ORIGINAL

The prevalence and clinical features of asthma-COPD overlap (ACO) definitively diagnosed according to the Japanese Respiratory Society Guidelines for the Management of ACO 2018

Kenta Yamamura, MD[1] ; Johsuke Hara, MD, PhD[2] ; Takafumi Kobayashi, MD[2] ; Noriyuki Ohkura, MD, PhD[2] ; Miki Abo, MD, PhD[2] ; Kyota Akasaki, MD[2] ; Syunichi Nomura, MD[2] ; Mizuki Yuasa, MD[2] ; Keigo Saeki, MD[1] ; Nanao Terada, MD[1] ; Hiroki Matsuoka, MD[1] ; Yuichi Tambo, MD[2] ; Shingo Nishikawa, MD, PhD[2] ; Takashi Sone, MD, PhD[3] ; Hideharu Kimura, MD, PhD[2] ; and Kazuo Kasahara, MD, PhD[2]

[1] *Department of Respiratory Medicine, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Ishikawa Japan,* [2]*Department of Respiratory Medicine, Kanazawa University Hospital, Kanazawa, Ishikawa Japan,* [3]*Department of Regional Respiratory Symptomatology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa Japan*

Abstract : Background Asthma-COPD overlap (ACO) is a disease that shares clinical features of both asthma and COPD. The purpose of this study is to investigate the prevalence and clinical features of ACO. Methods We retrospectively reviewed data for 170 patients with persistent airflow limitation and diagnosed them according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018". Results Of the 170 patients, 111 were diagnosed as follows : COPD (74 patients, 66.6%), ACO (34 patients, 30.6%), and asthma (3 patients, 2.8%). There was no significant difference in clinical features between ACO and COPD patients. The following pulmonary function tests were significantly lower in ACO than in COPD patients : forced expiratory volume in 1 second/forced vital capacity, peak expiratory flow, maximal mid-expiratory flow, and the maximum expiratory flow at 50% and 75%. The following respiratory impedance parameters were significantly higher in ACO than in COPD patients : respiratory resistance (Rrs) at 5 Hz (R5), Rrs at 20 Hz (R20), R5-R20, and low-frequency reactance area. Conclusions About 30% of patients with persistent airflow limitation were diagnosed with ACO. ACO patients had lower lung function and higher respiratory impedance compared with COPD patients. J. Med. Invest. 66 : 157-164, February, 2019

Keywords **:** *Asthma-COPD overlap (ACO), bronchial asthma (BA), chronic obstructive pulmonary disease (COPD), prevalence, pulmonary function*

INTRODUCTION

Bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are both obstructive pulmonary diseases that are frequently encountered in clinical practice. BA is defined as follows : "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"(1). On the other hand, COPD is defined as follows : "COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases"(2). As the pathogenesis, pathophysiology, and clinical features are different, BA and COPD are recognized as essentially distinct diseases. However, it has been known that some patients have clinical features of both BA and COPD (3-5), and it is sometimes difficult to clearly distinguish these diseases. In view of this situation, in 2014, the Joint Committee of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposed the term "asthma-

Abbreviations :
BA, bronchial asthma ; COPD, chronic obstructive pulmonary disease ; GINA, Global Initiative for Asthma ; GOLD, Global Initiative for Chronic Obstructive Lung Disease ; ACOS, asthma-COPD overlap syndrome ; ACO, asthma-COPD overlap ; IgE, immunoglobulin E ; FeNO, fraction of exhaled nitric oxide ; FEV_1, forced expiratory volume in 1 second ; FVC, forced vital capacity ; HRCT, high-resolution computed tomography ; SABA, short-acting β2-adrenoceptor agonists ; Rrs, respiratory resistance ; Xrs, respiratory reactance ; R5, respiratory resistance at 5Hz ; R 20, respiratory resistance at 20Hz ; X5, respiratory reactance at 5Hz ; Fres, resonant frequency ; ALX, low-frequency reactance area ; SD, standard deviation ; BMI, body mass index ; PEF, peak expiratory flow ; MMF, maximal mid-expiratory flow ; MEF, maximum expiratory flow ; LABA, long-acting beta-2 agonists ; LAMA, long-acting muscarinic antagonists ; ICS, inhaled corticosteroids

Received for publication August 10, 2018 ; accepted January 17, 2019.

Address correspondence and reprint requests to Kenta Yamamura, MD, Department of Respiratory Medicine, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, 13-1, Takara-machi, Kanazawa, Ishikawa 920-8641, Japan and Fax : +81-76-234-4252

COPD overlap syndrome (ACOS)" defined as follows : "ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified in clinical practice by the features that it shares with both asthma and COPD"(6). Later, in 2017, GINA recommended the more appropriate term, "asthma-COPD overlap (ACO)", which represents the disease features(7).

There have been no unified diagnostic criteria of ACO, and each previous report diagnosed ACO according to its own definition (6, 8-11). The prevalence of ACO widely varied according to not only the difference in definition but also population characteristics and study design(12). Furthermore, the clinical features of ACO compared to BA and COPD have been unclear. To clarify the epidemiology and clinical features of ACO, a unified definition and diagnostic criteria were essential. Therefore, the Japanese Respiratory Society developed "The Japanese Respiratory Society Guidelines for the Management of ACO 2018" that is the first unified diagnostic criteria in Japan. It defined ACO as follows : "the coexistence of asthma and COPD in patients with chronic airway obstruction"(13, 14). In the future, when patients with chronic airway obstruction visit the hospital, it is expected that we can definitively diagnose them according to this guideline and clarify the epidemiology and clinical features of ACO.

In this study, we retrospectively reviewed the all of 1348 consecutive patients who first visited our institute between April 2017 and March 2018 ; we extracted the data for all patients with persistent airflow limitation in pulmonary function tests to investigate the prevalence and clinical features of ACO that was definitively diagnosed according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018".

PATIENTS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethical review board of Kanazawa University Hospital (Approval date : July 30, 2018 ; Approved number : 2837). We retrospectively reviewed the all of 1348 consecutive patients aged 40 years or over who first visited the Department of Respiratory Medicine, Kanazawa University Hospital between April 2017 and March 2018. The clinical data for the patient characteristics and laboratory data including peripheral blood eosinophil counts, serum immunoglobulin E (IgE) levels, specific IgE, pulmonary function test results, fraction of exhaled nitric oxide (FeNO) levels, bronchial reversibility test results, and respiratory impedance values were collected from medical records. We extracted the data for all patients with persistent airflow limitation (post-bronchodilator forced expiratoryvolume in 1 second [FEV_1]/forced vital capacity [FVC] < 0.7) on pulmonary function tests who were diagnosed as having BA, COPD or ACO according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018" (Table 1). The patients who shared features of both COPD and BA were diagnosed as having ACO. The patients who had only features of COPD were diagnosed as having COPD, and those who had only features of BA were diagnosed as having BA. According to the guidelines, we ruled out other diseases that can cause airflow limitation (e.g. diffuse panbronchiolitis, congenital sinobronchial syndrome, obstructive bronchiolitis, bronchiectasis, pulmonary tuberculosis, pneumoconiosis, pulmonary lymphangiomyomatosis, congestive heart failure, interstitial lung disease, and lung cancer). We investigated the prevalence of each disease and compared the clinical features of ACO with those of COPD.

Pulmonary emphysema was evaluated using high-resolution computed tomography (HRCT), and HRCT findings were analyzed by two radiologists. Pulmonary function tests were performed using a computerized spirometer (CHESTAC-9800 ; CHEST, Tokyo, Japan). A flow-volume curve was performed before and 20 minutes after inhalation of short-acting β2-adrenoceptor agonists (SABA) (20 μg of procaterol hydrochloride) to evaluate the reversibility after SABA. FeNO was measured using an electrochemical analyzer (NIOX MINO ; CHEST, Tokyo, Japan). Respiratory impedance was measured using a multifrequency forced oscillation technique device (MostGraph-01 ; CHEST, Tokyo, Japan). Respiratory impedance is composed of respiratory resistance (Rrs) and respiratory reactance (Xrs). We evaluated the Rrs at 5 Hz (R5), Rrs at 20 Hz (R20), R5-R20, Xrs at 5 Hz (X5), resonant frequency (Fres), and low-frequency reactance area (ALX).

The continuous variables are shown as mean ± standard deviation (SD). The discrete variables are shown as a number. The statistical differences between pairs of groups were analyzed by the Mann-Whitney *U* test or Fisher's exact test. A P-value less than 0.05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (15), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

There were 170 patients with persistent airflow limitation on pulmonary function tests, and the initial clinical diagnoses were as

Table 1. Criteria for the diagnosis of ACO(13)

Features of COPD The presence of at least one of the following features (1, 2, or 3)	Features of BA The presence of at least two of features 1, 2, or 3 ; or at least one of features 1, 2, or 3 plus two of features 4-1 to 4-4
1. Smoking history (10 pack-years or more) or equivalent exposure to air pollution	1. Variable or paroxysmal clinical symptoms
2. Emphysematous changes on high-resolution CT	2. A documented history of asthma before the age of 40 years
3. Decreased gas exchange (%DLco < 80% or %DLco/V_A < 80%)	3. FeNO > 35 ppb
	4-1. A history of perennial allergic rhinitis 4-2. Airway reversibility (FEV_1 > 12% and > 200ml) 4-3. Peripheral blood eosinophils > 5% or > 300 cells/μl 4-4. Elevated IgE level (total or allergen-specific IgE)

Abbreviations : ACO, asthma-COPD overlap ; COPD, chronic obstructive pulmonary disease ; CT, Computed Tomography ; DLco, diffusing capacity of carbon monoxide ; V_A, alveolar volume ; BA, bronchial asthma ; FeNO, fraction of exhaled nitric oxide ; FEV_1, forced expiratory volume in 1 second ; IgE, Immunoglobulin E

follows : COPD, 106 (62.4%) ; ACO, 48 (28.2%) ; BA, 12 (7.1%) ; and other diseases, 4 (2.3%). Four patients having other diseases that can cause airflow limitation were excluded. Of the remaining 166 patients, 23 were well evaluated on all items necessary to confirm the features of BA and COPD and were definitively diagnosed. Of the remaining 143 patients, 92 patients could be definitively diagnosed using the results of the conducted medical interviews and examinations. However, 51 patients could not be diagnosed due to insufficient medical interviews or examinations. There were 4 patients with neither BA nor COPD features. That is, we could finally make a definitive diagnosis in 111 of 166 patients with persistent airflow limitation. For the 111 patients, the diagnoses were as follows : COPD, 74 (66.6%) ; ACO, 34 (30.6%) ; and BA, 3 (2.8%) (Figure 1). Only 14 patients (12.6%) were under treatment for BA or COPD at the first visit to our institute, and most patients were untreated (data not shown). There were many deficits of data for making a definitive diagnosis according to the Japanese Respiratory Society guidelines, and we investigated the implementation rate of medical interviews and examinations in this study necessary to confirm the features of BA and COPD (Table 2). Among the features of COPD, smoking history and emphysematous changes on HRCT were evaluated in most patients ; however, there were many patients who were not evaluated for decreased gas exchange. Among the features of BA, variable or paroxysmal clinical symptoms, a documented history of asthma, FeNO, airway reversibility, and peripheral blood eosinophils were evaluated in most patients ; however, there were many patients who were not evaluated for a history of perennial allergic rhinitis and serum or specific IgE.

There were few BA patients ; therefore, we compared the clinical features of ACO with COPD. Table 3 shows the positive rate of each item necessary to confirm the features of COPD and BA. In COPD group, there were few patients with variable or paroxysmal clinical symptoms (5.6%), a documented history of asthma (0%), high level of FeNO (FeNO > 35 ppb) (2.8%), and a history of perennial allergic rhinitis (2.3%). On the other hand, there were many patients with high level of IgE (total or allergen-specific IgE) (41.7%) even in COPD group. In ACO group, the positive rate of each items necessary to confirm the features of BA was 30 to 70%. Table 4 shows the results of a comparison of patient characteristics and laboratory data from patients with COPD and ACO. Of the 108 patients, 95 (88.0%) patients were male. The majority (97 patients, 89.8%) of chief complaints for visits to our institute were evaluation of preoperative pulmonary function, and there were only 6 (5.6%) patients who visited for respiratory symptoms such as wheezes and shortness of breath. There were no significant differences in age, sex, body mass index (BMI), and smoking status. Among the features of BA, the peripheral blood eosinophil counts were signifi-

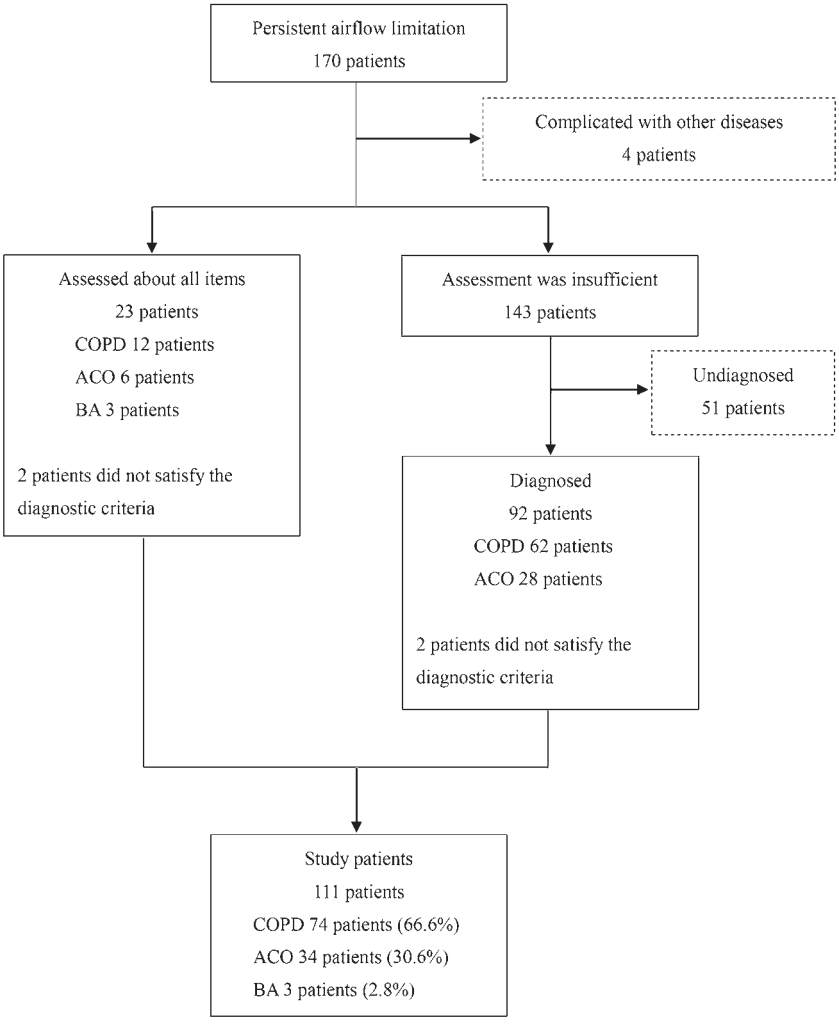

Figure 1
The number of patients included in this study and the prevalence of COPD, ACO, and BA

Table 2. The implementation rate of medical interviews and examinations necessary to confirm the features of COPD and BA

	n = 166
Features of COPD, n (%)	
1. Smoking history or equivalent exposure to air pollution	166 (100)
2. Emphysematous changes on high-resolution CT	149 (89.8)
3. Decreased gas exchange (%DLco < 80% or %DLco/V_A < 80%)	100 (60.2)
Features of BA, n (%)	
1. Variable or paroxysmal clinical symptoms	144 (86.7)
2. A documented history of asthma	147 (88.6)
3. FeNO > 35 ppb	156 (94.0)
4-1. A history of perennial allergic rhinitis	78 (47.0)
4-2. Airway reversibility (FEV_1 > 12% and > 200ml)	166 (100)
4-3. Peripheral blood eosinophils > 5% or > 300 cells/μl	161 (97.0)
4-4. Elevated IgE level (total or allergen-specific IgE)	41 (24.7)

Abbreviations : n, number ; COPD, chronic obstructive pulmonary disease ; CT, Computed Tomography ; DLco, diffusing capacity of carbon monoxide ; V_A, alveolar volume ; BA, bronchial asthma ; FeNO, fraction of exhaled nitric oxide ; FEV_1, forced expiratory volume in 1 second ; IgE, Immunoglobulin E

Table 3. The positive rate of each item necessary to confirm the features of COPD and BA

	Over all	COPD	ACO
Features of COPD, n (%)			
1. Smoking history or equivalent exposure to air pollution	102/108 (94.4%)	71/74 (95.9%)	31/34 (91.2%)
2. Emphysematous changes on high-resolution CT	57/95 (60%)	43/67 (64.2%)	14/28 (50%)
3. Decreased gas exchange (%DLco < 80% or %DLco/V_A < 80%)	56/69 (81.2%)	38/46 (82.6%)	18/23 (78.3%)
Features of BA, n (%)			
1. Variable or paroxysmal clinical symptoms	27/105 (25.7%)	4/72 (5.6%)	23/33 (69.7%)
2. A documented history of asthma	18/105 (17.1%)	0/73 (0%)	18/32 (68.8%)
3. FeNO > 35 ppb	24/103 (23.3%)	2/71 (2.8%)	22/32 (68.8%)
4-1. A history of perennial allergic rhinitis	9/61 (14.8%)	1/43 (2.3%)	8/18 (44.4%)
4-2. Airway reversibility (FEV_1 > 12% and > 200ml)	18/108 (16.7%)	7/74 (9.5%)	11/34 (32.4%)
4-3. Peripheral blood eosinophils > 5% or > 300 cells/μl	30/106 (28.3%)	9/74 (12.2%)	21/32 (65.6%)
4-4. Elevated IgE level (total or allergen-specific IgE)	23/54 (42.6%)	15/36 (41.7%)	10/18 (55.6%)

Abbreviations : n, number ; COPD, chronic obstructive pulmonary disease ; CT, Computed Tomography ; DLco, diffusing capacity of carbon monoxide ; V_A, alveolar volume ; BA, bronchial asthma ; FeNO, fraction of exhaled nitric oxide ; FEV_1, forced expiratory volume in 1 second ; IgE, Immunoglobulin E

cantly higher in ACO than in COPD, and the serum IgE was also higher in ACO than in COPD ; however, there was no statistical difference in this study. Of the pulmonary function tests, the following parameters were significantly lower in ACO than in COPD patients : FEV_1/FVC, peak expiratory flow (PEF) (%predicted), maximal mid-expiratory flow (MMF) (%predicted), maximum expiratory flow at 50% (MEF_{50}) (%predicted) and at 75% (MEF_{75}) (%predicted). FeNO and the reversibility after SABA, included in the features of BA, were significantly higher in ACO than in COPD patients. The data for respiratory impedance is shown in Table 5. R5, R20, and R5-R20 were overall higher in ACO than in COPD patients and significantly different at the inspiratory phase. Furthermore, X5 was lower and ALX was higher in ACO than in COPD patients and were significantly different at the inspiratory phase.

DISCUSSION

This is the first report to investigate the prevalence and clinical features of ACO in patients that were definitively diagnosed according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018". In this study, about 30% of the patients with persistent airflow limitation shared clinical features of both BA and COPD and satisfied the diagnostic criteria of ACO. There was no significant difference between COPD and ACO patients for patient characteristics including sex, age, BMI, and smoking status. In terms of pulmonary function tests, FEV_1/FVC, PEF, MMF, MEF_{50} and MEF_{75} were significantly lower in ACO than in COPD patients. Regarding respiratory impedance, R5, R20, R5-R20, and ALX were significantly higher and X5 was significantly lower in ACO than in COPD patients. These results suggested that the airway obstruction is more prominent in ACO than in COPD patients.

BA and COPD are both obstructive pulmonary diseases that can cause common respiratory symptoms such as cough, wheezing, and dyspnea. Although both diseases are characterized by chronic airway inflammation and various extent of airflow limitations, the pathogenesis, pathophysiology, and clinical features are different. BA is characterized by variable respiratory symptoms and variable expiratory airflow limitation triggered by factors such as allergen or irritant exposure, viral infections, exercise, and change in weather. Although BA is a heterogenous disease and the underlying disease process is different in individuals, it is characterized by predominantly eosinophilic inflammation involving type-2 helper T lymphocytes and mast cells(1, 16). On the other hand, COPD is characterized by persistent respiratory symptoms and irreversible airflow limitation caused by significant exposure to noxious substances such as tobacco smoke. COPD is characterized by predominantly neutrophilic inflammation involving type-1 helper T lymphocytes and macrophages(2, 17). Because of these differences in clinical features, BA and COPD are recognized as essentially distinct diseases. However, it has been known that some patients have clinical features of both BA and COPD, and it is sometimes difficult to clearly distinguish these diseases. In 2014, the Joint Committee of GINA and GOLD proposed the term "asthma-COPD

Table 4. Comparison of patient characteristics and laboratory data in patients with COPD and ACO

	Over all n = 108	COPD n = 74	ACO n = 34	P value
Age, years, median (range)	70 (40-88)	71 (49-88)	68 (40-77)	0.07
Sex male, n (%) female, n (%)	95 (88.0) 13 (12.0)	64 (86.5) 10 (13.5)	31 (91.2) 3 (8.8)	0.49
BMI, kg/m^2	22.8 ± 3.0	22.9 ± 3.2	22.8 ± 2.8	0.75
Smoking history yes/no pack-years	102/6 49.3 ± 28.1	71/3 49.8 ± 26.3	31/3 47.5 ± 32.1	0.38 0.37
Peripheral blood eosinophil counts, mm^3 (COPD n = 74, ACO n = 32)	237.8 ± 257.6	175.5 ± 178.3	383.2 ± 346.0	< 0.01
Total serum IgE, IU/ml, median (range) (COPD n = 26, ACO n = 11)	298 (7-8632)	249.5 (7-1779)	583 (28-8632)	0.10
Chief complaints, n (%) Evaluation of preoperative pulmonary function Abnormal pulmonary function Respiratory symptoms	 97 (89.8) 5 (4.6) 6 (5.6)	 69 (94.6) 3 (4.0) 2 (1.4)	 28 (79.4) 2 (5.9) 4 (14.7)	0.11
Pulmonary function (Pre-bronchodilator)				
FVC, %predicted	104.9 ± 18.9	106.3 ± 16.1	102.1 ± 23.7	0.22
FEV_1, %predicted	77.2 ± 18.3	80.5 ± 16.0	70.4 ± 21.0	0.13
FEV_1/FVC, %	58.8 ± 7.6	60.6 ± 6.5	55.2 ± 8.5	< 0.01
RV, %predicted (COPD n = 47, ACO n = 23)	122.9 ± 24.7	120.9 ± 22.0	126.7 ± 29.3	0.11
TLC, %predicted (COPD n = 47, ACO n = 23)	110.1 ± 13.5	110.0 ± 12.9	110.3 ± 14.8	0.98
DLco, %predicted (COPD n = 47, ACO n = 23)	63.5 ± 16.6	64.2 ± 16.9	62.2 ± 16.3	0.50
DLco/VA, %predicted (COPD n = 47, ACO n = 23)	82.5 ± 19.4	83.0 ± 17.5	81.7 ± 23.1	0.77
PEF, %predicted	75.6 ± 21.9	78.7 ± 20.2	69.0 ± 24.2	0.04
MMF, %predicted	25.7 ± 10.2	27.5 ± 10.2	21.8 ± 9.4	0.02
MEF_{50}, %predicted	35.7 ± 15.0	38.4 ± 14.5	30.2 ± 14.8	0.03
MEF_{75}, %predicted	20.5 ± 10.1	22.2 ± 11.1	16.8 ± 6.2	0.02
Reversibility to beta-2 agonists, ml	136.6 ± 110.6	107.9 ± 90.6	196.3 ± 125.2	< 0.01
FeNO, ppb (COPD n = 70, ACO n = 32)	31.7 ± 26.4	20.8 ± 8.6	55.4 ± 35.4	< 0.01

Abbreviations : n, number ; COPD, chronic obstructive pulmonary disease ; ACO, asthma-COPD overlap ; BMI, body mass index ; IgE, Immunoglobulin E ; FVC, forced vital capacity ; FEV_1, forced expiratory volume in 1 second ; RV, residual volume ; TLC, total lung capacity ; DLco, diffusing capacity of carbon monoxide ; V_A, alveolar volume ; PEF, peak expiratory flow ; MMF, maximal mid-expiratory flow ; MEF_{50}, maximum expiratory flow at 50% of FVC ; MEF_{75}, maximum expiratory flow at 75% of FVC ; FeNO, fraction of exhaled nitric oxide

Table 5. Comparison of respiratory impedance in patients with COPD and ACO

	COPD (n = 74)	ACO (n = 34)	P value
R5, $cmH_2O/L/s$			
Whole breath	3.6 ± 1.5	4.1 ± 2.4	0.05
Inspiratory phase	3.1 ± 1.3	4.0 ± 1.9	0.02
Expiratory phase	4.0 ± 1.8	5.0 ± 3.1	0.12
R20, $cmH_2O/L/s$			
Whole breath	2.7 ± 1.1	3.4 ± 1.6	0.05
Inspiratory phase	2.6 ± 1.0	3.2 ± 1.4	0.04
Expiratory phase	2.9 ± 1.2	3.6 ± 1.9	0.10
R5-R20, $cmH_2O/L/s$			
Whole breath	0.8 ± 0.5	1.1 ± 0.9	0.18
Inspiratory phase	0.5 ± 0.4	0.8 ± 0.6	0.03
Expiratory phase	1.1 ± 0.7	1.4 ± 1.2	0.39
X5, $cmH_2O/L/s$			
Whole breath	-1.0 ± 1.0	-1.5 ± 1.7	0.12
Inspiratory phase	-0.7 ± 0.5	-1.1 ± 0.8	0.04
Expiratory phase	-1.4 ± 1.6	-2.0 ± 2.9	0.22
Fres, Hz			
Whole breath	10.7 ± 4.3	12.6 ± 4.8	0.06
Inspiratory phase	9.5 ± 3.1	11.4 ± 4.6	0.06
Expiratory phase	12.0 ± 5.8	13.8 ± 5.7	0.11
ALX, $cmH_2O/L/s{\cdot}Hz$			
Whole breath	7.0 ± 9.5	10.0 ± 14.0	0.14
Inspiratory phase	3.3 ± 3.4	6.2 ± 7.6	0.04
Expiratory phase	9.8 ± 15.3	14.4 ± 24.1	0.17

Abbreviations : n, number ; COPD, chronic obstructive pulmonary disease ; ACO, asthma-COPD overlap ; R5, respiratory resistance at 5Hz ; R20, respiratory resistance at 20Hz ; X5, respiratory reactance at 5Hz ; Fres, resonant frequency ; ALX, low-frequency reactance area

overlap syndrome (ACOS)"(6), which is now called "asthma-COPD overlap (ACO)"(7). The Japanese Respiratory Society made "The Japanese Respiratory Society Guidelines for the Management of ACO 2018" that is the first unified diagnostic criteria in Japan (13, 14).

Although there have been many reports about the epidemiology of ACO, the prevalence of ACO was widely varied due to the difference in definition, population characteristics, and study design. In a Japanese survey, the prevalence of ACO was also quite different and ranged from 0.9 to 49.7%(12, 18-29). In the cross-sectional study in Hisayama, Japan, Matsumoto *et al.* investigated the prevalence of ACO among the general residents over 40 years old. They defined ACO as a not fully reversible airflow limitation (FEV_1/FVC < 70% after inhalation of SABA) with variable airflow limitation (increase of 200 ml and 12% or more in FEV_1 after inhalation of SABA) and with a clinical history suggestive of asthma. Their prevalence of ACO was only 0.9%(18). Kitaguchi *et al.* retrospectively investigated the prevalence of ACO among the population with airway obstruction. They diagnosed ACO using a combination of persistent airflow limitation (FEV_1/FVC < 70% after inhalation of SABA), smoking history, and asthmatic symptoms. They showed that the prevalence of ACO is 18.1%(19). In the Hokkaido COPD cohort study in Japan, Suzuki *et al.* investigated the prevalence of ACO that was diagnosed using asthma-like features such as bronchodilator reversibility ($\Delta FEV_1 \geqq 12\%$ and 200 ml after inhalation of SABA), blood eosinophilia (peripheral blood eosinophil counts ≧ 300 cells/μl), and/or atopy (positive specific IgE for any inhaled antigen). Their prevalence of ACO was 49.7% among the COPD patients who had not been clinically diagnosed by physicians as having asthma(20). In our study, the prevalence of ACO diagnosed according to the Japanese Respiratory Society guideline was 30.6% among the population with persistent airflow limitation, and this result was relatively higher compared to a previous study for similar patients(19). In the Japanese Respiratory Society guideline, several items such as FeNO, peripheral blood eosinophils, serum IgE, and a history of perennial allergic rhinitis, and the suspected existence of allergic airway inflammation are included in the diagnostic criteria as features of asthma. Therefore, the patients potentially suspected of having asthma were diagnosed as having ACO, and the prevalence of ACO was higher than in the previous study.

There have also been many reports about the clinical features of ACO. In Japan, the main cause of COPD is tobacco smoke, so the gender of patients with ACO is predominantly male, similar to the gender of those with a smoking habit(18-29). The prevalence of COPD is well known to increase with age, so the prevalence of ACO generally increases as the age rises ; thus, ACO patients are generally older than BA patients(23, 24). However, there have been reports that the age of ACO patients was no different from that of COPD patients(19-22, 25) and reports that ACO patients were younger than COPD patients(18, 24, 26, 27). The previous studies have shown the following clinical features of ACO in comparison with COPD : the frequency of exacerbations is higher(30, 31), health-related quality of life (QOL) is more impaired(32), and the decline of lung function is higher(33). On the other hand, some studies showed that the pulmonary function of ACO patients is no different compared to that of COPD patients, and the decline of lung function in ACO patients is inversely lower than in COPD patients (19, 34). In our study, there was no significant difference in sex, age, BMI, and smoking status between COPD and ACO patients. However, most patients were elderly men who visited our institute for evaluation of preoperative pulmonary function, and there were few patients who complained of respiratory symptoms. More studies in other populations are necessary to compare the difference in age, sex, and symptoms among diseases. On pulmonary function testing, the FEV_1/FVC, PEF, MMF, MEF_{50}, and MEF_{75} were significantly lower in ACO than in COPD patients. In terms of respiratory impedance in ACO versus COPD patients, the R5, R20, R5-R20 and ALX were significantly higher, and the X5 was significantly lower. Although BA and COPD are both obstructive pulmonary diseases characterized by chronic airway inflammation, their features of airflow limitation and structural alterations are different. In BA, the variable airflow limitation is caused by bronchoconstriction, airway mucosal edema, airway mucus hypersecretion, and airway remodeling accompanied by the subepithelial fibrosis under the basement membrane, smooth muscle hypertrophy, and submucosal gland hyperplasia(1, 16). On the other hand, in COPD patients, the persistent airflow limitation is caused by a mixture of narrowing of small airways and parenchymal destruction that leads to the loss of alveolar attachments to the small airways and decreases of lung elastic recoil(2, 17). In ACO patients who shared clinical features of both BA and COPD, the degree of airflow limitation is theoretically higher than in BA and COPD patients. The results of our study are consistent with this idea.

To determine the appropriate treatment strategy in the patients with persistent airflow limitation, it is important to confirm whether there are asthmatic features and to distinguish ACO from COPD. In other words, the treatment strategies of COPD and BA are quite different. The mainstay of COPD maintenance therapy is bronchodilators such as long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) (2, 17). The efficacy of inhaled corticosteroids (ICS) in COPD patients is controversial (35-41). In terms of adverse effects, regular use of ICS may increase the risk of pneumonia, especially in those with severe diseases(41, 42). Therefore, ICS is not recommended for daily use and is considered for add-on therapy in the COPD patients with repeated exacerbations or peripheral blood eosinophilia(38, 39). On the other hand, the mainstay of BA maintenance therapy is ICS, and regular use of only a bronchodilator such as SABA and LABA is contraindicated because it may enhance airway hyperresponsiveness and adversely affect a prognosis(1, 16). In ACO that is a coexistence of COPD and BA, it is important to treat with ICS according to BA treatment recommendations and to avoid treatment with a bronchodilator alone(43). In clinical practice, a LABA or LAMA is often simultaneously added to improve airway obstruction and to relieve symptoms(44). In the current study, the patients diagnosed as having ACO have been mainly treated with ICS+LABA. In the near future, we plan to investigate the therapeutic efficacies, rate of exacerbations, and long-term prognosis in ACO patients compared with COPD patients.

Our study has several limitations. First, it was a single-center retrospective study of a limited number of patients, and investigations in other populations are needed to confirm the epidemiology and clinical features of ACO. In our study, most patients were elderly men who visited our institute for evaluation of preoperative pulmonary function, and we could not appropriately compare the difference in age, sex, and symptoms among diseases. In addition, there were few BA patients, and we could not evaluate the clinical features of BA compared with COPD and ACO. In this study, the majority of patients had a smoking history of 10 pack-years or more. In the Japanese Respiratory Society Guidelines for the Management of ACO 2018, the patients with persistent airflow limitation having smoking history is automatically satisfied the features of COPD. We strictly diagnosed the patients according to the guidelines, and almost all patients were satisfied the features of COPD due to having smoking history and diagnosed as COPD or ACO. In the current guidelines, when patients have smoking history, we cannot distinguish BA with persistent airflow limitation from ACO. In regard to this point, the diagnostic criteria of ACO may be capable for revise. Second, in many patients, medical interviews and examinations necessary to confirm the features of BA and COPD were insufficient, and we could not definitively

diagnose according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018". In particular, in our study, evaluations of decreased gas exchange, a history of perennial allergic rhinitis, and serum or specific IgE were insufficient. In this study, the majority of chief complaints for visiting to our institute were evaluation of preoperative pulmonary function, and there were few patients who visited for respiratory symptoms. Moreover, the follow-up periods were short and visit numbers are small. We presume that the primary reason of many deficits of data is due the low rate of symptomatic patients and insufficiency of follow-up. To confirm the exact prevalence of ACO in the patients with persistent airflow limitation, we should evaluate all items necessary to confirm the features of BA and COPD regardless of respiratory symptoms. And repeatable evaluation of the features of BA, i.e., peripheral blood eosinophil counts, serum IgE levels, specific IgE, FeNO levels and bronchial reversibility test must not be forgotten. Third, although it is important to clarify which item is most useful to differentiate ACO from COPD, we could not exactly evaluate due to the many data deficits. In COPD group, there were few patients with variable or paroxysmal clinical symptoms, a documented history of asthma, high level of FeNO, and a history of perennial allergic rhinitis. Therefore, when patients satisfy these items, they may be more likely to be ACO than COPD alone. However, even in ACO group, the positive rate of each item necessary to confirm the features of BA was only 30 to 70%. Therefore, even if these items are not satisfied, the possibility of ACO cannot be denied and it is necessary to comprehensively diagnose using all items. Finally, the follow-upperiod was only one year and a half at the longest, and we could not evaluate the exacerbation rate of ACO compared to COPD. To confirm the prognosis of ACO compared to COPD, we need to prospectively follow up the patients definitively diagnosed in this study. However, there have been no reports about the prevalence and clinical features of ACO among the patients definitively diagnosed according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018". In the patients with persistent airflow limitation, we showed that about 30% of patients met the diagnostic criteria of ACO, and ACO patients had lower lung function and higher respiratory impedance compared with COPD patients. In the future, to clarify the epidemiology, clinical features, pathophysiology, and prognosis of ACO, it is essential to accumulate patients definitively diagnosed using the unified diagnosis criteria. When patients with persistent airflow limitation visit the hospital, it is important to investigate in detail regarding the existence of clinical features of BA and COPD and to make a definitive diagnosis according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018".

In conclusion, we showed that about 30% of the patients with persistent airflow limitation shared clinical features of both BA and COPD and satisfied the diagnostic criteria of ACO. ACO patients had lower lung function and higher respiratory impedance compared with COPD patients. To clarify the epidemiology, clinical features, pathophysiology, and prognosis of ACO, it is essential to accumulate the patients that are definitively diagnosed using unified diagnostic criteria.

CONFLICT OF INTERESTS-DISCLOSURE

The authors declare no conflicts of interest associated with this manuscript.

ACKNOWLEDGEMENTS

We would like to thank Yusuke Nakade, Akiko Nakata, Hatsune Mochida (Department of Clinical Laboratory at Kanazawa University Hospital, Kanazawa, Ishikawa, Japan) for their valuable technical assistance in pulmonary function testing.

This research did not receive any specific grant from funding agencies in the public, commercial, or Units.

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