Original Article

Clinical implications of wheezing in patients with chronic obstructive pulmonary disease

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Background: Studies on the prevalence of wheezing in both the asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) and non-ACO groups, as well as the clinical characteristics of wheezing patients in each group, are rare. We examined the prevalence of wheezing in ACO patients and non-ACO patients, respectively. In addition, we aimed to determine clinical characteristics of patients with wheezing compared to those without wheezing in the ACO and non-ACO groups.

Methods: We analyzed the data from the Korean COPD Subgroup Study (KOCOSS), a multicenter prospective cohort. We classified patients into four groups according to whether they were ACO patients or had self-reported wheezing based on the patient's answer to the COPD-specific version of St. George's Respiratory Questionnaire (SGRQ-C): ACO with wheezing, ACO without wheezing, non-ACO with wheezing, and non-ACO without wheezing. Clinical characteristics and exacerbations during 1-year follow up were compared among four groups.

Results: Wheezing was present in about 56% of patients in the ACO and non-ACO groups. In both groups, patients with wheezing exhibited more severe symptoms, worse lung function, and a higher risk of exacerbation than those without wheezing. There was no association between blood eosinophil count and wheezing in both the ACO and non-ACO groups. During 1-year follow-up, the ACO with wheezing group experienced exacerbations the most frequently, followed by the non-ACO with wheezing group. Moreover, wheezing was an independent predictor of the risk of exacerbation in patients with COPD, irrespective of both the ACO phenotype and the severity of airflow limitation. The exacerbation risk was higher in COPD patients who experienced wheezing more frequently.

Conclusions: Wheezing, reflecting more prominent airflow limitation and predicting exacerbation development, may serve as a severe phenotype of COPD rather than being indicative of an ACO phenotype.

Keywords: Chronic obstructive pulmonary disease (COPD); wheezing; asthma-COPD overlap (ACO); exacerbation

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms and persistent airflow limitation due to abnormalities of the airways and/or alveoli (1). There are several COPD phenotypes, including chronic bronchitis, emphysema, asthma-COPD overlap (ACO), and frequent exacerbator, and these phenotypes exhibit different prognosis, such as exacerbations, response to treatment, and disease progression (2,3). Since COPD causes significant morbidity and mortality (4,5), phenotype assessment is important to predict prognosis and guide appropriate management.

Wheezing may arise from any mechanisms that causes the narrowing of the airway caliber, and asthma and COPD are common clinical conditions exhibiting wheezing (6). Some previous studies used the presence of wheezing as a characteristic of ACO in COPD patients (7,8), because wheezing might reflect airway hyper-responsiveness (9). Wheezing is present not only in patients with ACO but also in those without ACO among individuals with COPD. However, studies on the prevalence of wheezing in the ACO and non-ACO groups, as well as the clinical characteristics of wheezing patients in each group, are rare. A previous study conducted in Taiwan investigated the prevalence and clinical characteristics of COPD patients with wheezing (10). They reported that 38% of COPD patients had a wheezing phenotype, and the wheezing group was associated with worse symptoms, diminished pulmonary function, and more exacerbations. However, the wheezing phenotype of COPD was not evaluated in terms of the association with ACO as a risk factor for worse outcomes.

In this study, we investigated the prevalence of self-reported wheezing in ACO and non-ACO patients, respectively. Furthermore, we aimed to identify clinical characteristics such as the severity of symptoms, lung function, and frequency of exacerbation in patients with wheezing compared to those without wheezing in the ACO and non-ACO groups. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1031/rc).

Highlight box

Key findings

- The presence of wheezing in chronic obstructive pulmonary disease (COPD) patients is associated with more severe symptoms, lower lung function, and a higher risk of exacerbation, irrespective of whether it is an asthma-COPD overlap (ACO) or non-ACO phenotype.

What is known and what is new?

- Wheezing, potentially indicating airway hyper-responsiveness, was considered as a trait associated with the ACO phenotype.
- Wheezing is an independent predictor of the risk of exacerbation in patients with COPD irrespective of both the ACO phenotype and the severity of airflow limitation, and the risk of exacerbation was higher in COPD patients with more frequent wheezing.

What is the implication, and what should change now?

- In COPD patients, wheezing may serve as a valuable marker for predicting the development of exacerbations, rather than being indicative of an ACO phenotype. A proactive pharmacological treatment should be considered in COPD patients with wheezing.

Methods

Study population

The Korean COPD Subgroup Study (KOCOSS) cohort is an ongoing, prospective, and multicenter cohort study that enrolled COPD patients from 54 medical centers in South Korea. The inclusion criteria were South Korean patients aged ≥40 years and with post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <70% of the normal predicted value. Enrolled patients underwent follow-up evaluations every six months after the initial assessment. All information was collected using the case report form that a doctor or trained nurse filled out. To assess the clinical characteristics of ACO and non-ACO patients with wheezing, we extracted the data from the KOCOSS cohort, which was registered between January 2012 and December 2018. This study excluded patients with a smoking history of less than 10 pack-years, and with missing values in eosinophil count, history of wheezing, and 1-year follow up exacerbation history. The study was conducted in accordance with the Declaration

of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of each participating hospital, and all patients provided written informed consent. The names of the approving ethics committees are mentioned in Appendix 1. The Institutional Review Board of the Kyungpook National University Hospital approved the study protocol (IRB No. 2012-01-001).

Clinical data

We obtained the baseline characteristics, including age, sex, smoking history, exposure to biomass fuel (firewood or briquette), and body mass index (BMI). Moreover, we collected the modified Medical Research Council (mMRC) dyspnea score (11), COPD Assessment Test (CAT) score (12), COPD-specific version of St. George's Respiratory Questionnaire (SGRQ-C) score (13), and 6-minute walk distance test score. In addition, a history of exacerbations in the previous year was obtained. Exacerbation was defined as the acute worsening of respiratory symptoms that requires additional therapy (14). Moderate exacerbation was defined as an exacerbation that necessitated the outpatient administration of antibiotics or systemic corticosteroids. Severe exacerbation was defined as an exacerbation that required hospitalization or an emergency room visit. In addition, results of pulmonary function tests and blood eosinophil count were collected. Inhalers used in baseline were classified as follows: long-acting beta2-agonist (LABA), long-acting muscarinic antagonist (LAMA), LABA/LAMA, inhaled corticosteroid (ICS)/LABA, and LABA/LAMA/ICS (triple therapy). Information about comorbidities and chest radiography findings were also obtained. According to the radiologist's interpretations, the chest radiography determined the following results: tuberculosis destroyed lung, old tuberculosis, emphysema, and bronchiectasis. In addition, the development of moderate and severe exacerbations during a 1-year follow-up was analyzed.

Definition of wheezing and ACO

In this study, the presence of wheezing was determined through the patient's answer to the SGRQ-C. For the question "I have attacks of wheezing", patients who answered "most days a week", "several days a week", "a few days a month", and "only with chest infections" were classified as the wheezing group. Those who answered "not at all" were classified as the non-wheezing group. ACO was defined according to the updated Spanish criteria (15). This study only included COPD patients aged ≥40 years with a post-bronchodilator FEV_1/FVC <0.7 and a smoking history of at least 10 pack-years. ACO was determined in case of very positive results on a bronchodilator test (FEV_1 ≥15% and ≥400 mL) and/or eosinophil in blood ≥300 cells/μL. We classified patients into four groups according to whether they were ACO patients or had wheezing: ACO with wheezing, ACO without wheezing, non-ACO with wheezing, and non-ACO without wheezing.

Statistical analysis

We used SPSS version 25.0 for Windows (IBM Corporation, Armonk, NY, USA) for statistical analysis. For categorical variables, we used the chi-squared or Fisher's exact test to compare the groups, and data were shown as numbers with percentages. For continuous variables, a one-way analysis of variance was performed to compare the groups, and data were presented as mean with standard deviation. P values <0.05 were regarded as statistically significant. In addition, multiple logistic regression analyses were conducted to evaluate the association between the presence of wheezing and the risk of COPD exacerbation, and Hosmer-Lemeshow test was performed to evaluate goodness-of-fit for logistic regression models.

Results

Study subjects

A total of 2,202 patients with spirometry-defined COPD were enrolled in the KOCOSS cohort from January 2012 to December 2018 (*Figure 1*). Patients with a smoking history <10 pack-years (n=286) and those with missing data for eosinophil count (n=392) or presence of wheezing (n=14) were excluded. After then, 448 patients were excluded due to missing value in exacerbation history during 1 year follow-up, and 1,121 patients were included in the study for analysis. Of the total enrolled patients, 273 (24.4%) were ACO, and 630 (56.2%) had wheezing: wheezing was present in 155 (56.8%) out of 273 ACO patients and in 475 (56.0%) out of 848 non-ACO patients. The numbers of the four groups according to whether the patients had ACO or wheezing were as follows: ACO with wheezing [155 (13.8%)], ACO without wheezing [118 (10.5%)], non-ACO with wheezing [475 (42.4%)], and non-ACO without wheezing [373 (33.3%)]. *Figure 2* shows the distribution

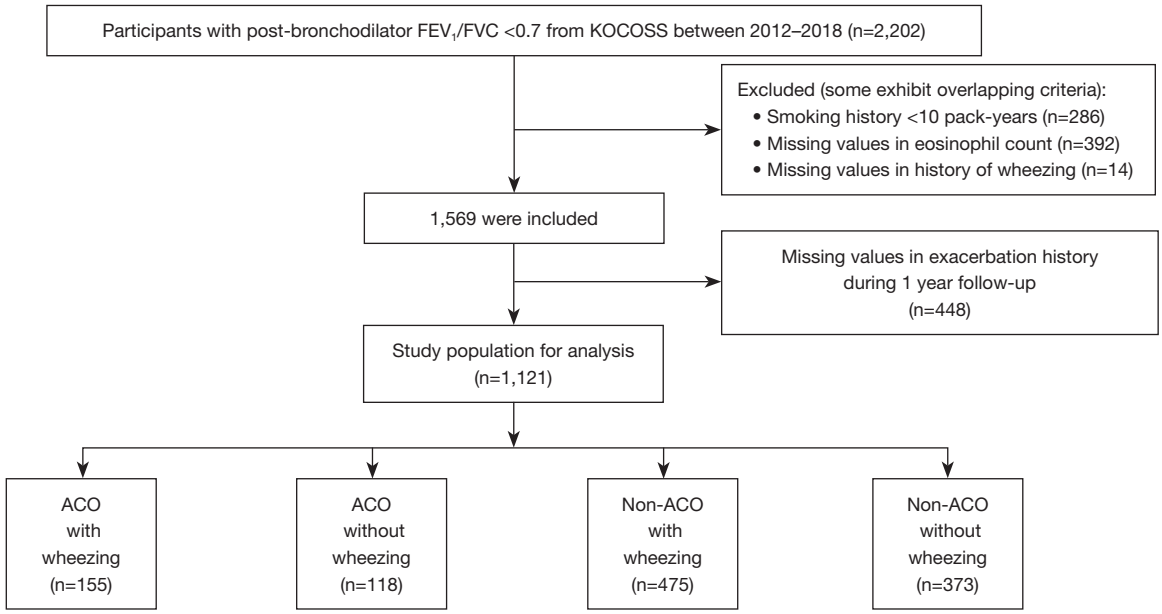

Figure 1 The flow chart of the study population. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; KOCOSS, the Korean COPD Subgroup Study; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

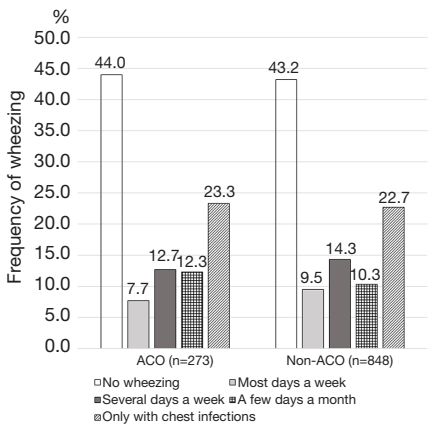

Figure 2 Frequency of wheezing in patients with COPD. ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease.

of patients according to the frequency of wheezing in ACO and non-ACO groups. There was no difference in the distribution of patients according to the frequency of wheezing between the two groups.

Baseline characteristics

Age, sex, smoking history, and biomass exposure did not differ among the four groups (*Table 1*). CAT score and mMRC grade were higher in patients with wheezing than those without wheezing in both ACO and non-ACO groups. There was no difference in blood eosinophil count between patients with wheezing and those without wheezing in both ACO and non-ACO groups. Among the four groups, the proportion of patients who experienced moderate to severe exacerbation in the previous year was the highest in ACO patients with wheezing, followed by non-ACO patients with wheezing. In terms of pulmonary function test parameters, post-bronchodilator FEV_1 and FEV_1/FVC were significantly lower in patients with wheezing than those without wheezing both in ACO and non-ACO patients. When compared to patients with wheezing in both ACO and non-ACO groups, the use of the ICS containing regimen was less common in non-ACO patients without wheezing. An ICS-containing regimen was more commonly utilized in the group that had experienced moderate to severe exacerbations in the previous year compared to the group that had not (54% *vs.* 32%, P<0.001). Additionally, there was no significant difference in comorbidities between the four groups. Regarding chest radiographic findings, emphysema was most commonly detected in ACO patients with wheezing, followed by non-ACO patients with wheezing (*Table 2*).

Table S1 shows a comparison of baseline characteristics

Table 1 Characteristics of enrolled patients with COPD

Characteristics	Total (n=1,121)	ACO (n=273)		Non-ACO (n=848)		P value
		With wheezing (n=155)	Without wheezing (n=118)	With wheezing (n=475)	Without wheezing (n=373)	
Age, years	68.9±7.6	68.3±7.8	68.8±7.2	68.6±7.8	69.4±7.3	0.324
Male sex	1,092 (97.4)	153 (98.7)	118 (100.0)	462 (97.3)	359 (96.2)	0.094
Smoking						
Current smoker	331 (29.5)	53 (34.2)	35 (29.7)	146 (30.7)	97 (26.0)	0.243
Pack-years	45.1±23.3	46.8±24.3	47.4±25.1	46.7±23.8	43.1±21.7	0.178
Biomass exposure	837 (74.7)	116 (74.8)	84 (71.2)	364 (76.6)	273 (73.2)	0.616
Body mass index, kg/m^2	22.9±3.4	23.0±3.2	22.8±3.6	23.1±3.4	22.7±3.3	0.468
CAT score	14.8±7.9	17.3±7.4	11.8±7.2	17.0±7.9	11.9±7.0	<0.001
CAT ≥10	804 (71.7)	136 (87.7)	69 (58.5)	390 (82.1)	209 (56.0)	<0.001
mMRC grade	1.3±0.9	1.5±0.9	1.2±0.9	1.5±0.9	1.1±0.8	<0.001
≥2	401 (35.8)	63 (40.6)	31 (26.3)	211 (44.4)	96 (25.7)	<0.001
SGRQ-C						
Symptom	43.1±21.0	56.1±19.4	29.6±14.6	52.6±19.0	29.8±14.7	<0.001
Activity	42.9±27.7	51.9±28.9	31.1±26.7	50.3±27.4	33.0±23.5	<0.001
Impact	24.2±22.5	33.2±23.8	16.7±17.4	30.5±23.8	15.0±16.9	<0.001
Total	33.3±21.3	42.9±21.9	24.2±17.5	40.6±21.5	23.1±15.8	<0.001
6MWD, m	378.1±116.5	370.2±118.1	383.0±114.6	370.0±109.2	391.3±125.4	0.105
Blood eosinophil count (cells/μL)	236.2±270.8	534.7±393.9	533.8±426.1	140.5±74.1	139.8±78.7	<0.001
Eosinophil ≥300 cells/μL	259 (23.1)	147 (94.8)	112 (94.9)	0	0	<0.001
100≤ eosinophil <300 cells/μL	566 (50.5)	7 (4.5)	5 (4.2)	318 (66.9)	236 (63.3)	<0.001
Eosinophil <100 cells/μL	296 (26.4)	1 (0.6)	1 (0.8)	157 (33.1)	137 (36.7)	<0.001
Moderate to severe exacerbation in the previous year	221 (19.7)	39 (25.2)	17 (14.4)	108 (22.7)	57 (15.3)	0.009
Pulmonary function test						
postBD FVC (L)	3.4±0.8	3.3±0.8	3.5±0.7	3.3±0.8	3.4±0.8	0.019
postBD FVC (% predicted)	81.3±16.2	78.2±16.8	82.3±15.7	80.6±16.2	83.1±16.0	0.008
postBD FEV_1 (L)	1.7±0.6	1.6±0.6	1.8±0.5	1.6±0.6	1.8±0.6	<0.001
postBD FEV_1 (% predicted)	58.2±18.2	54.2±18.6	61.4±18.0	56.1±17.9	61.6±17.7	<0.001
≥80% pred	137 (12.2)	16 (10.3)	18 (15.3)	45 (9.5)	58 (15.5)	0.033
50% pred ≤ FEV_1 <80% pred	618 (55.1)	73 (47.1)	68 (57.6)	257 (54.1)	220 (59.0)	0.079
30% pred ≤ FEV_1 <50% pred	308 (27.5)	53 (34.2)	29 (24.6)	143 (30.1)	83 (22.3)	0.013
<30% pred	58 (5.2)	13 (8.4)	3 (2.5)	30 (6.3)	12 (3.2)	0.028
postBD FEV_1/FVC (%)	50.5±11.7	48.9±11.6	52.8±11.6	49.1±11.8	52.3±11.4	<0.001
DL_{CO} (% predicted)	63.0±20.4	63.8±22.3	63.6±19.1	62.3±20.5	63.5±19.9	0.798

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=1,121)	ACO (n=273)		Non-ACO (n=848)		P value
		With wheezing (n=155)	Without wheezing (n=118)	With wheezing (n=475)	Without wheezing (n=373)	
Baseline inhaler use						
LABA	122 (10.9)	18 (11.6)	13 (11.0)	51 (10.7)	40 (10.7)	0.991
LAMA	302 (26.9)	48 (31.0)	29 (24.6)	124 (26.1)	101 (27.1)	0.618
LABA + LAMA	171 (15.3)	13 (8.4)	23 (19.5)	64 (13.5)	71 (19.0)	0.006
ICS + LABA	132 (11.8)	20 (12.9)	16 (13.6)	63 (13.3)	33 (8.8)	0.200
ICS + LABA + LAMA	267 (23.8)	42 (27.1)	21 (17.8)	134 (28.2)	70 (18.8)	0.004
ICS containing treatment	409 (36.5)	63 (40.6)	40 (33.9)	201 (42.3)	105 (28.2)	<0.001
Comorbidities						
Myocardial infarction	45 (4.0)	5 (3.2)	5 (4.2)	22 (4.6)	13 (3.5)	0.800
Heart failure	38 (3.4)	7 (4.5)	4 (3.4)	16 (3.4)	11 (2.9)	0.844
Diabetes mellitus	220 (19.6)	27 (17.4)	22 (18.6)	97 (20.4)	74 (19.8)	0.861
Hypertension	410 (36.6)	54 (34.8)	47 (39.8)	189 (39.8)	120 (32.2)	0.113
Previous pulmonary tuberculosis	261 (23.3)	40 (25.8)	23 (19.5)	108 (22.7)	90 (24.1)	0.629
Allergic rhinitis	90 (8.0)	15 (9.7)	10 (8.5)	45 (9.5)	20 (5.4)	0.127

Data are presented as mean ± standard deviation or n (%). COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; CAT, COPD assessment test; mMRC, modified Medical Research Council; SGRQ-C, COPD-specific version of St. George's Respiratory Questionnaire; 6MWD, 6-minute walk distance; postBD, post bronchodilator; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity for carbon monoxide; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

Table 2 Chest radiography findings in patients with COPD

Variables	Total (n=886)	ACO (n=219)		Non-ACO (n=667)		P value
		With wheezing (n=120)	Without wheezing (n=99)	With wheezing (n=374)	Without wheezing (n=293)	
Tuberculosis destroyed lung	42 (4.7)	3 (2.5)	5 (5.1)	16 (4.3)	18 (6.1)	0.422
Old tuberculosis	109 (12.3)	17 (14.2)	14 (14.1)	46 (12.3)	32 (10.9)	0.749
Emphysema	304 (34.3)	48 (40.0)	35 (35.4)	139 (37.2)	82 (28.0)	0.040
Bronchiectasis	56 (6.3)	10 (8.3)	9 (9.1)	20 (5.3)	17 (5.8)	0.418

Data are presented as n (%). COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

when enrolled patients were divided into the wheezing and non-wheezing group. Individuals in the wheezing group showed elevated CAT score, mMRC grade, and SGRQ-C score, as well as reduced post-bronchodilator FVC, FEV_1, and FEV_1/FVC than the non-wheezing group. The blood eosinophil count showed no statistically significant difference between the groups with and without wheezing. The use of the ICS containing regimen and the presence of emphysema in chest radiography were more common in the wheezing group compared with the non-wheezing group.

Wheezing and risk of exacerbations during 1-year follow-up

During the 1-year follow-up, moderate to severe

Table 3 Exacerbations during 1-year follow-up

Variables	Total (n=1,121)	ACO (n=273)		Non-ACO (n=848)		P value
		With wheezing (n=155)	Without wheezing (n=118)	With wheezing (n=475)	Without wheezing (n=373)	
Moderate to severe exacerbation	467 (41.7)	92 (59.4)	38 (32.2)	226 (47.6)	111 (29.8)	<0.001
Severe exacerbation	127 (11.3)	25 (16.1)	10 (8.5)	69 (14.5)	23 (6.2)	<0.001
Frequency of moderate exacerbation	0.94±1.80	1.61±2.22	0.62±1.22	1.11±2.05	0.55±1.22	<0.001
Frequency of severe exacerbation	0.19±0.71	0.30±0.97	0.22±1.11	0.23±0.63	0.09±0.45	<0.001

Data are presented as mean ± standard deviation or n (%). COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

exacerbation occurred more frequently in patients with wheezing than those without wheezing in both ACO and non-ACO groups (*Table 3*), and proportion of patients who experienced moderate to severe exacerbation was the highest in the ACO patients with wheezing. Additionally, the non-ACO patients with wheezing experienced moderate to severe exacerbation more frequently than the ACO patients without wheezing.

We performed multiple logistic regression analyses to evaluate the association between presence of wheezing and the risk of exacerbations during 1-year follow-up in COPD patients (*Table 4*). In model 1, we adjusted age, sex, smoking pack-year, and post-bronchodilator FEV_1 (% predicted). In model 2, we further adjusted ACO and exacerbation history during the previous year in addition to model 1. COPD patients with wheezing were associated with a higher risk of moderate to severe exacerbation [adjusted odds ratio (OR) 2.074, 95% confidence interval (CI): 1.592–2.702 in model 1; adjusted OR 2.005, 95% CI: 1.529–2.630 in model 2]. In addition, the risk of severe exacerbation was also higher in COPD patients with wheezing (adjusted OR 1.950, 95% CI: 1.260–3.017 in model 1; adjusted OR 1.804, 95% CI: 1.160–2.806 in model 2).

Additionally, we evaluated the risk of exacerbation according to the frequency of wheezing. Regardless of the frequency of wheezing, individuals with wheezing had a greater risk of moderate to severe exacerbation compared to those without wheezing. Patients who experienced wheezing on most days of the week had the highest OR for moderate to severe and severe exacerbations, while those who had wheezing on several days of the week had the second highest OR.

Discussion

In the present study, the proportion of patients with self-reported wheezing in both the ACO and non-ACO groups was similar, about 56%. In both ACO and non-ACO groups, patients with wheezing had more severe symptoms, lower lung function, and a higher risk of exacerbation compared to those without wheezing. Association between blood eosinophil count and wheezing was not observed in both the ACO and non-ACO groups. During the 1-year follow-up, exacerbations were most frequent in ACO patients with wheezing among the four groups, followed by non-ACO patients with wheezing. In addition, self-reported wheezing was an independent predictor of the risk of exacerbation in patients with COPD irrespective of both the ACO phenotype and the severity of airflow limitation, and the risk of exacerbation was higher in COPD patients with more frequent wheezing.

In previous studies, the prevalence of wheezing in patients with COPD ranged from 18% to 60% (7,10,16,17). The variation in the degree of airflow limitation among the included patients may contribute to the variable prevalence observed across studies. Prevalence of wheezing was higher in studies including COPD patients who had more severe airflow limitations. Furthermore, the disparity in the prevalence of wheezing could be attributed to the distinct approaches, such as chart review and questionnaire, employed in each study to identify wheezing. Our study comprised COPD patients with mild to very severe airflow limitation, and presence of wheezing was determined using a questionnaire; the prevalence of wheezing was approximately 56%.

This study demonstrated that presence of wheezing in patients with COPD was associated with more severe symptoms, poorer lung function, and a higher risk of exacerbation in both ACO and non-ACO patients. A previous study using data from the Korean national survey investigated the heterogeneity of ACO (7). They included subjects who were ≥40 years and had prebronchodilator FEV_1/FVC <0.7 and FEV_1 ≥50% of predicted value in

Table 4 Risk of exacerbations during 1-year follow-up in COPD patients with wheezing

Variables	Moderate to severe exacerbation			Severe exacerbation		
	OR	95% CI	P value	OR	95% CI	P value
Wheezing						
Crude	2.339	1.826–2.997	<0.001	2.434	1.606–3.689	<0.001
Model 1	2.074	1.592–2.702	<0.001	1.950	1.260–3.017	0.003
Model 2	2.005	1.529–2.630	<0.001	1.804	1.160–2.806	0.009
Frequency of wheezing						
Model 1						
No wheezing	1 (ref.)			1 (ref.)		
A	2.595	1.583–4.253	<0.001	2.657	1.363–5.179	0.004
B	2.236	1.498–3.337	<0.001	1.970	1.093–3.553	0.024
C	1.818	1.198–2.759	0.005	1.747	0.915–3.333	0.091
D	2.014	1.443–2.810	<0.001	1.868	1.100–3.173	0.021
Model 2						
No wheezing	1 (ref.)			1 (ref.)		
A	2.350	1.418–3.895	0.001	2.338	1.191–4.588	0.014
B	2.169	1.440–3.266	<0.001	1.827	1.009–3.308	0.047
C	1.709	1.116–2.616	0.014	1.562	0.807–3.022	0.186
D	1.974	1.403–2.777	<0.001	1.728	1.011–2.953	0.045

Model 1: adjusted for age, sex, smoking pack-year, and post bronchodilator FEV_1 (% predicted). Model 2: adjusted for age, sex, smoking pack-year, post bronchodilator FEV_1 (% predicted), ACO, and exacerbation history during the previous year. According to the answer to "I have attacks of wheezing", patients were classified as follows: A, most days a week; B, several days a week; C, a few days a month; D, only with chest infections. Patients without wheezing were the reference group. COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ACO, asthma-COPD overlap.

the study and divided four groups based on their smoking history and the presence of wheezing. They reported that COPD patients with wheezing had lower lung function, poorer quality of life, and higher hospitalized rates compared with those without wheezing, regardless of smoking history. These results are consistent with our findings, as our study revealed that patients with wheezing had lower lung function in both the ACO and non-ACO groups. This implies that the presence of wheezing is not indicative of an ACO phenotype, but rather signifies more prominent airflow obstruction. This correlation could potentially be associated with heightened symptoms and an increased risk of exacerbations. For individuals facing challenges in performing lung function tests, the presence of wheezing could potentially signal a higher degree of airflow obstruction.

Several previous studies reported that ACO patients exhibited more severe symptoms, worse lung function, and increased exacerbation risk than non-ACO patients (18-20). However, in this study, there was no difference in the severity of symptoms and lung function between the ACO and non-ACO patients in both wheezing and non-wheezing groups, respectively. Various diagnostic criteria exist for ACO, and a prior study suggests that the prevalence and clinical characteristics of ACO vary depending on the criteria used for diagnosis (21). Therefore, it is thought that the discrepancy between the results of previous studies and ours might be related to different diagnostic criteria of ACO. During the 1-year follow-up, the proportion of patients who experienced moderate to severe exacerbation was the highest in the ACO patients with wheezing, followed by non-ACO with wheezing, ACO without

wheezing, and non-ACO without wheezing. This result was partially consistent with previous studies which demonstrated that ACO patients had a greater propensity for experiencing exacerbations than non-ACO patients. Furthermore, this study indicated that COPD patients with wheezing had a higher risk of exacerbation irrespective of the presence of ACO.

A previous study examining risk factors for inconsistencies between the risk of exacerbation and the severity of airflow limitation in COPD patients found that the presence of wheezing was an independent risk factor for a high risk of exacerbation in those with mild airflow limitation (22). This result suggests that the presence of wheezing is associated with an increased risk of exacerbation, even in COPD patients with less severe airflow limitation, and is consistent with our findings. In our study, the presence of wheezing was independently associated with exacerbation even after adjusting confounding variables such as age, sex, smoking amount, FEV_1, ACO, and exacerbation history during the previous year. Moreover, COPD patients who experienced wheezing more frequently had an increased risk of exacerbation. This implies that wheezing is a significant trait that can predict exacerbation in COPD patients. Therefore, a proactive pharmacological treatment strategy should be considered to prevent exacerbation in COPD patients with wheezing.

Previous studies examining the findings of chest computed tomography (CT) in patients with COPD reported that the presence of wheezing was associated with airway wall thickening (23,24). However, studies investigating the relationship between the presence of wheezing and radiological emphysema are limited. Although chest radiography has limitations in determining the existence of emphysema, our results showed more frequent emphysema in patients with wheezing compared to those without wheezing, which might be related to the loss of elastic recoil due to the reduction of elastic tissue in emphysema. Further studies using chest CT will be required to confirm the relationship between emphysema and the presence of wheezing. Moreover, our study revealed that the presence of wheezing did not correlate with eosinophil count, regardless of patients being classified into either the ACO or non-ACO group. While eosinophilic inflammation can also manifest in ACO patients, it is plausible that chronic non-eosinophilic inflammation or the decline in lung elasticity like emphysema exert a more predominant impact on driving wheezing episodes within the ACO or non-ACO patient population.

The present study has several limitations. First, since the KOCOSS cohort mainly comprises patients treated in a tertiary hospital, it may not accurately reflect the general COPD population. Second, the one-year follow-up period may be short to assess the association between the presence of wheezing and exacerbation risk. In addition, the relatively large number of patients excluded from the study due to missing exacerbation data may be a limitation in evaluating the exacerbation risk. Later, it will be necessary to assess the long-term follow-up results. Third, since the presence of wheezing was assessed using a questionnaire rather than a physical examination by a physician, it is possible that it differs slightly from the actual presence and frequency of wheezing. Fourth, our study determined the definition of ACO using marked positive bronchodilator response or elevated blood eosinophil count according to the updated Spanish criteria, but the information about the diagnosis of current asthma was not included, which might have led to an underestimation of ACO. Finally, assessing the effectiveness of ICS in preventing exacerbations based on the presence of wheezing was hindered by the inherent bias associated with an observational study.

Conclusions

In conclusion, the presence of self-reported wheezing in COPD patients was associated with severe symptoms, poor lung function, and a high risk of exacerbation in both the ACO and non-ACO groups. Moreover, the presence of wheezing independently predicted the risk of exacerbation in COPD patients, and the exacerbation risk was higher in COPD patients who experienced wheezing more frequently. Wheezing, as an indicator of more pronounced airflow restriction and a predictor of exacerbation development, could be considered a severe phenotype of COPD rather than a characteristic of an ACO phenotype.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1031/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1031/coif). K.S.J. serves as an unpaid editorial board member of *Journal of Thoracic Disease*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of each participating hospital, and all patients provided written informed consent. The names of the approving ethics committees are mentioned in Appendix 1. The Institutional Review Board of the Kyungpook National University Hospital approved the study protocol (IRB No. 2012-01-001).

References

1. Celli B, Fabbri L, Criner G, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. Am J Respir Crit Care Med 2022;206:1317-25.
2. Miravitlles M, Soler-Cataluña JJ, Calle M, et al. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J 2013;41:1252-6.
3. Corlateanu A, Mendez Y, Wang Y, et al. "Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art.". Pulmonology 2020;26:95-100.
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
5. Meghji J, Mortimer K, Agusti A, et al. Improving lung health in low-income and middle-income countries: from challenges to solutions. Lancet 2021;397:928-40.
6. Meslier N, Charbonneau G, Racineux JL. Wheezes. Eur Respir J 1995;8:1942-8.
7. Kim MH, Rhee CK, Kim K, et al. Heterogeneity of asthma and COPD overlap. Int J Chron Obstruct Pulmon Dis 2018;13:1251-60.
8. Kim J, Kim YS, Kim K, et al. Socioeconomic impact of asthma, chronic obstructive pulmonary disease and asthma-COPD overlap syndrome. J Thorac Dis 2017;9:1547-56.
9. Burney PG, Chinn S, Britton JR, et al. What symptoms predict the bronchial response to histamine? Evaluation in a community survey of the bronchial symptoms questionnaire (1984) of the International Union Against Tuberculosis and Lung Disease. Int J Epidemiol 1989;18:165-73.
10. Huang WC, Tsai YH, Wei YF, et al. Wheezing, a significant clinical phenotype of COPD: experience from the Taiwan Obstructive Lung Disease Study. Int J Chron Obstruct Pulmon Dis 2015;10:2121-6.
11. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988;93:580-6.
12. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648-54.
13. Meguro M, Barley EA, Spencer S, et al. Development and Validation of an Improved, COPD-Specific Version of the St. George Respiratory Questionnaire. Chest 2007;132:456-63.
14. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370:786-96.
15. Plaza V, Álvarez F, Calle M, et al. Consensus on the Asthma-COPD Overlap Syndrome (ACOS) Between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA). Arch Bronconeumol 2017;53:443-9.
16. Kulich K, Keininger DL, Tiplady B, et al. Symptoms and impact of COPD assessed by an electronic diary in patients

with moderate-to-severe COPD: psychometric results from the SHINE study. Int J Chron Obstruct Pulmon Dis 2015;10:79-94.
17. Jankrift N, Kellerer C, Magnussen H, et al. The role of clinical signs and spirometry in the diagnosis of obstructive airway diseases: a systematic analysis adapted to general practice settings. J Thorac Dis 2021;13:3369-82.
18. Menezes AMB, Montes de Oca M, Pérez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. Chest 2014;145:297-304.
19. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. Respir Med 2013;107:1053-60.
20. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. Respir Res 2011;12:127.
21. Lim JU, Kim DK, Lee MG, et al. Clinical Characteristics and Changes of Clinical Features in Patients with Asthma-COPD Overlap in Korea according to Different Diagnostic Criteria. Tuberc Respir Dis (Seoul) 2020;83:S34-45.
22. Huang WC, Wu MF, Chen HC, et al. Characteristics and risk factors for inconsistency between the risk of exacerbations and the severity of airflow limitation in COPD based on GOLD 2017: A retrospective, cross-sectional study. PLoS One 2018;13:e0193880.
23. Dijkstra AE, Postma DS, ten Hacken N, et al. Low-dose CT measurements of airway dimensions and emphysema associated with airflow limitation in heavy smokers: a cross sectional study. Respir Res 2013;14:11.
24. Kitaguchi Y, Fujimoto K, Kubo K, et al. Characteristics of COPD phenotypes classified according to the findings of HRCT. Respir Med 2006;100:1742-52.

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Appendix 1

The names of ethics committees

Gacheon University Gil Medical Center, Hallym University Kangnam Sacred Heart Hospital, Gangnam Severance Hospital, Kyung Hee University Hospital at Gangdong, Hallym University Kangdong Sacred Heart Hospital, Kangbuk Samsung Hospital, Kangwon National University Hospital, Konkuk University Hospital, Konkuk University Chungju Hospital, Kyungpook National University Hospital, Gyeongsang National University Hospital, Korea University Guro Hospital, Korea University Anam Hospital, Seoul Eulji Hospital, Dongguk University Gyeongju Hospital, Dongguk University Ilsan Hospital, Keimyung University Dongsan Medical Center, Dong-A University Hospital, Hallym University Dongtan Sacred Heart Hospital, Pusan National University Hospital, Inje University Busan Paik Hospital, The Catholic University of Korea Bucheon St Mary's Hospital, Soonchunhyang University Hospital Bucheon, Seoul National University Bundang Hospital, Bundang CHA Hospital, Seoul Metropolitan Government Seoul National University Bora-mae Medical Center, Samsung Medical Center, Soonchunhyang University Hospital Seoul, The Catholic University of Korea Seoul St Mary's Hospital, The Catholic University of Korea St Paul's Hospital, The Catholic University of Korea St Vincent's Hospital, Severance Hospital, Asan Medical Center, Ajou University Hospital, The Catholic University of Korea Yeouido St Mary's Hospital, The Catholic University of Korea Uijeongbu St Mary's Hospital, Yeungnam University Medical Center, Ulsan University Hospital, Wonkwang University Sanbon Hospital, Wonju Severance Christian Hospital, Ewha Womans University Mokding Hospital, Incheon St Mary's Hospital, Inha University Hospital, Chonnam National University Hospital, Chonbuk National University Hospital, Hanyang University Seoul Hospital, Kyung Hee University medical center, Chungnam National University Hospital, Inje University Ilsan Paik Hospital, Jeju National University Hospital, Soonchunhyang University Hospital Cheonan, Hallym University Chuncheon Sacred Heart Hospital, Hallym University Sacred Heart Hospital, and Hanyang University Guri Hospital.

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Table S1 Comparison of baseline characteristics between the wheezing and non-wheezing group

Characteristics	Wheezing group (n=630)	Non-wheezing group (n=491)	P value
Age, years	68.5±7.8	69.3±7.3	0.102
Male sex	615 (97.6)	477 (97.1)	0.623
Smoking			
Current smoker	199 (31.6)	132 (26.9)	0.087
Pack-year	45.9±23.9	44.1±22.6	0.205
Body mass index, kg/m^2	22.1±3.4	22.7±3.4	0.123
CAT score	17.1±7.8	11.9±7.1	<0.001
mMRC grade	1.5±0.9	1.1±0.8	<0.001
SGRQ-C, total	41.2±21.6	23.4±16.2	<0.001
6MWD, m	370.0±111.2	389.1±122.6	0.016
Blood eosinophil count (cells/μL)	237.5±266.4	234.5±276.5	0.853
Moderate to severe exacerbation in the previous year	147 (23.3)	74 (15.1)	0.001
Pulmonary function test			
postBD FVC, L	3.3±0.8	3.4±0.7	0.005
postBD FVC, % pred	80.0±16.4	82.9±15.9	0.003
postBD FEV_1, L	1.6±0.6	1.8±0.6	<0.001
postBD FEV_1, % pred	55.6±18.1	61.6±17.7	<0.001
postBD FEV_1/FVC	49.1±11.7	52.4±11.5	<0.001
DLCO (% predicted)	62.6±20.9	63.5±19.7	0.503
Baseline inhaler use			
LAMA	172 (27.3)	130 (26.5)	0.757
LABA	69 (11.0)	53 (10.8)	0.933
LABA + LAMA	77 (12.2)	94 (19.1)	0.001
ICS + LABA	83 (13.2)	49 (10.0)	0.100
ICS + LABA + LAMA	176 (27.9)	91 (18.5)	<0.001
ICS containing treatment	264 (41.9)	145 (29.5)	<0.001
Comorbidities			
Myocardial infarction	27 (4.3)	18 (3.7)	0.600
Heart failure	23 (3.7)	15 (3.1)	0.584
Diabetes mellitus	124 (19.7)	96 (19.6)	0.956
Hypertension	243 (38.6)	167 (34.0)	0.116
Previous pulmonary tuberculosis	148 (23.5)	113 (23.0)	0.872
Allergic rhinitis	60 (9.5)	30 (6.1)	0.034
Chest radiography findings	n=494	n=392	
Tuberculosis destroyed lung	19 (3.8)	23 (5.9)	0.160
Old tuberculosis	63 (12.8)	46 (11.7)	0.526
Emphysema	187 (37.9)	117 (29.8)	0.013
Bronchiectasis	30 (6.1)	26 (6.6)	0.734

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