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Real-World Evidence on the Diagnostic and Clinical Characteristics of Asthma in Japanese Patients with COPD: The ACO Japan Cohort Study

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Introduction: The ACO Japan Cohort Study, a multicenter observational study, investigated the proportion of patients with chronic obstructive pulmonary disease (COPD) who met the Japanese Respiratory Society (JRS) asthma–COPD overlap (ACO) diagnostic criteria, characteristics of ACO and non-ACO patients, and the patient transitions between ACO/non-ACO diagnosis over 2 years.

Patients and Methods: Patients with COPD were consecutively enrolled between June and December 2018 and followed up continuously for 2 years. All participating study sites were medical institutions where respiratory specialists routinely conducted medical examinations/tests required for ACO diagnosis.

Results: Among 708 patients with COPD, 101 (14.3%), 118 (16.7%), and 125 (17.7%) were diagnosed with ACO at registration, 1 year, and 2 years, respectively. In total, 22.6% of patients lacked the data necessary for ACO diagnosis throughout the 2 years. Among patients who had the necessary data for ACO diagnosis, 24.7% were diagnosed with ACO at 2 years. More ACO patients had moderate or severe exacerbations in the past year than non-ACO patients at registration (15.8% vs 6.3%, p = 0.049) and 1 year (19.4% vs 7.6%, p = 0.025). ACO patients had a greater decrease in mean forced expiratory volume in one second over 2 years than non-ACO patients (−92.0 vs 43.4 mL). Among patients diagnosed with ACO at registration, 21.4% transitioned to non-ACO after 1 year. Conversely, almost all non-ACO patients at registration remained non-ACO after 1 year.

Conclusion: COPD patients with ACO determined by the JRS criteria had a high risk of exacerbations and a rapid decline in respiratory function, indicating that the JRS criteria for ACO are useful for identifying high-risk COPD patients. Testing necessary for ACO diagnosis is insufficiently performed even in real-world clinical practice of COPD specialists.

Keywords: asthma, chronic obstructive pulmonary disease, exacerbation, FEV_1 decline, inhaled corticosteroid

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and progressive respiratory disease characterized by expiratory airflow limitation that is partially reversible, and with or without alveolar abnormalities.[1] COPD symptoms are persistent, vary in severity, and include dyspnea, cough, and sputum production. Asthma is characterized by airway hyper-responsiveness, airway inflammation, and airflow obstruction; symptoms include cough, dyspnea, and wheezing, although the severity can vary considerably, both day-to-day and year-on-year.[2] The management and prognosis of patients with COPD with asthmatic characteristics vs those with COPD alone differ.[3] Current guidelines for the management of COPD[1] and asthma[2] state that inhaled corticosteroids (ICS) can improve exacerbations and reduce

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mortality in patients with asthmatic components. Therefore, it is important to determine whether a patient with COPD has components of asthma to ensure they receive appropriate treatment.[4–6]

When COPD and asthma coexist, this is referred to as asthma–COPD overlap (ACO).[7] Several criteria have been published for the diagnosis of ACO.[4,8–11] The Japanese Respiratory Society (JRS) ACO Guideline was published in 2018, and the criteria for ACO diagnosis in Japan were established.[11] The ACO Japan Cohort Study[12] was conducted to clarify the real-world status and reported the proportion of patients with ACO (n = 101, 14.3%) who met the JRS ACO diagnostic criteria among patients with COPD (n = 708) at registration, and that there was an inconsistency between the number of patients diagnosed with ACO based on the JRS criteria and that based on the physician's diagnosis.[13] However, the long-term clinical characteristics, diagnosis, and treatment of Japanese patients with ACO based on the JRS criteria in real-world clinical practice have not previously been reported.

The objectives of this 2-year follow-up analysis were to 1) clarify how the proportion of COPD patients who met the JRS ACO diagnostic criteria varied over 2 years in the full analysis set (FAS); 2) identify differences in the characteristics of COPD patients who met/did not meet the JRS ACO diagnostic criteria during the study; and 3) describe the transition of patients between ACO and non-ACO among patients with COPD who had data necessary for ACO diagnosis.

Materials and Methods

Study Design and Patients

The details of the study design have been published previously.[12] Briefly, the ACO Japan Cohort Study was a multicenter, 2-year observational study conducted at 27 sites in Japan. Patients with COPD were enrolled consecutively in each institution between June and December 2018, to avoid selection bias. The 2-year follow-up comprised visits 1 and 2 years after registration.

Table 1 shows the characteristics of COPD and asthma and the examinations and tests used to confirm ACO diagnosis, based on the JRS ACO criteria.[11,14] The study sites comprised medical institutions with respiratory specialists on staff who could perform the specified examinations for ACO diagnosis.

The inclusion and exclusion criteria have been described in detail previously.[12] Patients were enrolled if they were outpatients aged ≥40 years with post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) <70% (basic criteria) and had characteristics of COPD as described in the JRS ACO criteria (Table 1).[11,14] Patients were also required to confirm their anticipated ability to comply with study visits at least once per year.

Among the COPD patient population, those who presented with characteristics of asthma as defined in the JRS ACO criteria (Table 1) were categorized as ACO patients, and their characteristics were evaluated during the 2-year follow-up period. The characteristics of non-ACO and ACO patients were compared.

The Ethical Committee of Tohoku University Hospital approved the study protocol (approval number 2018-2-147-1), and the study was registered at ClinicalTrials.gov under the identifier NCT03577795. All participants provided informed consent before study participation. The study conduct adhered to the Declaration of Helsinki and national and international ethical guidelines for medical and health research involving humans. Medical data were collected, stored, and used in compliance with the Personal Information Protection Act and local and international laws and regulations concerning data protection.

Study Outcomes and Measures

The outcome measures included the proportion of COPD patients who met the ACO criteria at least once at the time of registration and 1 and 2 years of follow-up; the characteristics of ACO/non-ACO patients during the 2-year follow-up; the proportion of patients who transitioned between ACO and non-ACO during the 2-year follow-up; and the reasons for the lack of data necessary for ACO diagnosis at registration. We assessed indicators for ACO diagnosis, which included lung function measures and biomarkers at registration and 1 and 2 years of follow-up, the presence of variable or paroxysmal symptoms, age at onset of asthma, fractional exhaled nitric oxide (FeNO), FEV_1 reversibility, peripheral blood eosinophil count, and immunoglobulin E (IgE).

Table 1 Japanese Respiratory Society Diagnostic Criteria for Asthma and COPD Overlap[11,14]

Basic Criteria **Age ≥40 years and chronic airflow obstruction: post-bronchodilator FEV_1/FVC <70%**	
[Characteristics of COPD] **One item from 1, 2, and 3**	**[Characteristics of asthma]** **Two items from 1, 2, and 3, or** **One item from 1, 2, and 3 and at least two from 4**
1. Smoking history (10 pack-years or more) or career involving significant air pollution or biomass exposure 2. Presence of low attenuation areas on the chest CT demonstrating emphysematous changes 3. Impaired pulmonary diffusing capacity (%D_{LCO} <80% or D_{LCO}/V_A <80%)	1. Variable (diurnally, daily, and seasonally) or paroxysmal respiratory symptoms (cough, sputum, and dyspnea) 2. History of asthma before age 40 years 3. FeNO >35 ppb 4. (1) Concomitant perennial allergic rhinitis (2) Airway reversibility (post-bronchodilator increases in FEV_1 >12% and >200 mL) (3) Peripheral blood eosinophils >5% or >300/μL (4) High IgE level[a] (total IgE or IgE specific to perennial inhalant antigens[b])
1. To be diagnosed as ACO, one item of the characteristics of COPD plus two items from 1, 2, and 3 or one item from 1, 2, and 3, or one and at least two items from criterion 4 of the characteristics of asthma are needed. 2. If the characteristics of COPD alone are present, it is diagnosed as COPD, and if the characteristics of asthma alone are present, it is diagnosed as asthma (without remodeling). 3. If the characteristics of asthma cannot be confirmed when diagnosing ACO, it is important to monitor for the presence of the characteristics of asthma over time. 4. Perennial inhalant antigens include house dust, mites, molds, scales from animals, and feathers, and seasonal inhalant antigens include pollen from trees, plants, and weeds.	

Notes: 1. Disease of differential diagnosis (diffuse panbronchiolitis, congenital sinobronchial syndrome, obstructive panbronchiolitis, bronchiectasis, pulmonary tuberculosis, pneumoconiosis, lymphangioleiomyomatosis, congestive heart disease, interstitial lung disease, and lung cancer) should be ruled out by standard chest x-rays, etc.
2. Respiratory symptoms such as cough, sputum, and dyspnea are variable (diurnally, daily, and seasonally) or paroxysmal in asthma and chronic and continuous in COPD. Adapted from ref. 11 with permission. [a]Determined according to the criteria of each study site. [b]Specific IgE to antigens from dogs, cats, house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), and fungi (*Aspergillus* and *Candida*).
Abbreviations: ACO, asthma–COPD overlap; COPD, chronic obstructive pulmonary disease; CT, computed tomography; D_{LCO}, diffusion capacity for carbon monoxide; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; Ig, immunoglobulin; V_A, alveolar volume.

Statistical Analysis

Details of the sample size calculations for the ACO Japan Cohort Study have been published.[12] In this report, we describe the final analyses conducted using data with a database lock date of 1 September 2021. Numbers and proportions of patients were used to report categorical variables. The chi-square test and Fisher's exact test were used for between-group comparisons. For the proportion of ACO patients, two-sided 95% confidence intervals (CI) of binomial proportions were calculated using the Wilson score method without continuity correction. Summary statistics, including mean (standard deviation [SD]), median (range), quartiles, or frequency, were used for quantitative variables. To compare groups, a pooled *t*-test was used for variables with homogeneity of variance, and the Satterthwaite method for the *t*-test was used for variables with heterogeneity of variance. To calculate rates, Poisson regression was performed. All statistical analyses were exploratory, without adjustments for multiplicity or missing data imputation, and were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient Characteristics

In total, 717 patients were registered. Of these, nine patients were considered ineligible or withdrew consent. Thus, 708 patients were included in the FAS (Figure S1). After enrollment, the 2-year follow-up visits took place until February 2021. Of note, the onset of the COVID-19 pandemic in Japan was in March 2020, with the timing of follow-up visits scheduled according to hospital pandemic response constraints. Table S1 shows the background characteristics of patients in the FAS at registration, updated for this final analysis. The updated background characteristics are similar to

the previously reported characteristics.[12,13] Among patients in the FAS, the majority (90.1%) of patients were male and the mean age was 73.5 years.

Proportion of Patients Diagnosed with ACO at Registration and Over 2 Years

Among 708 patients with COPD, 101 (14.3%) at registration, 118 (16.7%) at 1 year of follow-up, and 125 (17.7%) patients at 2 years of follow-up were diagnosed with ACO (Table 2). At 1 year of follow-up, 5 and 12 patients were newly diagnosed as ACO among non-ACO patients and patients who had been lacking data for ACO diagnosis at registration, respectively. Similarly, at 2 years of follow-up, some patients who were previously non-ACO or lacked data for ACO diagnosis at 1 year were newly diagnosed as ACO. Among patients who had the data necessary for ACO diagnosis, 101/396 (25.5%), 118/478 (24.7%), and 125/507 (24.7%) were diagnosed with ACO. Of note, 160 patients (22.6%) lacked the data necessary for ACO diagnosis throughout the 2 years.

Characteristics of Patients with ACO at Registration and Patients Who Remained Non-ACO for 2 Years

We compared the previously reported characteristics of patients with ACO at registration (even if they did not meet ACO criteria at the later time points due to treatment, ie, they subsequently became patients with COPD only; n = 101)[12] with patients who remained non-ACO for 2 years throughout the follow-up (ie, definitively regarded as non-ACO; n = 79). In terms of characteristics at the time of registration, the patients with ACO at registration were younger, with a mean (SD) age of 71.5 (9.6) years, than the patients with non-ACO for 2 years (74.7 [8.4] years) (p = 0.018). The patients with ACO at registration also had a higher incidence of allergic rhinitis than the patients with non-ACO for 2 years (37 [36.6%] vs 4 [5.1%]; p < 0.001). The patients with ACO at registration had lower incidences of heart failure (3 [3.0%] vs 29 [36.7%]; p < 0.001) and gastroesophageal reflux disease (9 [8.9%] vs 16 [20.3%]; p = 0.029) than the patients with non-ACO for 2 years. The incidences of these comorbidities remained largely unchanged at 1 and 2 years of follow-up in both groups.

The differences in other clinical characteristics between these two groups of patients during the 2-year follow-up are shown in Table 3. The patients with ACO at registration had a greater number of moderate or severe exacerbations in the past year at the time of registration (16 [15.8%] vs 5 [6.3%]; p = 0.049) and at 1 year (19 [19.4%] vs 6 [7.6%]; p = 0.025) than the patients with non-ACO for 2 years. In addition, the patients with ACO at registration showed a trend toward an increased incidence of moderate or severe exacerbations in the past year at the time of registration (17 [0.17 events per patient] vs 5 [0.06]; p = 0.055) and at 1 year (25 [0.26] vs 11 [0.14]; p = 0.094) than the patients with non-ACO for 2 years. At 2 years, there were no significant differences in the rate of exacerbations or the rate of patients who experienced exacerbations. There were no major differences in mean post-bronchodilator FEV_1, post-bronchodilator FEV_1% predicted, or mean post-bronchodilator FEV_1/FVC% at the time of registration or at 1 and 2 years of follow-up between the two groups of patients. The mean (SD) FEV_1 change from registration was greater at 2 years in the patients with ACO at registration than in the patients with non-ACO for 2 years (−92.0 [249.5] mL and 43.4 [208.4] mL, respectively; p = 0.001). Compared with the patients with non-ACO for 2 years, a higher proportion of the patients with ACO at registration were using ICS-containing therapy

Table 2 Proportions of Patients Who Had the Data Necessary for ACO Diagnosis at Least Once During the Study

FAS (N = 708)	At Registration	At 1 Year	At 2 Years
Patients who had data necessary for ACO diagnosis at least once at each time point, n (%)[a]	396 (55.9)	478 (67.5)	507 (71.6)
Patients lacking data necessary for ACO diagnosis at each time point, n (%)[a]	312 (44.1)	214 (30.2)	160 (22.6)
Not visited at each time point, n (%)[a]	N/A	16 (2.3)	41 (5.8)
Patients diagnosed with ACO at least once during the study period	101	118	125
Proportion of patients from the FAS, % (95% CI)[a]	14.3 (11.9–17.0)	16.7 (14.1–19.6)	17.7 (15.0–20.6)
Proportion of patients diagnosed with ACO who had data necessary for ACO diagnosis, %[b]	25.5	24.7	24.7

Notes: Data are n (%) unless otherwise stated. [a]Percentages were calculated using N = 708. [b]Percentages were calculated using N = 396 (registration), N = 478 (at 1 year), and N = 507 (at 2 years).

Abbreviations: ACO, asthma–chronic obstructive pulmonary disease overlap; CI, confidence interval; FAS, full analysis set; N/A, not applicable.

Table 3 Clinical Characteristics of ACO Patients at Registration Compared with Non-ACO Patients During the 2-Year Follow-Up

	Data at Registration			1-Year Data			2-Year Data		
	ACO at Registration[a] (n = 101)	**Non-ACO for 2 Years[b] (n = 79)**	**p-value**	**ACO at Registration[a] (n = 101)**	**Non-ACO for 2 Years[b] (n = 79)**	**p-value**	**ACO at Registration[a] (n = 101)**	**Non-ACO for 2 Years[b] (n = 79)**	**p-value**
Lung function									
Post-BD FEV_1				n = 73			n = 56	n = 76	
mL, mean (SD)	1850.1 (589.2)	1697.7 (586.4)	0.086	1733.8 (556.8)	1675.2 (592.2)	0.531	1807.3 (575.3)	1740.4 (619.5)	0.528
% predicted, mean (SD)	69.2 (20.6)	66.9 (19.8)	0.45	65.3 (16.9)	66.0 (19.8)	0.828	68.2 (17.7)	68.3 (20.2)	0.977
Post-BD FEV_1/FVC				n = 73			n = 56	n = 76	
%, mean (SD)	53.3 (9.9)	52.9 (12.0)	0.785	51.9 (9.4)	53.4 (13.4)	0.439	54.0 (10.7)	53.6 (13.4)	0.849
FEV_1 change from registration				n = 73			n = 56	n = 76	
mL, mean (SD)	N/A	N/A	N/A	−68.8 (365.3)	−22.5 (164.8)	0.324	−92.0 (249.5)	43.4 (208.4)	0.001
Reversibility: improvement rate	n = 61	n = 31		n = 39	n = 29		n = 24	n = 26	
%, mean (SD)	6.4 (7.8)	4.5 (6.4)	0.245	7.7 (10.3)	2.2 (8.1)	0.022	6.6 (6.4)	4.5 (4.3)	0.182
ICS[c] use				n = 96			n = 90		
n (%)	78 (77.2)	19 (24.1)	<0.001	77 (80.2)	25 (31.6)	<0.001	72 (80.0)	27 (34.2)	<0.001
Moderate or severe exacerbation in the past year				n = 98			n = 90		
Total exacerbation events, n (event per patient)	17 (0.17)	5 (0.06)	0.055	25 (0.26)	11 (0.14)	0.094	10 (0.11)	6 (0.08)	0.461
Patients who reported exacerbation, n (%)	16 (15.8)	5 (6.3)	0.049	19 (19.4)	6 (7.6)	0.025	8 (8.9)	6 (7.6)	0.761
Questionnaire score									
CAT				n = 87	n = 75		n = 74	n = 78	
mean (SD)	10.7 (7.8)	9.4 (6.9)	0.242	11.5 (8.6)	7.6 (6.3)	0.001	11.0 (8.2)	9.1 (6.9)	0.127
mMRC				n = 85	n = 85		n = 74	n = 77	
mean (SD)	1.0 (1.0)	1.0 (1.1)	0.92	1.0 (1.0)	1.0 (1.0)	0.414	1.1 (1.1)	1.3 (1.0)	0.299
ACQ		n = 78		n = 87	n = 76		n = 72	n = 76	
mean (SD)	0.9 (1.0)	0.2 (0.4)	<0.001	0.8 (1.0)	0.3 (0.6)	<0.001	0.7 (1.0)	0.3 (0.5)	0.001
Biomarkers									
FeNO	n = 86	n = 72		n = 60	n = 64		n = 42	n = 60	
ppb, mean (SD)	47.8 (35.5)	20.5 (9.4)	<0.001	43.5 (38.0)	20.2 (12.1)	<0.001	37.4 (26.7)	18.0 (8.2)	<0.001
Peripheral blood eosinophil count	n = 92	n = 77		n = 63	n = 76		n = 54	n = 75	
cells/μL, mean (SD)	392.8 (472.2)	182.4 (126.5)	<0.001	297.2 (311.3)	191.3 (165.9)	0.017	244.8 (197.6)	165.7 (122.4)	0.011
Peripheral blood eosinophil ratio	n = 92	n = 77		n = 63	n = 76		n = 54	n = 75	
%, mean (SD)	5.9 (6.0)	3.2 (2.2)	<0.001	4.8 (4.6)	3.3 (2.8)	0.022	4.1 (3.3)	2.9 (2.2)	0.022

Notes: [a]Patients who met the diagnostic criteria for ACO at registration. [b]Patients who did not meet the diagnostic criteria for ACO throughout the 2-year follow-up period. [c]As monotherapy or any combination.

Abbreviations: ACO, asthma–COPD overlap; ACQ, asthma control questionnaire; BD, bronchodilator; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; mMRC, modified Medical Research Council questionnaire; N/A, not applicable; SD, standard deviation.

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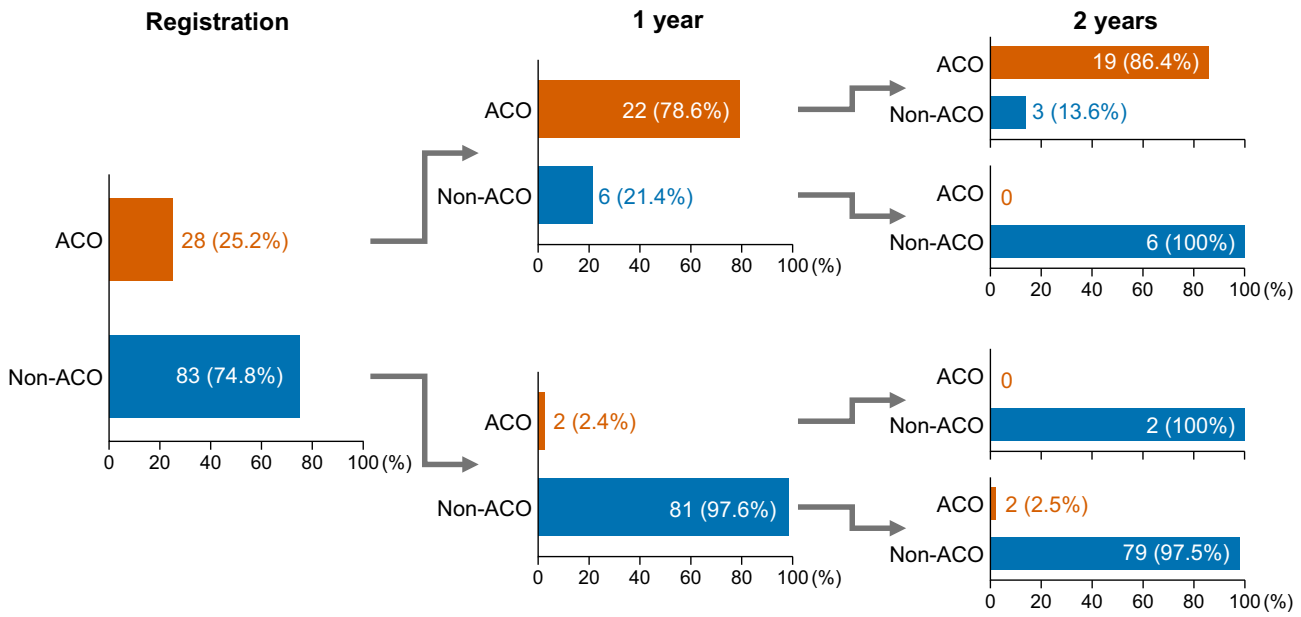

Figure 1 Transition of 111 patients with the data necessary to meet the JRS ACO diagnosis criteria between ACO and non-ACO status at registration, 1 year, and 2 years during the study.
Abbreviation: ACO, asthma–chronic obstructive pulmonary disease overlap.

(monotherapy or any combination) at the times of registration (77.2% vs 24.1%; $p < 0.001$), at 1 year (80.2% vs 31.6%; $p < 0.001$), and at 2 years (80.0% vs 34.2%; $p < 0.001$).

Transition of Patients Between ACO and Non-ACO

Figure 1 shows the transition of 111 patients who had the data necessary for ACO diagnosis at all three time points (ie, at registration and 1 and 2 years of follow-up). Of the 28 patients who met the ACO diagnostic criteria at registration, 78.6% (22/28) retained the same status, and 21.4% (6/28) transitioned to non-ACO status at 1 year. At the 2-year follow-up, of the 22 patients who met ACO criteria at 1 year, 86.4% (19/22) maintained the same status, and 13.6% (3/22) transitioned to non-ACO status, while all six patients who had transitioned to non-ACO status at 1 year remained as non-ACO at 2 years. Among the six patients who transitioned from ACO to non-ACO status, no treatment changes were recorded in four patients, and ICS was added in the remaining two patients. Of the 83 (74.8%) patients who did not meet the ACO diagnostic criteria at registration, 81 (97.6%) remained as non-ACO, and two (2.4%) transitioned to ACO at 1 year. Of the 81 (97.6%) patients who did not meet the ACO diagnostic criteria at 1 year, 79 (97.5%) maintained the same status, and two (2.5%) transitioned to ACO at 2 years.

Table 4 Reason for Lack of Data Required for the Diagnosis of ACO at the Time of Registration

Patients Lacking Data for ACO Diagnosis at Registration (n = 312)	
The patient was assessed as not having ACO based on clinical features	100 (32.1)
The patient was assessed as having ACO based on clinical features	85 (27.2)
Examinations/tests had already been performed (≥1 year before registration)	47 (15.1)
Other	44 (14.1)
Examinations/tests could not be performed due to the examination/testing system of the study site (eg, reservation is required)	32 (10.3)
Examinations/tests could not be performed due to the patient's refusal	4 (1.3)

Note: Data are n (%).
Abbreviation: ACO, asthma–chronic obstructive pulmonary disease overlap.

Reasons for Lacking the Data Necessary for ACO Diagnosis at the Time of Registration

Table 4 summarizes the main reasons for lacking the data necessary for ACO diagnosis at registration. Among the 312 patients who lacked these necessary data, the most frequent reasons were as follows: patients were assessed as not having ACO based on clinical features (32% [n = 100]); patients were evaluated as having ACO based on clinical features (27.2% [n = 85]); and examinations/tests had previously been performed more than 1 year before registration (15.1% [n = 47]).

Discussion

This is the first observational study to continuously monitor ACO diagnosis patterns based on JRS criteria,[11] over 2 years of follow-up, depicting the real-world situation of COPD patients at multiple facilities with respiratory specialists in Japan. The percentage of patients in the FAS diagnosed with ACO remained relatively stable during 2 years (between 14.3% and 17.7%). Similar results regarding stability, but higher prevalence, were observed in patients with the data necessary for ACO diagnosis throughout the study period (between 24.7% and 25.5%), indicating the robustness of the finding. Our study also revealed that approximately one-fifth of patients still lacked the data necessary for ACO diagnosis at any of the evaluated time points during 2 years. Therefore, from the perspective of public health implications, our findings suggest that not all tests/examinations required for the diagnosis of an asthma component in patients with COPD are conducted or considered essential even by specialists in real-world clinical practice.

The criteria for ACO differ among the different guidelines published by different societies (eg, JRS,[11] ATS roundtable,[8] Global Initiative for Chronic Obstructive Lung Disease and Global Initiative for Asthma,[1,2,4] and Spanish asthma and COPD guidelines[10]). The reported prevalence of ACO differs between the different study types, the ACO criteria used, and the populations evaluated. For example, in one analysis, the prevalence of ACO according to different diagnostic criteria was reported to range between 12.9% and 24.7%.[15] ACO prevalence has also been found to vary widely in the general population (0.9–11.1%), COPD patient populations (4.2–66.0%), and asthma patient populations (11.1–61.0%).[16] In the present study, the proportion of patients with ACO was determined based on JRS ACO criteria and was between 14.3% and 17.7%. These proportions were within the ranges reported previously.

We found that ACO patients had a higher frequency of moderate or severe exacerbations in the past year compared with non-ACO patients at registration. The risk of exacerbation events between ACO and non-ACO patients has been inconsistent in the literature: many previous studies have shown that exacerbations were more frequent in ACO patients,[16] whereas some previous studies, including the Hokkaido COPD cohort study in Japan, reported no difference in exacerbation frequency between COPD patients with and without asthmatic components.[3,16] The discrepancy between the risk of exacerbation in these studies may be because of the differences in the study populations, the differences in ACO criteria used, and differences in the treatment situation. The population in the Hokkaido COPD cohort study consisted of COPD patients who were not clinically considered to have asthma,[3] whereas the present study included COPD patients regardless of their clinical asthma diagnosis, and we revealed that the JRS ACO criteria may help identify patients at high risk of ACO among the COPD patient population. Furthermore, at 2 years' follow-up, we noted that the incidence of exacerbations in ACO patients was similar to that in non-ACO patients, which may be because of the lower number of reported exacerbations in ACO patients at this time point. It is likely that countermeasures for the COVID-19 pandemic (eg, social distancing, masks, and other infection-prevention measures) might have reduced the number of exacerbations, as reported in other studies conducted at the same time in Japan and elsewhere.[17–20]

In our study, FEV_1 decreased greatly in the ACO group but remained sustained in the non-ACO group. This finding differs from that of a previous study conducted in Japan with a population that was similar to that of the present study.[3] In the previous study, the FEV_1 decline was similar in patients with asthma-like features and those without asthma-like features. In another published study conducted in Denmark, the FEV_1 decline was less rapid in ACO patients with early asthma onset and more rapid in ACO patients with late asthma onset.[21] However, these comparisons should be interpreted with caution given the differences between the studies (eg, number of study sites, region, study period), which may have led to differences in the treatment options. Our 2-year data showed a rapid FEV_1 decline in COPD patients who met JRS ACO criteria. This may have been due to a greater number of exacerbations in these patients.

We also observed that the proportion of ACO patients using ICS-containing therapy remained stable (approximately 80%) at all evaluated time points. Current guidelines[1,11] recommend that patients diagnosed with ACO at least once should be considered to have ACO and be appropriately treated using ICS-containing therapies; these have been shown to reduce the risk of COPD exacerbations.[22,23] However, not all ACO-diagnosed patients were receiving ICS-containing therapies in our study, suggesting that even respiratory specialists are not treating ACO patients as recommended by the guidelines.[1,11] The reason why approximately 20% of ACO patients did not receive ICS-containing therapy may be because many Japanese COPD patients are older and have a lower body mass index compared with those in Western countries. Elderly or lower BMI patients are relatively susceptible to pneumonia, and ICS use increases the risk of pneumonia in COPD patients.[24,25] This may explain why ICS-containing therapy is prescribed relatively carefully to COPD patients in Japan. In previous worldwide studies of COPD patients, the proportion of patients receiving ICS-containing therapy at baseline was lower in the Japanese population compared with that in the global population.[26,27]

At all three time points, we evaluated whether patients with data necessary for ACO diagnosis had transitioned between ACO and non-ACO status, per the JRS criteria. In patients who were diagnosed as non-ACO at baseline, the diagnosis was maintained over time with low transition rates from non-ACO to ACO (approximately 2.5%). These transition rates were lower than those observed in a COPD cohort in Spain, which found that approximately 10% of non-ACO patients transitioned to ACO after 1 year of follow-up.[9] However, the Spanish study applied different ACO diagnostic criteria, which may explain the variability between these reported transition rates. While most of the parameters assessed in the JRS ACO diagnostic criteria are relatively stable over time, FeNO levels and peripheral blood eosinophil counts are known to change seasonally, with allergen exposure, and following the use of ICS-containing therapies.[28–31] Our results showed the stability of ACO diagnoses according to the JRS criteria over at least 2 years.

In the present study, six patients transitioned from ACO to non-ACO, as a variety of symptoms in this group that were originally present were resolved. No changes in treatment were reported in four of these patients, and treatment with ICS was added in two patients. In these two patients, asthma symptoms improved after adding ICS, which may explain why the diagnosis for these patients was converted from ACO to non-ACO. The reasons for transition are unclear in the remaining four patients.

We acknowledge the limitations of our study. Enrollment was limited to patients from sites where tests used for ACO diagnosis were conducted in routine clinical practice, and specialists treated the registered patients in a relatively well-equipped environment. This may have affected patient demographics and clinical outcomes, limiting the application of this study's results to patient populations in other medical facilities, including those that cannot perform the required tests. As this study was restricted to outpatients who could visit the study sites regularly, the results of this study cannot be extrapolated to patients who make irregular visits to primary care facilities or as inpatients. The study included both treatment-naïve patients and those who had received prior drug treatment and the proportion of patients who underwent examinations or tests was evaluated only within 1 year prior to registration. Thus, there may have been patients with ACO who did not meet the ACO diagnostic criteria due to prior clinical intervention. The data for the follow-up period consisted of patients who could be followed up, which may have resulted in a selection bias. Finally, the number of patients was not very large, and changes in lung function were observed for only 2 years. A longer-term study with more patients is warranted in the future.

Conclusion

Findings from this prospective, 2-year, multicenter cohort study revealed that COPD patients with ACO determined by the JRS criteria had a higher risk of exacerbations and faster FEV_1 decline than non-ACO patients, indicating that the JRS criteria for ACO are useful for identifying high-risk COPD patients. Testing necessary for ACO diagnosis is insufficiently performed even in the real-world clinical practice of COPD specialists.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Compliance with Ethics Guidelines

This study was conducted following the Declaration of Helsinki and all applicable national and international ethical guidelines for medical and health research involving human participants. The Ethics Committee of Tohoku University Hospital (approval reference: 2018-2-147-1) approved all study documentation. All participants gave informed consent before registration. Medical data were collected and stored in compliance with the relevant laws/regulations concerning data protection and the Personal Information Protection Act. This study was registered with ClinicalTrials.gov (identifier: NCT03577795).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; and took part in drafting, revising, or critically reviewing the article. All authors, except for Shu Hashimoto who passed away before the manuscript draft was finalized, gave approval for the final version to be published, and hold accountability for the accuracy and integrity of the findings presented.

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Disclosure

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