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Letter to the Editor

Prevalence and clinical features of asthma-COPD overlap in patients with COPD not using inhaled corticosteroids

Dear Editor,

Various studies have been conducted on severity, frequency of acute exacerbations, and the prognosis of asthma-COPD overlap (ACO), however, it is controversial whether ACO has more clinical symptoms than COPD.^{1–4} In these studies, most patients with ACO had already undergone ICS treatment, which may have masked the clinical features of asthma in ACO; especially, ICS decreases the risk of exacerbations and improves asthma control and lung function in patients with asthma.⁵ The prevalence and clinical features of patients with ICS-naïve ACO, i.e., patients with ACO who were unaffected by ICS have not been examined.

This was a multicenter, cross-sectional study conducted between March 2019 and March 2020. We investigated the prevalence and clinical features of ACO among 197 outpatients with COPD who had been followed for at least 1 year at each hospital. Diagnoses of COPD were made according to the Global Initiative for Chronic Obstructive Lung Disease criteria.⁶ The following inclusion criteria were applied: age ≥ 40 years, smoking history of ≥ 10 pack-years, previous treatment with a bronchodilator for longer than 1 year, and consent to participate in this study. The following exclusion criteria were also applied: acute exacerbation of COPD within a 4-week period, presence of current asthma diagnosed by a respiratory specialist, regular prescription of ICS or oral corticosteroids, concomitant chronic respiratory diseases, and an inability to read and understand the questionnaires. Among the 229 patients with COPD enrolled in this study, 32 were excluded: 26 had used ICS within the past year, 3 were unable to accurately answer the questionnaire, 2 were unable to perform the fractional exhaled nitric oxide (FeNO) test, and 1 had a confirmed lung cancer diagnosis. ACO diagnosis was performed using the Japanese ACO guideline,^{7,8} as described in [Supplementary Table 1](#). If they met two or more major criteria, or one major criterion with two or more minor “features of asthma” criteria, they were diagnosed with ACO. COPD exacerbation was defined as the acute worsening of respiratory symptoms, and the frequency was assessed within the past one year. Moderate COPD exacerbation was defined as an exacerbation that required the administration of antibiotics and/or systemic steroids but no hospitalization, and severe COPD exacerbation was defined as an exacerbation requiring hospitalization.

In total, 197 patients with COPD (males, 86.3%) with a median age of 74.0 years (IQR, 69–79 years) were enrolled in this study ([Supplementary Table 2](#)). Of the 197 patients, 38 (19.3%) met the

ACO diagnostic criteria. There were no statistical differences in age, sex, mood disorders, smoking habit, pack years of smoking, respiratory function, respiratory medication, or time between the first visit to each hospital and the enrollment between patients with ACO and those with COPD-only. However, there were statistically significant differences in CAT and mMRC scores between ACO and COPD-only groups, respectively [CAT, 15.5 (9.5–22) vs 11 (7–18); $P = 0.02$; mMRC, 1.6 ± 1.01 vs 1.2 ± 0.97 ; $P < 0.01$]. A history of asthma and variable or paroxysmal respiratory symptoms were more common in patients with ACO than those with COPD-only ($P < 0.01$). FeNO, peripheral eosinophil counts, and IgE levels were higher in patients with ACO than those with COPD-only ($P < 0.01$).

The frequency of acute exacerbations during the year prior to study participation was 0.70 times/year. As shown in [Figure 1](#), the frequency of moderate-to-severe exacerbations was significantly higher in patients with ACO than those with COPD-only (ACO, 1.52 times/year; COPD-only, 0.50 times/year; $P < 0.01$). Further analysis showed a significantly higher frequency of moderate and severe exacerbations in patients with ACO than those with COPD-only (moderate, 1.24 vs 0.39; $P < 0.01$; severe, 0.28 vs 0.11, $P < 0.01$; [Fig. 1](#)). A multivariate model showed that ACO had a high impact on the frequency of acute exacerbations, resulting from an independent contribution [β , standardized regression coefficient: 0.34 (95%CI, 0.20 to 0.48); $P < 0.01$] after adjusting for CAT, % FEV₁, and mMRC ([Table 1](#)).

We examined the impact of each diagnostic factor on ACO diagnosis. Among the factors that contributed to ACO diagnosis, the odds ratios (ORs) were high for the following major diagnostic criteria: “History of asthma before the age of 40”, “FeNO > 35 ppb”, and “presence of variable or paroxysmal respiratory symptoms.” (OR: 92.2, 25.4, and 11.0, respectively) ([Supplementary Table 3](#)). Of the 15 patients who had a history of asthma before the age of 40, 14 (93.3%) had ACO and only 1 (6.7%) had COPD-only. Minor criteria such as “presence of perennial allergic rhinitis”, “high peripheral blood eosinophil counts” and “high total IgE or positive for specific IgE” had lower ORs than the major criteria (OR: 7.8, 6.2, and 4.5, respectively).

One of the strengths of this study is that we excluded patients with COPD who had undergone ICS treatment. Our study demonstrates the following clinically important points. First, approximately 19% of patients with ACO were latent among patients with ICS-naïve COPD. Second, patients with ICS-naïve ACO had more respiratory symptoms, reflected by CAT and mMRC scores, and more frequent acute exacerbations than those with COPD-only. Our study corresponds to a previous report that has also suggested that

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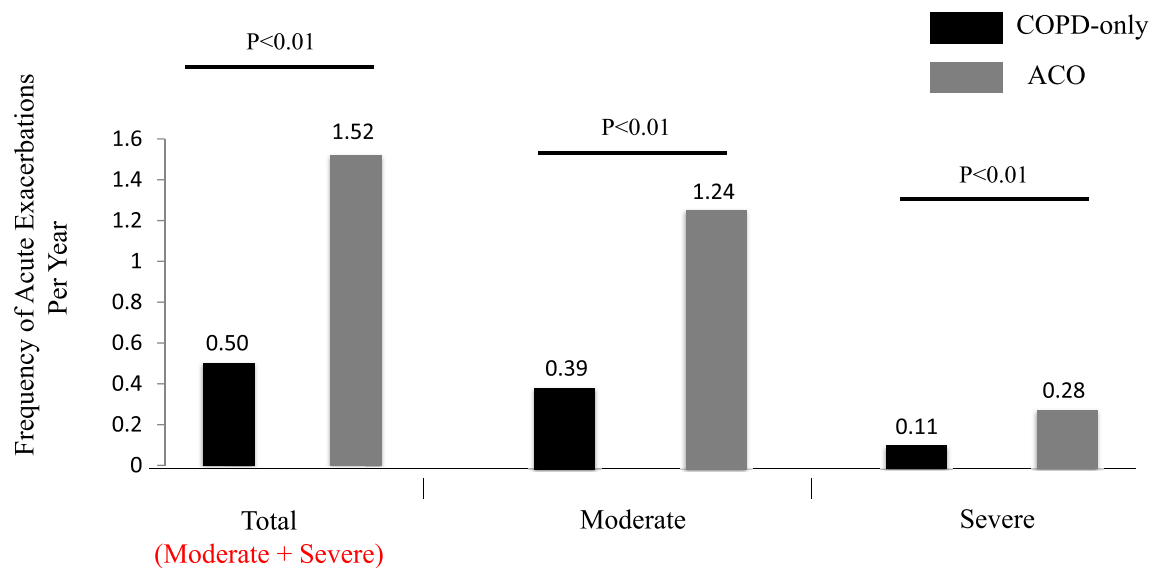


Fig. 1. Frequency of acute exacerbations per year in patients with COPD and in patients with asthma-COPD overlap (ACO).

Table 1

Multiple linear regression analysis for acute exacerbations in the past year.

Multivariate analysis [†]	Standard error	B, Standardized coefficient	P-value
ACO	0.083	0.34 (0.20–0.48)	<0.01
CAT	0.010	0.30 (0.15–0.45)	<0.01
%FEV ₁	0.003	–0.21 (–0.35 to –0.07)	<0.01
mMRC	0.077	0.02 (–0.13 to 0.17)	0.77

ACO, Asthma-COPD overlap; CAT, COPD Assessment Test; %FEV₁, percent predicted forced expiratory volume in the first second; mMRC, modified Medical Research Council.

[†] Adjusted for indicated clinical factors: ACO, CAT, %FEV₁, mMRC.

patients with ACO are latent in severe COPD⁹ and the study showed the potential for COPD patients who could be treated with ICS. Third, the clinical factor “history of asthma before the age of 40 years” in patients with COPD indicates a high probability of having ACO. This demonstrates the validity of Sin’s ACO diagnostic criteria¹⁰

This study has several limitations. First, since we did not study patients with COPD who had already been treated with ICS, the prevalence of ACO in the overall COPD population is unknown. Further studies should be conducted to compare the prevalence and clinical characteristics of ACO between patients who do and do not use ICS. Second, since most patients could be diagnosed with ACO without using the bronchodilator reversibility test, not all patients were subjected to this test. Therefore, we did not examine its contribution to ACO diagnosis. The lack of the test in some patients did not affect the prevalence and features of ACO in this study. Third, we were unable to investigate the extent of emphysematous changes.

This is the first study to evaluate the clinical characteristics of ACO in ICS-naïve patients. As ICS-naïve patients with ACO had more respiratory symptoms and high acute exacerbations frequency, physicians should actively check for ACO in patients with COPD who can be treated with ICS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.07.009>.

Conflict of interest

The authors have no conflict of interest to declare.

Kuniaki Hirai ^{a,*}, Akihiko Tanaka ^a, Tetsuya Homma ^a, Tomoko Kawahara ^b, Naruhito Oda ^b, Hatsuko Mikuni ^c, Yoshitaka Uchida ^c, Tomoki Uno ^a, Yoshito Miyata ^a, Hideki Inoue ^a, Shin Ohta ^a, Fumihiko Yamaguchi ^d, Shintaro Suzuki ^a, Hironori Sagara ^a

^a Department of Medicine, Division of Respiratory Medicine and Allergy, Showa University School of Medicine, Tokyo, Japan

^b Yamanashi Red Cross Hospital, Yamanashi, Japan

^c Asahi General Hospital, Chiba, Japan

^d Showa University Fujigaoka Hospital, Kanagawa, Japan

* Corresponding author. Department of Medicine, Division of Respiratory Medicine and Allergy, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.

E-mail address: hiraik@med.showa-u.ac.jp (K. Hirai).

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Supplementary Table 1. ACO Diagnostic Criteria.

Features of COPD	Features of Asthma
Must meet one or more of the following criteria:	Must meet two or more of 1, 2, or 3; or any one of 1,2,3 and two or more of 4-1 to 4-4
1. History of smoking tobacco (10 pack-years or more) or equivalent air pollution exposure	1. Presence of variable or paroxysmal respiratory symptoms
2. Presence of a low attenuation area showing emphysematous changes, as indicated by a chest CT	2. History of asthma before the age of 40
3. Low diffusing capacity (%DLCO<80% or %DLCO/VA<80%)	3. FeNO>35ppb
	4-1. Presence of perennial allergic rhinitis
	4-2. Positive of bronchodilator test (FEV ₁ > 12% and >200ml)
	4-3. Peripheral blood eosinophil > 5% or 300 cells/μL
	4-4. High IgE level (Total IgE or specific IgE against perennial inhaled antigen)

ACO: Asthma-COPD overlap

COPD: Chronic obstructive pulmonary disease

CT: Computed tomography

DLco: diffusing capacity of carbon monoxide in the lungs

FeNO: fractional exhaled nitric oxide

FEV₁: forced expiratory volume in the first second

HRCT: High-resolution computed tomography

IgE: immunoglobulin E

VA: alveolar volume

Supplementary Table 2. Patient's background data.

	Total (n=197)	COPD-only (n=159)	ACO (n=38)	P-value
Age (years)	74.0(69-79)	74(69-79)	72(65.5-80.2)	0.42
Sex (male)	170(86.3%)	136(85.5%)	34(89.4%)	0.61
CAT	12(7-19)	11(7-18)	15.5(9.5-22)	0.02
mMRC	1.3±1.00	1.2±0.97	1.6±1.01	<0.01
HADS-Anxiety	4(2-7)	4(2-7)	5(1-8)	0.95
HADS-Depression	6(3.2-8.7)	6(3-8)	6(4-11)	0.16
BMI	22.6(20.0-25.5)	22.6(19.8-25.3)	22.9(20.2-27.3)	0.39
FVC(L)	3.09(2.5-3.7)	3.1(2.5-3.7)	3.2(2.8-3.9)	0.28
FEV ₁ (L)	1.69±0.59	1.70±0.60	1.61±0.52	0.19
%FEV ₁ (%pred)	66.0±20.7	66.8±20.8	62.1±19.8	0.21
FEV ₁ (%)	56.6(45.9-63.3))	57.7(48.4-63.4)	52.3(42.1-61.9)	0.11
Smoking habit				
Former smoker	147(74.6%)	28(73.7%)	119(74.8%)	
Current smoker	50(25.4%)	40(25.2%)	10(26.3%)	0.88
Pack years of smoking	48(35-69)	48(35-70)	49(34.2-62.5)	0.59
Time between the first visit to each hospital and the enrollment (month)	30(19-52)	30(18-46)	35(23-84.5)	0.07
History of asthma	15(7.6%)	1(0.63%)	14(36.8%)	<0.01

Presence of variable or paroxysmal respiratory symptoms	30(15.2%)	12(7.5%)	18(47.4%)	<0.01
FeNO > 35ppb	41(20.8%)	14(8.8%)	27(71.1%)	<0.01
Peripheral blood eosinophil > 5% or 300 cells/ μ L	44(22.3%)	24(15.1%)	20(52.6%)	<0.01
Presence of perennial allergic rhinitis	37(18.8%)	18(11.3%)	19(50.0%)	<0.01
High total IgE or specific IgE	95(48.2%)	66(41.5%)	29(76.3%)	<0.01
FeNO(ppb)	23(16-33)	21(15-28)	51.5(27.2-69)	<0.01
Peripheral blood eosinophil counts (cells/ μ L)	170(89.8-280.2)	159.1(82.8-239.7)	278.9(122.8-358.1)	<0.01
Peripheral blood eosinophil counts (%)	2.9(1.6-4.4)	2.6(1.5-3.9)	4.5(2.3-5.7)	<0.01
IgE(KU/L)	1.91 $\pm$ 0.72	1.79 $\pm$ 0.71	2.38 $\pm$ 0.59	<0.01
Respiratory medication				
None		5(3.1%)	2(5.3%)	
LAMA monotherapy		30(18.9%)	7(18.4%)	
LABA monotherapy		19(12.0%)	3(7.9%)	
LAMA/LABA combinations		105(66.0%)	26(68.4%)	0.83

BMI: Body mass index

CAT: COPD Assessment Test

FeNO: fractional exhaled nitric oxide

%FEV₁: percent predicted forced expiratory volume in the first second

FEV₁: forced expiratory volume in the first second

FVC: forced vital capacity

HADS: Hospital Anxiety and Depression Scale

IgE: immunoglobulin E

LAMA: long acting muscarinic antagonist

LABA: long-acting β_2 -agonist

mMRC: modified Medical Research Council

Continuous variables with a normal distribution are shown as mean $\pm$ standard deviation, while the other variables are shown as median and interquartile range (IQR).

Supplementary Table 3. Impact of diagnostic criteria on ACO diagnosis.

	Total	ACO	COPD-only	Odds ratio	95% CI	P value
History of asthma before age 40 (+)	15	14(93.3%)	1(6.7%)	92.2	11.8-733.1	<0.01
History of asthma before age 40 (-)	182	24(13.1%)	158(86.9%)			
FeNO>35ppb	41	27(65.9%)	14(34.1%)	25.4	10.4-61.9	<0.01
FeNO≤35ppb	156	11(7.0%)	145(93.0%)			
Variable or paroxysmal respiratory symptoms (+)	30	18(60.0%)	12(40.0%)	11.0	4.6-26.2	<0.01
Variable or paroxysmal respiratory symptoms (-)	167	20(12.0%)	147(88.0%)			
Perennial allergic rhinitis (+)	37	19(51.3%)	18(48.7%)	7.8	3.5-17.5	<0.01
Perennial allergic rhinitis (-)	160	19(11.9%)	141(88.1%)			
Peripheral blood eosinophil (+)	44	20(45.5%)	24(54.5%)	6.2	2.9-13.5	<0.01
Peripheral blood eosinophil (-)	153	18(11.8%)	135(88.2%)			
Total IgE or specific IgE (+)	95	29(30.5%)	66(69.5%)	4.5	2.0-10.2	<0.01
Total IgE or specific IgE (-)	102	9(8.8%)	93(91.2%)			

ACO: asthma-COPD overlap

CI: Confidence interval

FeNO, fractional exhaled nitric oxide

IgE: immunoglobulin E