STUDY REPORT SYNOPSIS

A prospective cohort study of asthma and COPD overlap in Japanese patients with COPD according to the diagnostic criteria of The Japanese Respiratory Society

Background/rationale:
Asthma and COPD Overlap (ACO) is captured as a condition that combines characteristics of asthma and COPD clinically, and patients with ACO generally have more frequent exacerbations, lower QoL, more rapid declines in respiratory function, and higher mortality rates than those who have asthma or COPD alone.

There are very few reports of long-term investigation on clinical characteristics of ACO patients including symptoms and exacerbations classified by treatments in Japan. Also the proportion of ACO in patients with COPD varied from 12% to 55% in previous studies. It has also been reported that the proportion of patients who meet the criteria of ACO varies over time even in the same patient population. And results from some studies about proportion of ACO patients and patietns characteristics with ACO were inconsistent, because there were no established definitions or diagnostic criteria for ACO.

Under these circumstances, the Japanese Respiratory Society published "Guidance on Diagnosis and Treatment of Asthma and COPD Overlap 2018" (hereinafter referred to as "ACO Guidance") in 2017. The Guidance defined ACO as "a disease with chronic airflow obstruction and characteristics of both asthma and COPD", and demonstrated the diagnostic criteria for ACO.

This study was planned to investigate to collect following data: how many patients may fulfill the diagnostic criteria for ACO in follow-up or new outpatients in Japan who have characteristics relevant to COPD according to the diagnostic criteria for ACO recommended by the Japanese Respiratory Society; how the proportion of such patients changes over time; and what is the difference of characteristics between patients who fulfill the diagnostic criteria for ACO and those who do not.

Objectives:
Primary objectives:

1. To investigate the proportion of patients who were diagnosed with ACO during the evaluation period.
2. To investigate the proportion of patients who were diagnosed with ACO (ACO patients) and patients who were diagnosed as not having ACO (non-ACO patients) among patients who have data required for the diagnosis of ACO at the time of registration.

Secondary objectives:

1. To compare the clinical background between patients diagnosed with ACO, patients diagnosed with non-ACO, and patients lacking data required for the diagnosis of ACO at the time of registration.
2. To compare the patient demographics at the time of registration and clinical parameters at the time of registration, 1 year later, and 2 years later between patients diagnosed with ACO at the time of registration and patients never diagnosed with ACO throughout 2 years.
3. To compare the patient demographics, clinical characteristics, symptoms, and results of the examinations/tests required for the diagnostic criteria for ACO at the time of registration between the groups of patients who are classified based on the diagnostic criteria for ACO during the evaluation period.
4. To investigate the status and results of the examinations/tests required for the diagnosis of ACO at the time of registration, 1 year later, and 2 years later between the ACO patients, the non-ACO patients, and the patients lacking data required for the diagnosis of ACO. Concerning patients who lacked data required for the diagnosis of ACO at the time of registration, the reason for lack of data will be investigated.

5. To compare the clinical characteristics, symptoms, results of the examinations/tests required for the diagnosis of ACO of patients whose diagnosis changed between the time of registration and 1 year later between the patients who were diagnosed with ACO at the time of registration and the patients who were diagnosed as not having ACO at the time of registration.

6. To investigate the number of patterns of ACO diagnosis and its proportion among patients who have the data required for the diagnosis of ACO at all time points during the evaluation period.

7. To compare the status and results of the examinations/tests required for the diagnosis of ACO by the presence or absence of variability in respiratory symptoms between the ACO patients and the non-ACO patients at the time of registration.

Exploratory objectives:

1. To investigate the clinical differences between patients diagnosed with asthma and patients diagnosed as not having asthma by a physician at the time of registration. The proportion of ACO patients and non-ACO patients in those groups will also be investigated.

2. To investigate the clinical differences between the group using ICS and the group not using ICS at the time of registration. The proportion of ACO patients and non-ACO patients in those groups will also be investigated.

3. To explore the criteria for discriminating between ACO patients and non-ACO patients using ACQ and CAT.

Study design:
This study was a multicenter non-interventional prospective cohort study.

The patients were registered sequentially with the central registration method, data including results of examinations/tests required for the diagnostic criteria for ACO were collected at the time of registration, 1 year later, and 2 years later. Data was collected from the electronic case report form (eCRF) completed by the investigators and the questionnaire completed by the patients.

Data source:
The study sites were medical institutions in which examinations/tests required for the ACO diagnostics (respiratory function test, FeNO measurement, peripheral blood eosinophil counts, airway reversibility, total IgE, and specific IgE, CT and lung diffusion test) were conducted as routine clinical practice for COPD patients, and tests such as respiratory function tests, FeNO measurement or peripheral eosinophil count were conducted in these patients at least once a year.

Study population:
This study was performed in adult outpatients (≥ 40 years) who fulfilled characteristics of COPD according to the diagnostic criteria for ACO of the Japanese Respiratory Society within the past year or at the time of registration, and were able to regularly visit the study sites.
It was planned to include 700 patients at about 30 study centers in Japan from June 2018 to January 2019, with the last study visit in March 2021. The study ulitimately took place from 19 June 2018 (first patient first visit) to 19 February 2021 (last patient last visit) and 708 patients were recruited at 27 sites.
Inclusion criteria:
Patients had to be outpatients, ≥ 40 years old, able to visit the site at least once a year and provide written consent to participate in this study. Patients had to have rate of forced expiratory volume in one second (FEV1/FVC) of less than 70% after inhalation of a bronchodilator within the past year or at the time of registration. Patients had to have a smoking history (≥10 pack-years) or equivalent air pollution exposure (including passive smoking) or a low absorption region showing emphysematous change on a chest CT or lung diffusion impairment (%DLco <80%, DLco/VA <80%).
Exclusion criteria:
Patients were excluded if they had participated in an interventional study within the last 8 weeks, were not appropriate for joining this study, judged by the investigators, due to the reasons such as not being able to comply with the procedures, restrictions and requirements of this study. Patients were also excluded if they had experienced exacerbation of COPD or asthma within the last 8 weeks or if they had diseases which could not be distinguished from COPD or asthma at the time of obtaining consent.

Statistical methods:
The analyses of this study were exploratory and primarily made use of descriptive statistical methods. In addition, exploratory statistical testing and modelling was used to highlight interesting aspects of the data.
Tables and listings were produced in accordance with the principles outlined by the ICH E3 guideline.
The continuous variables were summarized using number of patients (Number), mean, standard deviation (SD), median, minimum (Min), maximum (Max), Quartile 1 (Q1), Quartile 3 (Q3), number of missing data (Missing).
The categorical variables were summarized using number of patients (Number), percentages for each category,

number of missing data (Missing), 95% confidence interval (CI) when specified in the analysis.
Tables were presented for the full analysis set (FAS).
Analysis sets:
Registered patients were defined as any patient included in the database.
The enrolment population consisted of those patients fulfilling the inclusion/exclusion criteria and having signed the Informed Consent Form (ICF).
The full analysis set (FAS) includeed enrolled patients from whom at least one clinical characteristic or symptom or examination/test required for the ACO diagnosis had been collected at any timepoint after registration.
The per protocol set (PPS) included all enrolled patients except the patients with major protocol deviations.
Major protocol deviations included not fulfilling the inclusion/exclusion criteria or not having provided informed consent. Other major or minor deviations could be defined during the study duration before the database lock. Patients having major or minor protocol deviations were not excluded from the FAS.
ACO evaluable population at registration was defined as patients who had the data required for the ACO diagnosis at the time of registration.
ACO evaluable population at 1 year after visit was defined as patients who had the data required for the ACO diagnosis at 1 year after visit.
ACO evaluable population at 2 year after visit was defined as patients who had the data required for the ACO diagnosis at 2 year after visit.
Overall ACO evaluable population was defined as patients who had the data required for the ACO diagnosis at all the timepoints of the study.
ACO population at registration consisted of the ACO evaluable patients at registration that were diagnosed with ACO at registration.
Non-ACO population at registration consisted of the ACO evaluable patients at registration that were not diagnosed with ACO at registration.

Results:
Of 708 COPD patients (FAS), the number with data necessary for ACO diagnosis were 396 (55.9%) at registration, 478 (67.5%) at 1 year, and 507 (71.6%) at 2 years.

In the primary endpoint 1, of 708 patients (FAS), the patients who met ACO criteria were 101 (14.3%) at registration, 118 (16.7%) after 1 year and 125 (17.7%) after 2 years.

In the primary endpoint 2, of 396 patients who have data necessary for ACO diagnosis at registration, 101 (25.5%) were diagnosed with ACO at registration and 295 patients (74.5%) did not have ACO at registration.

In the secondary endpoint 1, there are 101 ACO patients and 295 non-ACO patients at registration, and 396 patients who had data for ACO diagnosis at registrations and 312 patients who did not have enough data for diagnosis.
With regards to demographics and clinical background, ACO patients were younger ($p=0.025$), more ACO patients had a family history of allergic disorders, a history of asthma, present asthma, at least one comorbidity, and allergic rhinitis (all $p<0.001$). ACO patients were also younger at onset of asthma ($p<0.001$). More non-ACO patients had heart failure ($p=0.002$) or lung diffusion impairment ($p=0.017$). More ACO patients were treated with ICS or LAMA and LABA and ICS ($p<0.001$ for all), while more non-ACO patients were treated only with LABA ($p=0.031$) or with LAMA and LABA ($p<0.001$). More ACO patients had a higher number of exacerbations and a higher exacerbation rate in the last year, with significant differences in the rate of moderate exacerbations (p-values between 0.009 and 0.038). ACO patients had higher ACQ5 scores.
With regards to ACO diagnosis criteria, ACO patients had a higher variability of symptoms and more paroxysmal symptoms ($p<0.001$ for all). More ACO patients had concomitant perennial allergic rhinitis ($p<0.001$), airway reversibility with improvement rate >12% and improvement amount >200 mL ($p=0.010$) or improvement amount >200 mL ($p=0.002$) and a higher improvement amount ($p=0.015$). Peripheral blood eosinophil count and ratio, FeNO, total IgE and IgE above the site normal ($p<0.001$) were also higher in ACO patients, with higher perennial allergens, and allergens to house dust 1, Dermatophagoides pteronyssinus, Dermatophagoides farina, or Japanese cedar (p-values between <0.001 and 0.048).
Patients with data for ACO diagnosis had a higher vital capacity after bronchodilator use, a higher predicted FEV1%, the duration of COPD was shorter in patients with data and the COPD grades lower. More patients with data had at least one comorbidity, in particular, asthma, allergic rhinitis, heart failure, cerebrovascular disorders, hypertension, or gastroesophageal reflux disease. More patients with data received ICS or LABA and ICS combinations, while more untested patients received treatment with LAMA and LABA combinations.
Patients with data had lower CAT scores ($p=0.001$), lower mMRC dyspnea scores ($p<0.001$) and more reported variability of symptoms ($p=0.006$) paroxysmal symptoms ($p<0.001$) or concomitant perennial allergic rhinitis ($p<0.001$). The FeNO value was lower in patients with data for ACO diagnosis ($p=0.009$) and less patients with data had a FeNO value of >35 ppb ($p<0.001$). Patients with data were less likely to have perennial allergens ($p=0.044$).
With regards to tests for ACO diagnosis, the rate of patients with data who had variable or paroxysmal respiratory symptoms at registration, history of asthma before the age of 40, or concomitant perennial rhinitis was higher while the rate of patients with data who had FeNO <35 ppb or total IgE above the normal range or positive specific IgE to perennial inhalant antigens was lower than in patients without data for ACO diagnosis. Patients with lack of data had particularly low test implementation rates for peripheral blood eosinophil count and ratio (62.5%),

FeNO (30.8%), airway reversibility (29.5%), and total IgE levels (14.1%).

In the secondary endpoint 2, there are 101 patients who met the diagnostic criteria for ACO at registration and 79 patients who never met the ACO criteria throughout the 2 years of the study were compared. There were few differences in patient characteristics, clinical features, symptoms, treatment status, or (clinical course) at the time of enrollment, at 1 year, or at 2 years for patients who met the ACO criteria at registration and those who were non-ACO for 2 consecutive years.The age was higher in non-ACO patients. There was no difference in COPD disease characteristics (CAT scores) between the groups. Of note, asthma was observed in 68.3% of ACO patients at registration and 60.8% of non-ACO patients throughout 2 years (p=0.291). Heart failure and gastroesophageal reflux disease were more common in non-ACO patients, and allergic rhinitis was more common in ACO patients throughout 2 years. Treatment with ICS or LAMA/ICS or LAMA/LABA/ICS was more common in ACO patients while treatment with LAMA or LAMA/LABA was more common in non-ACO patients. The proportion of ACO patients prescribed ICS was 77.2% at enrollment, 80.2% at 1 year, and 80.0% at 2 years, while the proportion of non-ACO patients prescribed ICS was 24.1% at entry, 31.6% at 1 year, and 34.2% at 2 years.The age-related decline in respiratory function (FEV1 after bronchodilator use) was ¬68.8 (365.3) mL/year in patients who met the ACO criteria at enrollment at 1 year and ¬54.8 (150.1) mL/year from year 1 to year 2. Patients with non-ACO for 2 consecutive years had -22.5 (164.8) mL/year and 62.1 (161.4) mL/year, respectively, which is an increase in respiratory function in the second year in non-ACO patients (p<0.001). The frequency of exacerbations in the previous year and number of patients who experienced exacerbations was higher in ACO patients at registration, and there was a higher proportion of patients with ACO with exacerbations after 1 year, but there was no significant difference at 2 years. Variability of symptoms, paroxysmal symptoms, and ACQ5 scores, all characteristic of asthma were consistently higher in ACO patients over the 2 years of the study. FeNO values and peripheral blood eosinophil counts and rates, which are necessary parameters for the diagnosis of ACO were also higher in ACO patients throughout the 2 years.

The previous results in the comparison of ACO and non-ACO patients were also confirmed in secondary endpoint 3, where 125 ACO patients who were diagnosed with ACO at least once and 79 patients who were never diagnosed with ACO during the study.
In the second part of endpoint 3, there are 19 patients diagnosed with ACO continuously, 79 patients never diagnosed with ACO throughout the 2 years of the study and 30 patients diagnosed with both throughout the study were compared. Again, ACO patients had a higher concomitant physician-diagnosed asthma (89.5%, compared to 60.8% in non-ACO patients and 56.7% in patients diagnosed with both, p=0.004). The diagnostic parameters, allergic rhinitis, variability of symptoms, paroxysmal symptoms, perennial allergic rhinitis, FeNO value, peripheral blood eosinophil count and ratio, and IgE level were higher in patients diagnosed with ACO continuously and patients diagnosed with both.
It should be noted that the comparison was restricted by small number of patients.

In the secondary endpoint 4, there are 396 patients with data for ACO diagnosis of whom 101 were ACO patients and 295 non-ACO patients at registration, and 312 patients who did not have enough data for diagnosis. After 1 year, 270 patients had data for ACO diagnosis of whom 53 were ACO patients and 217 non-ACO patients, while 404 patients who did not have enough data for diagnosis. After 2 years, 215 patients had data for ACO diagnosis of whom 35 were ACO patients and 180 non-ACO patients, and 396 patients who did not have enough data for diagnosis.
Patients who lacked data for ACO diagnosis had low implementation rates for lung diffusion impairment, FeNO values, airway reversibility peripheral blood eosinophil count/ratio and total IgE levels, and a persistently low number of these patients fulfilled two or more of the following tests: concomitant perennial allergic rhinitis, airway reversibility (with an improvement rate >12% and improvement amount >200 mL), peripheral blood eosinophil count >5% or >300 cells/μL or total IgE below the site's normal range or a positive specific IgE test to perennial inhalant antigens. The implementation rate of the IgE test 7 to 20% higher in patients who met ACO criteria at any time. The rate at which physicians performed each test did not change over time.
Reason for lack of data at the time of registration was also investigated. The most frequently reported reason was that the physician assessed patients to have ACO (27.2%) or non-ACO (32.1%) based on the clinical characteristics and did not perform the test. In 15.1% of the 312 patients with lack of data, the doctors did not perform the test(s), as they had been performed before in the year before registration.

In the secondary endpoint 5, there are 36 patients who had ACO after 1 year and 11 patients who did not have ACO after 1 year, and there are 5 patients who had ACO after 1 year and 136 patients who did not have ACO after 1 year.
In the patients who had ACO at registration and after 1 year, ACQ5 score, CAT score and FeNO values were higher than in patients who had switched from ACO to non-ACO after 1 year.
Among non-ACO patients at registration, who had switched to ACO after 1 year, the peripheral blood eosinophil ratio and FeNO value were higher.

In the secondary endpoint 6, 111 patients who were diagnosed either with ACO or with non-ACO at all 3 time points in the study. Of the 28 patients who met the ACO criteria at registration, 22 (78.6%) were still diagnosed with ACO after 1 year. Of these, 19 (86.4%) were diagnosed with ACO 2 years later. Of the 83 patients who were non-ACO at registration, 81 (97.6%) remained non-ACO at 1 year. Of these, 79 (97.5%) were non-ACO at 2 years.

In the secondary endpoint 7, overall, there were mostly the same differences between ACO and non-ACO patients, regardless of variability of symptoms. In exploratory endpoint 1, the presence or absence of comorbid asthma based on the ACO diagnostic criteria and the presence or absence of comorbid asthma based on the physician's diagnosis did not always match, and in exploratory endpoint 2, the present findings clearly show that some patients were not being treated with ICS despite having ACO.

Conclusion:

This study gives a comprehensive insight of the medical background and disease characteristics of ACO patients and non-ACO patients from 27 respiratory specialist institutes across Japan. Among the patients who were diagnosed either with ACO or with non-ACO at all 3 time points, most of the patients who were non-ACO at registration are continuously non-ACO throughout 2 years. On the other hand, among the patients who did not have enough data for ACO diagnosis, there are patients who met the ACO criteria in 2 years, which indicates that the ACO diagnosis is necessary. Overall the disease burden of ACO patients are larger, so the appropriate treatment especially ICS treatment is necessary.

Publications:

One publication was released based on the results of this study:

- Hashimoto S, Sorimachi R, Jinnai T, Ichinose M. Asthma and Chronic Obstructive Pulmonary Disease Overlap According to the Japanese Respiratory Society Diagnostic Criteria: The Prospective, Observational ACO Japan Cohort Study. *Adv Ther.* 2020 https://doi.org/10.1007/s12325-020-01573-x