in a specialty clinic. The problem is that there is no universally accepted working definition of ACOS. Thus, it is likely that even a specialist might use their own definition of ACOS. The difference in the diagnostic criteria leads to a wide variance of the prevalence

of ACOS in various types of studies.²⁹ Furthermore, the application of different ACOS definitions or diagnostic criteria also leads to dissimilar clinical characteristics and outcomes.³⁰ Interestingly, most diagnostic criteria were developed to define ACOS among patients with COPD,³¹⁻³⁴ not among patients with asthma. As in the consensus criteria of ACOS in Spain,³¹ we asked the specialists to name the key features of COPD that are considered in the diagnosis of ACOS in patients with asthma. The characteristics of COPD were given in detail, and were classified as major or minor criteria by the respondents. Intriguingly, most respondents selected a history of smoking as a major criterion for ACOS in asthma. It is obvious that smoking affects lung function decline and contributes to the development of COPD.³⁵ However, considering that a high percentage of COPD patients have never smoked,³⁶ it seems an oversimplification to consider only smoking in the determination of ACOS. In addition to smoking, a spirometric index such as persistently low FEV1 or low FEV1 variation over time were selected as major characteristics of ACOS. These findings suggest that specialist support in the diagnosis of ACOS in patients with asthma should be made in consideration of smoking and changes in lung function over time. Emphysema was also selected as a major criterion by allergists more than pulmonologists. Although the presence of emphysema does not indicate COPD *per se*, COPD must be considered in asthma patients showing emphysema on chest images. Furthermore, emphysema by itself might be a link between asthma and COPD, both in smokers and in patients who have never smoked.³⁷

There have been attempts by a Spanish group and a global expert panel, the ATS roundtable discussion, to define diagnostic criteria by consensus.^{31,34} Both consensus definitions included the previous diagnosis of asthma and positive BDRs as major criteria.³⁸ While a positive BDR was selected as a major criterion by many respondents, the highest scores were given to high FEV1 variation over time and AHR. In a recent study by Tkacova et al.,³⁹ AHR, not BDR, was found to be associated with accelerated lung function decline and higher mortality in patients with COPD. These findings suggest that AHR should be considered as a key element in the determination of ACOS. The previous history of asthma diagnosis before 40 years of age was classified as a major criterion in previous consensus documents on ACOS. However, many adult patients with asthma in some countries, including Korea, experience symptoms onset at a very old age, and the duration of asthma is very short.¹⁹ Given this late diagnosis of asthma, the previous diagnosis before 40 years of age could not be practically and universally used. Thus, we did not include the previous diagnosis of asthma as a candidate characteristic of ACOS in this study. Rather, we added a personal history of allergic diseases, which was selected as a major criterion by many specialists. As rhinitis and atopy are considered significant risk factors for the future development of asthma,⁴⁰ it seems reasonable to consider a past history of allergies when

diagnosing ACOS in patients with COPD.

Two different pathways may exist for the development of ACOS; it may stem from asthma, or from COPD.⁴¹ Thus, some experts suggest that ACOS can be divided into asthma with features of COPD (COPD-like asthma) and COPD with features of asthma (asthma-like COPD).⁴² Our data support this idea, as more than half of the respondents (62.1%) did not agree that asthma patients diagnosed with ACOS are the same population as COPD patients diagnosed with ACOS. As the previously developed consensus definition of ACOS was developed in order to define ACOS as a subtype of COPD, there are limitations to applying that definition to the whole population of ACOS patients. ACOS cannot be a single disease entity or a subtype of COPD, as stated in the GINA update in 2017.¹³ It is acknowledged that asthma is a heterogeneous disease, as is COPD.⁴³ Therefore, it is apparent that ACOS, which shares features of both asthma and COPD, is a heterogeneous disease and has various phenotypes.^{44,45} Understanding of ACOS varies even among specialists. Universal application of the definition of ACOS looks tempting, but is impractical both in clinical practice and research.

A few studies regarding the perceptions and insights of ACOS have been published, primarily by pulmonologists.^{46,47} The advantages of our study are the inclusion of both pulmonologists and allergists, and the comparison of their insights and clinical practices concerning severe asthma and ACOS. Some differences according to subspecialty (allergy or pulmonology) were found in responses to some questions of severe asthma and ACOS. Differences included the use of diagnostic tests in asthma phenotyping, assessment of the percentage of the ACOS population among COPD patients, and the definition of ACOS among patients with asthma or COPD. Previous studies also showed that the characteristics and management of asthma differed between allergists and pulmonologists.^{48,49} We speculate that this discord according to subspecialty resulted from the variance in patient populations and different perspectives on asthma and COPD.

However, the results of this study must be interpreted with caution. As this survey was based on the views of the participants and the response rate of the invited subjects was low, the findings cannot be over-generalized. In this regard, the difference between allergists and pulmonologists cannot be over-emphasized, since the respondents do not represent for each subspecialty group. Moreover, as this was a nationwide survey in Korea, it might reflect country- or ethnic-specific conditions of clinical practices and insurance status. Lastly, because the responses of the respondents were based on their own experience and perceptions, not on the objective assessment from the patient cohort or registry, the results of this study might be different from the real-world assessments.

In conclusion, the results showed that specialists' estimation of the prevalence of severe asthma and ACOS varies widely. Their understandings and practices of severe asthma and ACOS di-

verged on some points depending on their specialty. These diverse opinions should be considered in future studies and the development of strategies to manage severe asthma and ACOS.

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Supplement 1. Survey Questionnaire
Basic information

1. What is your age? (_____)
2. What is your gender?
 - 1) male
 - 2) female
3. What is your specialty board?
 - 1) allergy
 - 2) pulmonology
 - 3) other specialty board
 - 4) not a specialist
4. What kind of institution do you practice in?
 - 1) university hospital
 - 2) general hospital
 - 3) hospital
 - 4) private clinic
 - 5) other
5. Which age group do you usually see in your practice?
 - 1) children
 - 2) adults
 - 3) both

I. Diagnosis of severe asthma

1. What percentage of patients with severe asthma in your practice have the following clinical features? (The sum of the subtypes may be over 100%.)

Uncontrolled asthma symptoms despite gina step 4-5 treatment	_____ %
Controlled asthma symptoms at gina step 4-5, but symptoms are aggravated by stepping down	_____ %
Serious exacerbation (≥ 1 hospitalization per year)	_____ %
Frequent exacerbation (≥ 2 uses of oral corticosteroid rescue per year)	_____ %

2. What is the approximate percentage of patients with severe asthma among the total number of asthma patients in your practice? (_____%)

3. The phenotype of severe asthma is known to be diverse. Please indicate the usual tests for the classification of severe asthma phenotypes in your practice.

Test	Yes	No
Serum total ige	<input type="checkbox"/>	<input type="checkbox"/>
Peripheral blood cell count	<input type="checkbox"/>	<input type="checkbox"/>
Induced sputum eosinophil count	<input type="checkbox"/>	<input type="checkbox"/>
Exhaled nitric oxide	<input type="checkbox"/>	<input type="checkbox"/>
Allergen skin tests or serum specific ige measurement	<input type="checkbox"/>	<input type="checkbox"/>
Chest computed tomography (ct)	<input type="checkbox"/>	<input type="checkbox"/>
Aspirin provocation test	<input type="checkbox"/>	<input type="checkbox"/>

4. What percentage of patients with severe asthma in your practice have the following diseases?

Allergic rhinitis	_____ %
Gastro-oesophageal reflux disease (GERD)	_____ %
Obesity	_____ %
Sleep apnoea	_____ %
Depression or anxiety disorder	_____ %
Aspirin intolerance	_____ %

II. Treatment of severe asthma

1. Of the patients with severe asthma you are seeing, what percentages use the following drugs as controller medications in addition to high-dose inhaled corticosteroids (ICS) / long-acting beta-2 agonists (LABA) and leukotriene receptor antagonists?

Very high dose ics	_____ %
Two or more icss	_____ %
Oral corticosteroids (≥ 20 mg/day)	_____ %
Oral corticosteroids (< 20 mg/day)	_____ %
Anti-ige	_____ %
Theophylline	_____ %
Tiotropium	_____ %
Roflumilast	_____ %
Methotrexate	_____ %
Cyclosporine	_____ %

2. What is most difficult when you see patients with severe asthma? (Multiple answers possible)

- 1) no effective add-on drugs
- 2) concern over misdiagnosis
- 3) difficulty with the patient relationship
- 4) insurance cuts
- 5) low patient compliance
- 6) high medical expenses
- 7) concern over adverse drug reactions
- 8) lack of severe asthma guidelines

III. Asthma-COPD overlap syndrome (ACOS)

1. What is the approximate percentage of patients with ACOS among the total number of asthma patients in your practice?
(_____ %)

2. What is the approximate percentage of patients with severe asthma among the total number of asthma patients in your practice?
(_____ %)

3. What is the approximate percentage of the patients with ACOS among the total number of COPD patients in your practice?
(_____ %)

4. This question is about **the ACOS criteria** among patients **initially** diagnosed with and treated for **asthma**. The list includes possible items which can be considered in the diagnosis of ACOS among asthma patients. Please check if each item in the list could be a major or minor criterion or not.

Diagnostic criterion	Major	Minor	No
Older age of onset (≥ 40 years old)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
History of smoking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No personal history of allergic diseases	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No family history of allergic diseases	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Negative skin prick test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Low serum total IgE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Persistently low FEV ₁ <80% predicted	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Low FEV ₁ variation over time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Negative bronchodilator response	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No sputum eosinophilia (<3%)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Low exhaled nitric oxide (<25 ppb)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Emphysema on chest images	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. This question is about **the ACOS criteria** among patients **initially** diagnosed with and treated for **COPD**. The list includes possible items considered in the diagnosis of ACOS among asthma patients. Please check if each item in the list could be a major or minor criterion or not.

Diagnostic criterion	Major	Minor	No
Younger age of onset (<40 years old)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wheeze	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No history of smoking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Personal history of allergic diseases	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Family history of allergic diseases	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Positive skin prick test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High serum total IgE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High FEV ₁ variation over time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Positive bronchodilator response (12% and 200 mL)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Positive airway hyper-responsiveness test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sputum eosinophilia (>3%)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High exhaled nitric oxide (>50 ppb)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lack of emphysema on chest images	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. Do you agree that asthma patients diagnosed with ACOS are the same population as COPD patients diagnosed with ACOS?

- 1) Yes
- 2) No