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Invited Review Article

Epidemiology of asthma-chronic obstructive pulmonary disease overlap (ACO)

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COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; CT, computed tomography

ABSTRACT

The term “asthma-COPD overlap” (ACO) has been applied to the condition in which a person has persistent airflow limitation with clinical features of both asthma and COPD. The certain definition and diagnostic criteria for ACO have not yet been established, and ACO prevalence has varied widely in studies: from 0.9% to 11.1% in the general population, from 11.1% to 61.0% in asthma patients, and from 4.2% to 66.0% in COPD patients. Furthermore, the frequency of exacerbations and prognosis in ACO patients have not been clearly demonstrated. Although ACO consists with several subgroups of patients with distinct clinical and pathophysiological features, it would be important to propose a standardized definition of and/or diagnostic criteria for ACO based on biomarkers and objective measures, even if it is tentative. It may lead cohort studies with large population or clinical trials around the world.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are typically considered different diseases with pathophysiological mechanisms as well as unique epidemiological features. Asthma is recognized as an allergic disease, usually starting in childhood and characterized by airway hyperresponsiveness leads to reversible airflow obstruction.¹ In contrast, COPD is typically caused by tobacco smoking, develops after the fourth decade of life and characterized by progressive and irreversible airflow obstruction.² Pathobiologically, asthma is characterized predominantly by eosinophilic inflammation and inflammation involving CD4⁺ T-lymphocytes, whereas COPD is characterized predominantly by

neutrophilic inflammation and inflammation involving CD8⁺ T-lymphocytes and macrophages.^{3–5} These features allow asthma and COPD to be recognized as distinct disease entities. Nevertheless, in daily clinical practice, it is sometimes difficult to reach a final diagnosis, especially in older patients who have clinical features of both asthma and COPD. Indeed, irreversible obstruction develops over time owing to airway remodelling in some patients with asthma, and some phenotypes in asthma are neutrophilic or combined eosinophilic and neutrophilic; reversible airway obstruction can occur in some patients with COPD, and respiratory viral infections in COPD may trigger eosinophilic inflammation or a type-2 immune response.

It has been recognized that features of asthma and COPD may coexist in patients with irreversible airflow obstruction and asthma-like symptoms. In 1961, Orie *et al.* stated that “bronchitis and asthma may be found in one patient at the same age but as a rule there is a fluent development from bronchitis in youth to a more asthmatic picture in adults, which in turn, develops into bronchitis of elderly patients”.⁶ Many years later, Fletcher *et al.*

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proposed the term “Dutch Hypothesis” to describe the phenomenon of “asthma” becoming “COPD”.⁷ After a while, there were many negative opinions on the “Dutch Hypothesis”, because it was main notion that asthma and COPD are unique conditions with distinct pathophysiologies and separate treatments. Nevertheless, in the 1990s, it was shown that increased airway responsiveness is positively associated with the development of chronic respiratory symptoms, and the “Dutch Hypothesis” has recently been reevaluated.⁸ In clinical practice, Gibson *et al.* described “the overlap syndrome of asthma and COPD” in 2009.⁹ After that, many manuscripts about asthma–COPD overlap were published.

In 2014, a joint project of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) has coined the term “asthma–COPD overlap syndrome” (ACOS), defined as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD.¹⁰ Later, the modified term “asthma–COPD overlap (ACO)” was recommended by GINA/GOLD, because ACOS has often been used as if it was a separate disease and because this condition does not represent a single discrete disease entity. The statement provides a list of common features of asthma and COPD, and a diagnosis of ACO is suggested if there are similar number of features for both asthma and COPD. However, it mentioned that “a specific definition for ACO cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms”,¹⁰ and certain definitions and diagnostic criteria for ACO did not yet existed. Therefore, the prevalence rate of ACO varied widely in previous studies.

In this review, the epidemiology of ACO is described with focussing on definition, diagnostic criteria and population. Furthermore, in this review, the term for “asthma and COPD overlap” is unified to ACO.^{1,11}

Definition and diagnostic criteria for ACO

As no generally accepted definition of ACO has been established yet, each previous report had each its own definition, and details of these definitions are given in Table 1, 2. Many previous studies defined ACO as a mixed phenotype with a combination of features of both asthma and COPD.^{14,18,20–22,27–29,31–34} A past history of asthma that was self-reported or based on medical records is one of the feature of asthma.^{14,17,18,20–23,28,29,31–34,39,44} A characteristic variable symptom of coughing and wheezing is also the feature of asthma.^{18,19,23,27,32,34,38,39,44} Concerning the asthmatic features of lung function, variable airflow limitation, reversibility and airway hyperresponsiveness are used as diagnostic criteria.^{12,18,19,23,24,26,27,32,34,35,38,44} For the features of COPD, most studies use post-bronchodilator irreversible airflow obstruction as a diagnostic criterion.^{12,13,17–19,21,23–25,27–30,32–40,43,44}

Some reports used a unique definition of ACO. Cosio *et al.* defined ACO as the presence of one major criterion, 1) a bronchodilator response to albuterol higher than 15% and 400 mL, 2) past medical history of asthma, or two minor criteria, 1) blood eosinophils >5%, 2) IgE >100 IU/mL, 3) two separate bronchodilator responses to albuterol higher than 12% and 200 mL.¹⁷

Louie *et al.* prefer the following major criteria for ACO: a physician diagnosis of asthma and COPD in the same patient, history or evidence of atopy, for example, hay fever, elevated total IgE, age of 40 years or more, smoking >10 pack-years, post-bronchodilator FEV₁ <80% predicted and FEV₁/FVC <70%. Minor criteria were a ≥15% increase in FEV₁ or ≥12% and ≥200 mL increase in bronchodilator treatment with albuterol.⁵

Sin *et al.* defined ACO as the existence of all three major criteria; 1) persistent airflow limitation in individuals 40 years of age or older, 2) at least 10 pack-years of tobacco smoking OR equivalent

indoor or outdoor air pollution exposure, 3) documented history of asthma before 40 years of age OR bronchodilator response of >400 mL in FEV₁, and at least one minor criteria; 1) documented history of atopy or allergic rhinitis, 2) bronchodilator response of ≥200 mL in FEV₁ and 12% from baseline values on 2 or more visits, 3) peripheral blood eosinophil count of ≥300 cells uL⁻¹.⁴⁵

Cataldo *et al.* defined ACO criteria in a COPD patient and in an asthma patient separately. COPD patients were diagnosed with ACO according to two major criteria; 1) high degree of variability in airway obstruction over time: FEV₁ variation ≥400 mL, 2) high degree of response to bronchodilators: >200 mL and 12% predicted above baseline, and at least one minor criteria; 1) personal or family history of atopy and/or IgE sensitivity to one or more airborne allergens, 2) elevated blood or sputum eosinophils or increased FeNO, 3) diagnosed with asthma before the age of 40, 4) symptom variability, 5) age (in favour of asthma). Asthma patients were diagnosed with ACO by the two major criteria; 1) persistence over time of airflow obstruction (persistence of FEV₁/FVC ratio <0.7 or <lower normal limit), 2) exposure to noxious particles or gases, with ≥10 pack-years in case of smoking for (ex-)smokers, and at least one minor criteria; 1) lack of response on acute bronchodilator test, 2) reduced lung diffusion capacity, 3) little variability in airway obstruction, 4) age in favour of COPD (>40 years), 5) presence of emphysema on chest CT scan.⁴⁶

In Japan, a few manuscripts about ACO have been published recently. Serum or sputum biomarker and CT image finding are used for definition of ACO.^{35,36,47,48}

For defining ACO, the other statements which are included smoking habit, past history, serological biomarker and respiratory function test were provided.⁴⁹ It is crucial to develop a standardized definition and diagnostic criteria for ACO.

Prevalence of ACO

Study population

The prevalence of ACO varies widely due to the difference of definition, population characteristics and study design. Of course, among the same population, the prevalence of ACO was different due to the definition.^{50–52} In the general population, the prevalence of ACO ranged from 0.9% to 11.1%.^{15,16,18,20,23,27,31,32,34,44,50} Menezes *et al.* defined ACO as a combination of features of both asthma and COPD, and the criteria for asthma were a positive answer to the question about wheezing in the 12 months plus post-bronchodilator airflow reversibility and the criterion for COPD was post-bronchodilator irreversible airflow obstruction in their cross sectional study. Their prevalence of ACO was 1.8% among participants who were over 40 years old.²⁷ Diaz-Guzman *et al.* defined ACO as a self-reported physician diagnosis of both asthma and COPD in their cohort study. Their prevalence of ACO was 2.7% among participants who were over 25 years old.²⁰

In a cross sectional cohort study in Hisayama, Japan, Matsumoto *et al.* described ACO as combination of not fully reversible airflow with variable airflow limitation, post-bronchodilator irreversibility and without a clinical history suggestive of asthma. Their prevalence of ACO was 0.9% among the participants who were over 40 years old.⁴⁴

Among the population who had airflow obstruction, the prevalence of ACO was between 3.1% and 55.5%.^{9,19,21,22,39,41,51} In Japan, that ranged from 15.4% to 20.7%.^{39,41}

In the patients with asthma, the prevalence of ACO was between 11.1% and 61.0%.^{23,26,40,53,54} In Japan, few studies of population with asthma have yet been published. Harada *et al.* found that the

Table 1

Definition and Prevalence of ACO.

	Study design/population	Definition of ACO, asthma and COPD	Prevalence
Alshabanat et al ¹² (2015)	Meta-analysis/COPD patients (17 manuscripts)	ACO: post-BD FEV ₁ /FVC < 70% AND physician diagnosed asthma or self reported physician diagnosis of asthma, reversibility to BD: 12% and at least 200 mL change in FEV ₁ , >20% variability in PEF, AHR COPD: post-BD FEV ₁ /FVC < 70%	27%: in population 28%: in hospital-based
Pascoe et al ¹³ (USA, 2015)	randomized control trial/COPD patients, age: >40 (n = 3,177)	ACO: blood eosinophil count > 2% and COPD COPD: post-BD FEV ₁ /FVC < 70%	66%
Vaz Fragoso et al ¹⁴ (USA, 2017)	cohort/asthma and COPD patients, age: from 40 to 80 (n = 3,486)	ACO: combination asthma and COPD asthma: self-reported physician diagnosis of asthma COPD: self reported chronic bronchitis or emphysema	17.4%
Barnes et al ¹⁵ (Denmark, 2017)	cohort/general population, age: from 50 to 64 (n = 57,053)	ACO: at least one hospital admission for asthma together with at least one admission for COPD asthma: history of admission for asthma COPD: history of admission for COPD	1.2%
Sorino et al ¹⁶ (Italy, 2016)	cohort/general population, age: from 65 to 100 (n = 1,065)	ACO: 1) post-BD FEV ₁ /FVC < 70% and previous diagnosis of asthma or reversibility to BD: >15% and 400 mL change in FEV ₁ 2) post-BD FEV ₁ /FVC < 70%, reversibility to BD: > 12% and 200 mL change in FEV ₁ , previous diagnosis of atopy and history of wheezing	11.1%
Cosio et al ¹⁷ (Spain, 2016)	cohort/COPD patients, age: >35 (n = 831)	ACO: 2 major criteria or 1 major criteria and 2 minor criteria major: self-reported previous history of asthma, reversibility to BD: >15% and 400 mL change in FEV ₁ minor: IgE > 100 IU, self-reported history of atopy, 2 separated reversibility to BD: >12% and 200 mL change in FEV ₁ , blood eosinophil count > 5% COPD: post-BD FEV ₁ /FVC < 70%	15.0%
de Marco et al ¹⁸ (USA, Canada, Australia, New Zealand, India, Algeria, 2015)	cohort/general population, age: from 20 to 40 (n = 6,984)	asthma: 1) self-reported asthma AND asthmatic symptoms, medication in the last year, AHR or transient airflow obstruction 2) self-reported asthmatic symptoms in the last year AND AHR COPD: pre-BD FEV ₁ /FVC < 70% AND 1) symptoms, 2) history of smoking or occupational exposure	3.1%
Fu et al ¹⁹ (Australia, 2014)	cohort/obstructive airway diseases age: >55 (n = 75)	ACO: asthma like symptoms, AHR or reversibility to BD AND post-BD FEV ₁ /FVC < 70%, %FEV ₁ < 80% asthma: asthmatic symptoms, post-BD FEV ₁ /FVC > 70%, %FEV ₁ > 80% AND AHR or reversibility to BD: 12% and 200 mL change in FEV ₁ COPD: post-BD FEV ₁ /FVC < 70%, %FEV ₁ < 80% AND no AHR or reversibility to BD	55.5%
Diaz-Guzman et al ²⁰ (USA, 2011)	cohort/general population, age: >25 (n = 15,203)	ACO: combination asthma and COPD asthma: self-reported physician diagnosis of asthma asthma: self-reported physician diagnosis of chronic bronchitis or emphysema	2.7%
van Boven et al ²¹ (Spain, 2016)	retrospective/obstructive airway diseases age: >18 (n = 68,578, subpopulation 3,667)	ACO: combination asthma and COPD asthma: medical record based physician diagnosis of asthma COPD: medical record based physician diagnosis of COPD subpopulation ACO: physician diagnosis of asthma, asthmatic symptoms AND age >40, physician diagnosis of COPD, FEV ₁ /FVC < 70%, smoking history and medication	7.40% in obstructive airway disease 19.3% in COPD patients
Gibson et al ⁹ (Australia, 2009)	retrospective/obstructive airway diseases age: >55 (n = 44)	ACO: FEV ₁ /FVC < 70%, post-BD %FEV ₁ < 80% AND AHR	65%
Soriano et al ²² (USA, UK, 2003)	retrospective/obstructive airway diseases (n = 310 million patients)	ACO: combination asthma and COPD asthma: medical record based or self-reported physician diagnosis of asthma COPD: medical record based or self-reported physician diagnosis of COPD	from 17.0% to 19.1% in obstructive airway disease from 51.9% to 57.7% in COPD patients
Montes de Oca et al ²³ (Argentina, Colombia, Venezuela, Uruguay, 2017)	cross section/general population, age: >40 (n = 1,743)	ACO: combination of COPD with the two asthma definitions asthma: either prior asthma diagnosis or wheezing in the last 12 months plus reversibility to BD: ≥200 mL and ≥12% change in FEV ₁ or FVC COPD: post-BD FEV ₁ /FVC < 70%	5.8% in general population 35.7% in asthma patients 32.7% in COPD patients
Ekerjung et al ²⁴ (Sweden, 2017)	cross section/general population age: from 16 to 75 (n = 2,215)	ACO: post BD FEV ₁ /FVC < 70% and fulfil at least one of 4 criteria 1. reporting a physician-diagnosed asthma with respiratory symptoms or use of asthma medication 2. AHR, 3. reporting ever asthma, and a positive methacholine challenge with asthma symptoms, 4. reporting ever asthma and asthma symptoms with increased blood eosinophils asthma: post BD FEV ₁ /FVC > 70% and fulfilling any of the 4 criteria COPD: post BD FEV ₁ /FVC < 70% and none of the asthma criteria	8.2%

(continued on next page)

Table 1 (continued)

	Study design/population	Definition of ACO, asthma and COPD	Prevalence
Ding et al. ²⁵ (USA, EU5, 2017)	cross section/asthma and COPD patients (n = 16,684)	ACO: in COPD population, post-BD FEV ₁ /FVC < 70% with physician-confirmed diagnosis of asthma asthma: age >12, physician-confirmed diagnosis of asthma and no diagnosis of COPD COPD: age >40, post-BD FEV ₁ /FVC < 70% and no diagnosis of asthma	3.1%
Kiljander et al. ²⁶ (Finland, 2015)	cross section/asthma patients, age: from 18 to 70 (n = 190)	ACO: post-BD FEV ₁ /FVC < 70% with the other asthma features asthma: post-BD FEV ₁ /FVC > 70% with 1. reversibility to BD; ≥200 mL and ≥12% change in FEV ₁ or FVC 2. post-BD response: >15% change or >20% variation in PEF 3. Airway hyper-responsiveness, 4. post-treatment response: >15% improvement in FEV ₁	27.4%
Menezes et al. ²⁷ (Brazil, Chile, Mexico, Uruguay, Venezuela, 2014)	cross section/general population, age: >40 (n = 5,044)	ACO: post-BD FEV ₁ /FVC < 70% AND reversibility to BD: 12% and 200 mL change in FEV ₁ asthma: wheezing in the last 12 months and reversibility to BD; ≥200 mL and ≥12% change in FEV ₁ or FVC COPD: post-BD FEV ₁ /FVC < 70%	1.8%
Hardin et al. ²⁸ (USA, 2014)	cross section / COPD patients, age: from 45 to 80 (n = 3,570)	ACO: combination asthma and COPD asthma: self-reported physician diagnosis of asthma before the age of 40 COPD: post-BD FEV ₁ /FVC < 70%, %FEV ₁ < 80%	12.6%
Miravittles et al. ²⁹ (Spain, 2013)	cross section/COPD patients, age: from 40 to 80 (n = 385)	ACO: combination asthma and COPD asthma: self-reported physician diagnosis of asthma COPD: post-BD FEV ₁ /FVC < 70%	17.4%
Izquierdo-Alonso et al. ³⁰ (Spain, 2013)	cross section/COPD patients, age: >40 (n = 331)	ACO: post-BD FEV ₁ /FVC < 70% AND DLco/VA > 80%, absence of pulmonary emphysema in imaging and self-reported physician diagnosis of asthma before the age of 40 COPD: post-BD FEV ₁ /FVC < 70%	12.1%
de Marco et al. ³¹ (Italy, 2013)	cross section/general population, age: >20 (n = 8,360)	ACO: combination asthma and COPD asthma: self-reported physician diagnosis of asthma COPD: self-reported physician diagnosis of chronic bronchitis or emphysema	from 1.6% to 4.5% in general population from 25% to 33% in COPD patients
Shirtcliffe et al. ³² (New Zealand, 2012)	cross section/general population, age: from 25 to 75 (n = 749)	ACO: combination asthma and COPD asthma: reversibility to BD; >15% change in FEV ₁ , > 20% variation in PEF, or self-reported physician diagnosis of asthma AND asthmatic symptoms or medication COPD: post-BD FEV ₁ /FVC < 70%	8.7% in general population 56.0% in COPD patients
Hardin et al. ³³ (USA, 2011)	cross section/COPD patients, age: from 40 to 80 (n = 915)	ACO: combination asthma and COPD asthma: self-reported physician diagnosis of asthma before the age of 40 COPD: post-BD FEV ₁ /FVC < 70%, %FEV ₁ < 80%	from 13.0% to 21.7%
Marsh et al. ³⁴ (New Zealand, 2008)	cross section/general population, age: >50 (n = 469)	ACO: combination asthma and COPD asthma: reversibility to BD; > 15% change in FEV ₁ , > 20% variation in PEF, or self-reported physician diagnosis of asthma AND asthmatic symptoms or medication COPD: post-BD FEV ₁ /FVC < 70%	10.7% in general population 55.2% in COPD patients

n, the numbers used final analysis; ACO, asthma - COPD overlap; COPD, chronic obstructive pulmonary disease; BD, bronchodilator; FEV₁ forced expiratory volume in 1 second; PEF, peak flow; AHR, airway hyper-responsiveness; FVC, forced vital capacity; DLco, diffusing capacity of the lung Carbon monoxide; VA, alveolar volume.

prevalence of ACO was 27.1% among patients who were previously diagnosed with asthma.⁴⁰

In patients with COPD, the prevalence of ACO ranged from 4.2% to 66.0%.^{12,13,17,21–23,28–30,33,35–37,42,43,52} Cosio *et al.* showed that the prevalence of ACO was 15.0% according to their definition above.¹⁷ In a meta-analysis, Alshabanat *et al.* defined ACO as a combination of post-bronchodilator airflow irreversibility and a diagnosis of asthma, airflow reversibility, peak expiratory flow variability or airflow hyperresponsiveness. Their prevalence of ACO was 27% and 28% in the population- and hospital-based studies, respectively.¹²

Among COPD patients in Japan, the prevalence of ACO was between 4.2% and 49.7%.^{35–37,42,43} Suzuki *et al.* describe ACO as the combination of bronchodilator reversibility, blood eosinophilia (peripheral blood eosinophil count of ≥300 cells μL^{-1}), and/or atopy (the presence of specific serum IgE to at least 1 of the 14 common inhaled allergens) in Hokkaido cohort study. Their prevalence of ACO was 49.7% in patients who were over 40 years old and had a smoking habit.³⁵

In Japan, the prevalence of ACO remains uncertain among any population because of the lack of data from multiple large-scale cohort studies. Furthermore, it is important to minimize potential selection bias for the estimation of prevalence, and it might be

valuable to perform consecutive recruitment of eligible patients at each study site or to use less-biased community surveys. One study, using the protocol regulating consecutive recruitment, reported that the proportion of patients identified as having ACO based on the stepwise approach stated in the GINA/GOLD report was 9.2% or 4.2%, depending on the FEV₁ variability cutoff used, among the 1008 outpatients medically treated for COPD in a real-life clinical setting.⁴²

Age and gender

The patients with ACO were older than those with asthma in many studies.^{14,18,20,23–27,40,41} In comparison with COPD patients, it was reported both that ACO patients were younger than COPD patients^{18,20,21,24,27,28,33,41–44} and that the age of ACO patients was not different from that of COPD patients.^{14,16,17,19,23,25,29,35–39} The prevalence of ACO increases as age rises, and this result is the same as that for COPD.^{22,23,31,41,44}

In Japan, all studies showed that the gender of ACO patients was predominantly male.^{35–44} Outside Japan, there were different gender distributions in ACO patients; some reports showed a predominantly male distribution^{13,16–18,23,25,30,33} and others shows a

Table 2
Definition and Prevalence of ACO in Japan.

	Study design/population	Definition of ACO, asthma and COPD	Prevalence
Suzuki et al. ³⁵ (Japan, 2016)	cohort/COPD patients, age: >40 (n = 268)	ACO: post-BD FEV ₁ /FVC < 70% AND reversibility to BD: 12% and 200 mL change in FEV ₁ , blood eosinophil count > 300 cells/ μ L, or presence of specific serum IgE to at least 1 of the 14 common inhaled allergens COPD: post-BD FEV ₁ /FVC < 70%	49.7%
Suzuki et al. ³⁶ (Japan, 2015)	cohort/COPD patients, age: from 40 to 85 (n = 140)	ACO: post-BD FEV ₁ /FVC < 70% AND reversibility to BD: 12% change in FEV ₁ , post-treatment response: >15% improvement in FEV ₁ , >20% variation in PEF or AHR COPD: smoking history and post-BD FEV ₁ /FVC < 70%	28.6%
Kitaguchi et al. ³⁷ (Japan, 2012)	cohort/COPD patients (n = 63)	ACO: COPD patients with asthmatic symptoms COPD: post-BD FEV ₁ /FVC < 70%	27.0%
Kurashima et al. ³⁸ (Japan, 2016)	retrospective/patients at one medical center (n = 332)	ACO: combination asthma and COPD asthma: reversibility to BD: 12% and 200 mL change in FEV ₁ and asthmatic symptoms COPD: smoking history and post-BD FEV ₁ /FVC < 70%	15.4%
Kitaguchi et al. ³⁹ (Japan, 2016)	retrospective, obstructive airway diseases (n = 177)	ACO: COPD patients with asthmatic symptoms asthma with airflow limitation: previous diagnosis of asthma, asthmatic symptom and post-BD FEV ₁ /FVC < 70% COPD: patients with clinical symptoms, post-BD FEV ₁ /FVC < 70%, no history of asthma or asthmatic symptoms	18.1%
Harada et al. ⁴⁰ (Japan, 2015)	retrospective/asthma patients (n = 650)	ACO: diagnosis based on the guidelines published by GINA previous diagnosis of asthma, smoking history, post-BD FEV ₁ /FVC < 70% and respiratory symptoms	27.1%
Yamauchi et al. ⁴¹ (Japan, 2015)	retrospective/obstructive airway diseases, age: >40 (n = 30,405)	ACO: patients admitted because of asthma exacerbation and had COPD as a comorbidity on admission or patients admitted because of COPD exacerbation and had asthma as a comorbidity on admission asthma: patients admitted because of asthma exacerbation but did not have COPD as a comorbidity on admission COPD: patients admitted because of COPD exacerbation but did not have asthma as a comorbidity on admission	20.7%
Inoue et al. ⁴² (Japan, 2017)	cross section/COPD patients (n = 1,008)	ACO: stepwise approach as stated in the GINA/GOLD report COPD: FEV ₁ /FVC < 70% in past medical record, age >40, current or ex-smoker with a history of >10 pack-years	9.2% and 4.2% (depending on the FEV ₁ variability cutoff used)
Kobayashi et al. ⁴³ (Japan, 2016)	cross section/COPD patients, age: from 40 to 90 (n = 257)	ACO: post-BD FEV ₁ /FVC < 70% AND self-reported physician diagnosis of asthma, asthmatic symptoms, reversibility to BD: 12% and 200 mL change in FEV ₁ or post-treatment response: > 12% and 200 mL improvement in FEV ₁ COPD: post-BD FEV ₁ /FVC < 70%	14.4%
Matsumoto et al. ⁴⁴ (Japan, 2015)	cross section/general population, age: >40 (n = 174)	ACO: post-BD FEV ₁ /FVC < 70% AND reversibility to BD: 12% and 200 mL change in FEV ₁ asthma: asthmatic symptom and post-BD FEV ₁ /FVC > 70% or asthmatic episode, previous diagnosis of asthma, previous medication AND post-BD FEV ₁ /FVC < 70 and reversibility to BD: 12% and 200 mL change in FEV ₁ COPD: post-BD FEV ₁ /FVC < 70% and no reversibility to BD	0.9%

n, the numbers used final analysis; ACO, asthma - COPD overlap; COPD, chronic obstructive pulmonary disease; BD, bronchodilator; FEV₁, forced expiratory volume in 1 second; PEF, peak flow; AHR, airway hyper-responsiveness; FVC, forced vital capacity; DLCO, diffusing capacity of the lung Carbon monoxide; VA, alveolar volume; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

predominantly female one.^{14,15,19–21,24,27–29} Because biomass exposure is one of the causes of COPD, there is a large population of female patients with COPD in some regions. However, in Japan, the cause of COPD is tobacco smoking mainly, so the gender distribution of ACO patients was affected by the gender distribution of the smoking habit.

Exacerbations and prognosis of ACO

In most cross sectional studies of ACO, the frequency of exacerbations in ACO patients was higher than that in COPD patients.^{23,25,27–29,33} However, some studies showed that the rate of exacerbations in ACO patients was not different from that in COPD patients.³⁰ In cohort studies, de Marco *et al.* showed that the frequency of exacerbation in ACO patients was higher than that in COPD patients,¹⁸ whereas, Cosio *et al.* found that it was not different between ACO and COPD patients.¹⁷

In Japan, the frequency of exacerbation in ACO patients was reported in only a few studies. Among those cross sectional and

cohort studies, the rate of exacerbations in ACO patients was not different from that in COPD patients.^{35,42,43}

In the prognosis of patients with ACO, no generally accepted definitive outcome has been reached yet. Diaz-Guzman *et al.* showed that ACO patients had a higher risk of obstruction on spirometry and a higher risk of death in comparison with those with asthma or COPD only.²⁰ Baarnes *et al.* also reported that the mortality rate was higher in ACO patients than in patients with either disease alone.¹⁵ Nevertheless, Fu *et al.* found that the prognosis did not differ among asthma, COPD and ACO patients in their cohort study.¹⁹ Likewise, Sorino *et al.* showed that the long-term mortality of ACO patients was similar to that of patients with COPD alone.¹⁶ In addition, Cosio *et al.* reported that ACO patients showed a better one-year prognosis than clinically similar patients with COPD only.¹⁷

In Japan, Suzuki *et al.* showed that COPD patients with two or more asthma-like features had significantly lower 10-year all-cause mortality than those with one or no asthma-like features in their cohort study.³⁵ Yamauchi *et al.* defined ACO as the patients who were admitted because of asthma exacerbation and had COPD as a

comorbidity on admission or those who were admitted because of COPD exacerbation and had asthma as a comorbidity on admission. In their retrospective study, they reported that ACO was associated with higher mortality than asthma alone and with lower mortality than COPD alone.⁴¹ In Japan, the prognosis of ACO patients was reported in only a few studies, so the prognosis of ACO was not definitive.

Discussion

Because certain definitions and diagnostic criteria for ACO have not been published, the outcomes with regard to the prevalence, frequency of exacerbation, and prognosis have varied widely in the respective studies.

For assessment regarding ACO, the evaluation of airway inflammation would be important. Asthma is more eosinophilic, and COPD is typically more neutrophilic. However, there is heterogeneity with each condition and overlap between both conditions. Although there are some variabilities over time and in response to therapies, many patients exhibit relative stability in inflammation phenotypes, suggesting consistent underlying molecular mechanisms. The advance in molecular technologies has the potential to distinguish subgroups within ACO on a molecular level.

Airflow irreversibility is a definition of COPD and can be valued accurately by a lung function test. However, airflow irreversibility due to COPD is not distinguished from that due to asthmatic airway remodelling. To evaluate whether patients have COPD, it may be necessary to consider not only airflow irreversibility but also tobacco or biomass exposure and emphysema, low attenuation area in computed tomography, and/or diffusion capacity for carbon monoxide.

To judge whether patients have asthma, it is important to prove that eosinophilic airway inflammation is not merely a past occurrence but a continuing condition. It is suggested that eosinophilic airway inflammation is a key prognostic factor for patients with ACO and COPD. Siva *et al.* compared the management for minimising eosinophilic airway inflammation with the treatment according to traditional guidelines. By reducing the sputum eosinophil count, the management strategy that aims to minimise eosinophilic airway inflammation was associated with a reduction in severe exacerbations of COPD.⁵⁵ Kitaguchi *et al.* compared the clinical features of COPD patients with asthmatic symptoms with those of COPD patients without asthmatic symptoms. The peripheral eosinophil counts and sputum eosinophil counts were significantly higher in the COPD with asthma group, and the increases in FEV₁ in response to treatment with an inhaled corticosteroid were significantly higher in the COPD with asthma group.³⁷ Pascoe *et al.* compared exacerbation rates according to baseline peripheral eosinophil cell count strata in COPD patients in a secondary analysis of data from two parallel randomized controlled trials. As the peripheral eosinophil counts increase, a combined inhaled corticosteroid and long-acting muscarinic antagonist reduced the frequency of exacerbations, in addition, increased FEV₁ in response to treatment with inhaled corticosteroid compared with long-acting muscarinic antagonist alone.¹³ Furthermore, Vestbo *et al.* found that in the subgroup with a higher blood eosinophil concentration among COPD patients, the inhibition of exacerbation by triple therapy with an inhaled corticosteroid, long-acting β_2 agonist, and long-acting muscarinic antagonist was greater than that with long-acting muscarinic antagonist monotherapy in the double-blind, parallel group, randomised controlled trial.⁵⁶ Based on these results, the suppression of eosinophilic airway inflammation has high potential to improve the prognosis of COPD and ACO. For that reason, in the definition of ACO, especially of the asthmatic component of ACO, criteria that correspond with

eosinophilic airway inflammation must be adopted. It is important to determine which tool, for example, peripheral eosinophil count, sputum eosinophil count, exhaled nitric oxide, or another biomarker, is most suitable for the evaluation of eosinophilic airway inflammation in a future large cohort study or clinical trial.

Conclusion

ACO is defined as persistent airflow limitation with several features usually associated with asthma and several usually associated with COPD. The prevalence of ACO ranged from 0.9% to 11.1% in the general population, from 11.1% to 61.0% in asthma patients and from 4.2% to 66.0% in COPD patients. Nevertheless, because certain definitions and diagnostic criteria for ACO have not been published, the outcome in terms of the prevalence, frequency of exacerbation, and prognosis has varied widely in previous studies.

At present, it is not an easy task to develop a single, universal definition of ACO for diagnosis and treatment. However, it would be important to propose a tentative, working standardized definition and/or diagnostic criteria for ACO based on biomarkers and objective measures. It may lead cohort studies with large population or clinical trials. Clinical trials should include smoking patients with asthma and COPD patients with atopy or eosinophilic inflammation, especially in studies involving molecular-targeted therapies.

Conflict of interest

The authors have no conflict of interest to declare.

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