Review

Current Status of Studies Investigating Asthma-Chronic Obstructive Pulmonary Disease Overlap in Korea: A Review

Yong Suk Jo

Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea

Correspondence: Yong Suk Jo, M.D.
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea.
Tel: +82-2-2224-2754,
Fax: +82-2-2224-2569,
E-mail: lucidyonge@gmail.com

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Abstract

A considerable number of individual exhibit features of both asthma and chronic obstructive pulmonary disease (COPD), defined as asthma-COPD overlap (ACO). Many studies have reported that these patients are known to have a greater burden of symptoms, including cough and dyspnea, and experience more exacerbations and hospitalizations than those with non-ACO COPD or asthma. Although diagnostic criteria for ACO have not yet been clearly established, their clinical significance remains to be determined. As interest in ACO grows, related studies have been conducted in South Korea as well. The present review summarizes ACO-related studies in South Korea to better understand Korean ACO patients and guide further research. Several cohort studies of asthma and COPD and population-based studies for ACO were reviewed and the key results from demographics, clinical features, lung function, biomarkers, treatment, and prognosis are summarized.

Introduction

Although asthma and chronic obstructive pulmonary disease (COPD) are traditionally believed to be distinctive chronic airway diseases, with different pathophysiologies, a significant number of patients exhibit features of both. Since Gibson et al. (1) first described asthma-COPD overlap (ACO), a considerable number of studies have investigated this disease entity. However, it is difficult to obtain consistent information for ACO patients because individuals simultaneously exhibiting features of both asthma and COPD have been excluded from clinical studies investigating either disease; furthermore, because there are no unified diagnostic criteria for ACO, it is difficult to understand. Although there are many COPD or asthma cohorts worldwide, the prevalence and clinical features vary depending on which criteria are used to define ACO. Many cohorts have been defined as ACO by applying
“homemade” diagnostic criteria, as the diagnostic approach to ACO proposed by the Global Initiative for Asthma (GINA) (2) is difficult to apply in clinical practice. It remains controversial whether ACO is distinctive from asthma and COPD, or one of the phenotypes of either disease, however, interest in ACO is high, and related studies in clinical practice are ongoing.

The present review summarizes the current state of ACO studies in South Korea, and contributes to a more comprehensive understanding of Korean patients with ACO. The epidemiology and clinical manifestations of ACO are reviewed, and outcomes, including exacerbation(s), lung function decline, and the effect of treatment on prognosis, are discussed.

Epidemiology of ACO

There are asthma and COPD cohorts in Korea; however, the prevalence of ACO varies according to the criteria adapted to each cohort (Table 1). In two asthma cohorts exhibiting bronchodilator response (BDR) or airway hyper-responsiveness (AHR) positivity, ACO was defined as concomitant fixed airflow obstruction (post-BD forced expiratory volume in 1 s [FEV₁]/forced vital capacity [FVC] ratio < 0.7) for 3 months from baseline. These studies identified 97 of 256 (38%) (3) and 228 of 959 (23.8%) (4) patients with ACO. In the Korean Severe Asthma Registry (KoSAR), ACO was diagnosed through a questionnaire administered to attending specialists comprising allergy or pulmonary physicians, with 114 of 482 (23.7%) patients classified as ACO (5). Individuals with ACO were predominantly male, and prevalence increased with age. This study also investigated the main factors affecting the diagnosis of ACO, with three clinical features being particularly relevant: history of smoking, fixed airflow limitation, and BDR positivity at any time. The most influential factors contributing to ACO diagnosis were smoking history (76%), followed by fixed airflow...
limitation (55%), and BDR positivity (41%).

A single-center study involving 2933 COPD patients with suspected ACO according to the GINA document, identified 767 patients (26.2%) with ACO (6). A COPD cohort study from three hospitals defined ACO according to suggestions from four different sources—modified Spanish (7), American Thoracic Society (ATS) roundtable (8), PLATINO (a Spanish acronym for the Latin American Project for Research in Pulmonary Obstruction) (9), and the 2017 updated GINA/Global Initiative for COPD (GOLD) recommendations. It was reported that 31.3%, 11.9%, 48.3%, and 46.1% of COPD patients, respectively, were diagnosed with ACO (10). Cluster analysis using six variables (age, body mass index [BMI], FEV₁ %predicted, self-reported wheezing, smoking status, and pack-years [PYs] smoking) in the Korean National Health and Nutrition Examination Survey (KNHANES) database included patients with airflow limitation and FEV₁ ≥ 60 % (11). Of the 2140 subjects, the asthma-predominant overlap was 893 (42%), and the COPD-predominant overlap was 586 (27%). The Korean COPD subgroup study (KOCOSS) is a prospective cohort study of patients with COPD from 48 referral hospitals in the Republic of Korea. Of 1504 COPD patients, ACO was diagnosed in 223 (14.8%) according to BDR positivity alone (12); however, when applying the five different diagnostic criteria, ACO was diagnosed in 138 of 1067 (12.9%) patients according to GINA/GOLD, 32 of 873 (3.0%) according to the ATS roundtable, 171 of 992 (16.0%) according to the modified Spanish, and 221 of 730 (20.7%) according to the updated Spanish criteria (13, 14).

Clinical characteristics of ACO

The recently updated GINA guideline states that there is broad agreement for ACO that those patients have a greater burden of symptoms and poor quality of life (QoL), experience
frequent exacerbations, a more rapid decline in lung function, greater use of healthcare
resources, and higher mortality compared to those with asthma or COPD alone (2). In recent
years, several studies have investigated ACO in South Korea, and the clinical features
reported varied according to the definition of ACO and across cohorts.

In two asthma cohorts (3, 4), ACO patients were older, more often male, and more often
former smokers than those with asthma alone. The KoSAR cohort also reported that ACO
patients were older, predominantly male, and more often smokers than patients with severe
asthma. However, there was no significant difference in QoL between patients with severe
asthma and those with ACO (5).

Across studies involving COPD cohorts, the clinical features of ACO and COPD alone
have been reported slightly differently. Some studies reported that ACO patients were older
and more often male and smokers than those with COPD alone (11, 12). In contrast, others
reported that ACO patients were less male predominant with less smoking than patients with
COPD alone (6, 14). Several studies have reported that ACO patients have a poorer QoL
status than those with COPD or asthma alone, according to indexes of QoL measurement
tools for asthma or COPD (10, 12, 15, 16).

Regarding exacerbation history within one year before enrollment, several COPD cohort
studies have reported that ACO patients experienced more moderate or severe exacerbation(s)
compared with COPD alone (10, 14, 17). Similarly, patients with ACO experienced more
exacerbations, required steroid burst therapy or emergency room visits or hospitalization than
those with severe asthma (5). However, some studies reported no differences in exacerbation
between patient with ACO and those with COPD (18, 19). Moreover, one study reported
fewer previous exacerbation events in patients with ACO than in those with COPD alone,
although the difference was not statistically significant (12).
**Lung function**

Two asthma studies reported lower FEV\(_1\) and FEV\(_1\)/FVC ratios in patients with ACO than in those with asthma (3, 4). Moreover, ACO patients exhibit a low provocation concentration causing a 20% fall in FEV\(_1\) (PC\(_{20}\)) or provocation dose causing a 15% decrease in FEV\(_1\) (PD\(_{15}\)) compared with asthmatic patients. Lung volume was measured in one asthma study and revealed that ACO patients have higher functional residual capacity and residual volume than asthmatic patients (3). In the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) cohort study, there was higher BDR positivity in patients with ACO than in those with asthma (4). Specialist-diagnosed ACO patients in the KoSAR cohort had lower FEV\(_1\), FVC, and FEV\(_1\)/FVC ratio than patients with severe asthma; however, fractional exhaled nitric oxide values were similar between the two groups (5).

Among studies of COPD cohorts, contradictory results regarding lung function measurements have been reported. Some reported that those with ACO exhibited lower FEV\(_1\), FVC, and a lower FEV\(_1\)/FVC ratio (6, 15), while others reported that those with ACO had higher FEV\(_1\), higher FVC, and higher FEV\(_1\)/FVC ratio than those with COPD alone (10, 14, 20). However, more BDR positivity has been consistently observed in patients with ACO than in those with COPD across studies (6, 10, 14, 20).

**Comorbid conditions of ACO**

ACO studies using a nationwide representative database including the National Health Insurance (NHI) and the KNHANES defining ACO according to the *International Classification of Diseases, 10th Revision* (ICD-10) codes for COPD and asthma reported that ACO patients often exhibit ischemic heart disease, diabetes mellitus, hypertension,
psychiatric disorders (e.g., depression and anxiety), and osteoporosis more frequently than those with COPD alone (17, 18). Other studies using the KNHANES database defined ACO based on history of asthma diagnosis or subjective wheezing reported that individuals with ACO had a lower BMI that was accompanied by osteoporosis and sarcopenia as comorbid conditions, compared to those with COPD (15, 21, 22). Among the KoSAR cohort, individuals with ACO have less allergic rhinitis or chronic rhinosinusitis and aspirin intolerance, but more hypertension and a history of pulmonary tuberculosis compared with patients with severe asthma (5). In contrast, ACO patients more often had a history of asthma, atopy, and allergic rhinitis as comorbid conditions than those with COPD alone in the KOCOSS cohort (14).

Biomarkers

Blood eosinophils

Two studies involving cohorts with asthma defined ACO according to BDR or AHR positivity with fixed airflow limitation reported inconsistent results on blood eosinophil levels between those with asthma and ACO. Lee et al. (3) reported that ACO patients had lower blood eosinophil counts compared to those with asthma alone; however, Park et al. (4) reported no significant difference in blood eosinophil levels between the groups. In the KoSAR cohort, patients with ACO had lower blood eosinophil levels but higher neutrophil counts than those with asthma alone, with no difference in the proportion of sputum eosinophils between the groups (5).

Individuals with ACO in the two COPD cohorts exhibited higher blood eosinophil counts than those with COPD alone. In addition, total immunoglobulin E (IgE) levels were higher in patients with ACO than in those with COPD alone (10, 14).
Urine L-histidine and serum club cell secretory protein 16

One small prospective cohort of patients with chronic airway disease, including patients aged ≥ 19 years in a stable state for > 3 months, analyzed urinary L-histidine and serum club cell secretory protein 16 (CC-16) using liquid chromatography-mass spectrometry and metabolomic analysis, or ELISA. This cohort comprised 32 asthma, 38 COPD, and 37 ACO patients diagnosed based on the GesEPOC (the Spanish COPD guidelines) and GEMA (Spanish Guidelines for the Management of Asthma) algorithms (23). Urinary L-histidine levels were higher in individuals with ACO than in those with asthma or COPD alone even when the ACO group was subdivided into those with smoking-related obstructive asthma (n = 27) and COPD with highly positive BDR and/or blood eosinophilia (n = 10), urinary L-histidine levels were higher in both groups than those with asthma or COPD (24). In addition, serum CC-16 levels were decreased in patients with ACO, especially in those with frequent exacerbations (25). The authors suggested that urinary L-histidine and serum CC-16 are potential biomarkers for ACO, regardless of the diversity of diagnostic criteria used or discrimination of frequent exacerbators.

Neutrophil gelatinase-associated lipocalin

Of the 137 patients from the COPD in the Dusty Areas (CODA) cohort, 77 were identified with ACO based on positive BDR or previous history of asthma, and plasma neutrophil gelatinase-associated lipocalin (NGAL) levels were analyzed using ELISA. NGAL levels were higher in females with ACO (17.0 ± 6.4 ng/mL versus [vs.] 11.1 ± 4.5 ng/mL; p = 0.01), and it demonstrated favorable predictive ability to discriminate ACO from non-ACO COPD (area under the receiver operating characteristic curve [AUROC], 0.79), which was similar to
blood eosinophil level (AUROC, 0.79) (26).

**Genome-wide association study in an asthma cohort**

Among the COREA cohort, genetic information was available for 1433 patients comprising those with ACO (n = 77) and those with asthma (n = 1356). There are no significant single nucleotide polymorphisms that can discriminate ACO from asthma (4).

**Imaging**

The Korean Obstructive Lung Disease (KOLD) study provides volumetric computed tomography (CT) scan measurements, and the emphysema index (EI), defined as the percentage of low attenuation area ≤ 950 Hounsfield units (HU), and airway thickening according to mean wall area (MWA, percentage of two segmental bronchi), were derived using in-house software from the KOLD study (27). Those with ACO (47 of 239 COPD patients) had a lower proportion of emphysema compared to those with COPD alone (17.1% vs. 22.1%, respectively; \( p = 0.044 \)) (20). The CODA study also provides volumetric CT scan measurements based on the KOLD study, and those with ACO in the CODA cohort (n = 77) exhibited a lower EI (7.9% vs. 9.7%, \( p = 0.06 \)) compared to those with COPD alone; however, there was no difference in MWA (%) (26).

Hwang et al. (28) assessed regional ventilation abnormalities in patients with ACO (n = 21) and COPD (n = 46) using xenon-ventilation dual-energy CT and quantified EI, airway wall thickness (Pi10), and mean ventilation values. There were three patterns: 1) peripheral wedge/diffuse defects, 2) diffuse heterogeneous defects, and 3) lobar/segmental/subsegmental defects. ACO was more common in pattern 1, and COPD was more common in patterns 2 and 3. The degree of peripheral lung ventilation was lower in the ACO group than in the non-ACO
group (21.3 vs 22.8 HU; $p = 0.045$). On the other hand, the EI was lower in the ACO group (7.7% vs. 12.0%; $p = 0.070$), and airway wall thickness was higher in those with ACO (5.0 vs. 4.7 mm; $p = 0.041$). This study suggested that ventilation abnormalities are different between patients with ACO and COPD; thus, physiological changes in these two groups of patients may be assessed using imaging methods.

**Prognosis of ACO**

**Changes in lung function**

The Canadian Cohort Obstructive Lung Disease (CanCOLD) study reported that faster FEV$_1$ decliners were more frequently observed in ACO (29) and GINA, and described that there was broad agreement for more rapid lung function decline in ACO than in those with asthma or COPD alone (2). However, there is still insufficient evidence for a change in the lung function of ACO. In addition, several Korean ACO studies have reported conflicting results on lung function change.

In the COREA cohort, which estimated the lung function changes at one and three years later, the ACO group showed greater FEV$_1$ and FVC decline than the asthma group only (4). In COPD studies, conflicting results have been reported for changes in lung function in patients with ACO. Park et al. (8) defined ACO based on the ATS roundtable criteria in the KOLD cohort. The FEV$_1$ changes between those with ACO ($n = 47$) and COPD ($n = 192$) for a median of 5.8 years’ follow-up were compared. The rate of FEV$_1$ change was -13.9 mL/year in those with ACO, and -29.3 mL/year in those with COPD; a favorable outcome was identified in terms of lung function decline in ACO (20). Park et al. (12) also reported favorable FEV$_1$ changes over a three-year follow-up in patients with ACO according to the BDR positivity criteria in the KOCOSS cohort. However, another study of the KOCOSS
cohort reported that ACO patients, defined according to four sets of diagnostic criteria, experienced greater FEV$_1$ decline than those with COPD in two distinct criteria for ACO (30).

**Exacerbation risk**

The risk of exacerbation across the ACO studies is summarized in Table 2. Lee et al. (31) reported that concomitant self-reported physician-diagnosed asthma was an independent risk factor for severe exacerbation of COPD through the KNHANES database (adjusted odds ratio [aOR] 1.67). Several other studies have also reported a higher future exacerbation risk in individuals with ACO than in those with asthma or COPD alone. In the COREA cohort, individuals with ACO experienced more exacerbations at one year (1.61 vs. 2.38, respectively; $p < 0.001$) and three years (0.73 vs. 0.65; $p = 0.07$) follow-up compared to those with asthma alone (4). In COPD studies, ACO defined according to the GINA guideline reported a high rate of hospitalizations for those with ACO (32), and ACO in the KOCOSS cohort, defined according to four sets of diagnostic criteria, experienced more exacerbations compared with COPD alone (10). In the KNHANES database, self-reported wheezing and smoking history-based COPD-predominant ACO patients experienced more severe exacerbations compared with both normal and smokers (adjusted hazard ratio [HR] 1.79 and 2.11, respectively) (15). Park et al. (12) reported a lower exacerbation risk in patients with ACO than in those with COPD alone (12). This study used only the BDR positivity criterion to define ACO in the KOCOSS cohort. However, Jo et al. (16) reported no significant difference in the exacerbation risk between ACO and COPD alone in a later study analyzing the KOCOSS cohort, although the authors assessed the risk for exacerbation at the 6-month follow-up (16). Recently, Kim et al. (33) reported that asthma as a comorbid condition of COPD was associated with exacerbation in the NHI Service-National Sample Cohort (OR, 1.57).
Mortality

The long-term outcomes of ACO in terms of mortality have been investigated in both population-based and cohort studies, with conflicting results. Population-based studies have reported higher mortality in ACO patients (34-36), but some cohort studies reported lower mortality in ACO patients (37-39). However, there are insufficient long-term data related to the mortality of ACO in Korea.

Lee et al. (40) conducted a retrospective cohort study using the KNHANES database, and found that chronic corticosteroid-dependent asthmatics aged 40 years of age or older had higher mortality when they had concomitant COPD than in those without COPD (9,955/100,000 person-years vs. 5,585/100,100 person-years, \( p < 0.001 \) and adjusted HR 1.29). Another retrospective, single-center study involving 2933 COPD patients, among which 767 were ACO, reported that ACO patients had a significantly higher mortality rate than patients with COPD alone (54.9% vs. 45.1%, respectively; \( p < 0.001 \)) (32). In a recent population-based cohort study of 3127 ACO and 31,868 COPD patients followed up for four years, Lee et al. (41) reported that exposure to particulate matter (PM\(_{10}\)) caused an increase in non-accidental mortality in all COPD patients, especially those diagnosed with ACO within the 1-, 3-, and 6-month follow-up periods. In addition, the adverse effects of PM\(_{10}\) exposure were more prominent in females (HR, 1.153) and never smokers (HR, 1.151).

Healthcare resource use and cost

ACO defined by fulfilling both the ICD-10 codes for COPD and asthma (17), or by COPD plus self-reported wheezing criteria (42) through the NHI database, reported significantly higher medical costs and longer total length of healthcare resource use in both outpatient and
inpatient services among ACO patients. Another population-based cohort study also reported significantly greater medical costs in patients with COPD-predominant ACO (15).

**Treatment and clinical impact on outcomes**

**Treatment status of ACO in clinical practice**

There was no significant difference in inhaled corticosteroid (ICS)/long-acting beta-2 receptor agonist (LABA), leukotriene receptor antagonist (LTRA), and omalizumab (anti-IgE) prescription in ACO, despite the administration of the long-acting muscarinic receptor agonist (LAMA), xanthine. More systemic steroids were administered to those with ACO compared to those with severe asthma (5). In contrast, more ICS-containing maintenance inhaler therapy was prescribed in patients with ACO than in those with COPD alone (14, 15, 17, 20, 32). However, conflicting results have been reported regarding the use of LAMA. A single COPD cohort study and a KNHANES database-derived study reported less LAMA use in ACO than in COPD (11, 32). However, another study of KNHANES that defined ACO according to subjective wheezing found that LAMA, LTRA, and even oral corticosteroids were more frequently prescribed to patients with ACO than those with COPD alone (15).

There were differences in the frequency of medications used, even among ACO patients in a single-center cohort, due to the heterogeneity of ACO itself (43). Patients with ACO were subdivided into four groups according to their blood eosinophil count of 300 cells/mL and 10 PYs. ACO with fewer PYs tended to be female, and ICS/LABA and LTRA were the most frequently prescribed. However, ACO with more PYs smoking tended to be male and ICS/LABA was prescribed the most, but LAMA was also frequently used, and LTRA was relatively less prescribed.
Effect of ICS treatment on lung function and future exacerbation

Several studies have analyzed the effects of treatment on prognosis, including lung function and exacerbation, which are summarized in Table 3.

Lim et al. (44) analyzed the effect of ICS use on exacerbation and lung function changes in patients with ACO in a COPD cohort. In this study, ACO defined according to BDR or AHR positivity was divided into two groups: ACO with ICS treatment (n = 90), and ACO without ICS treatment (n = 35). As a result, ICS treatment had no beneficial effect on severe exacerbation (adjusted incidence rate ratio [IRR] 1.24 [95% confidence interval (CI) 0.44–3.46]) and FEV₁ decline (-9.61 ml/year vs. -15.68 mL/year in the ICS vs. non-ICS treatment group, respectively; p = 0.598). However, Lee et al (45) reported ICS/LABA (fixed dose 50μg salmeterol/500μg fluticasone or 9μg formoterol/320μg budesonide, twice daily) treatment for three months improved FEV₁ and FVC better in those with ACO compared to those with COPD alone (FEV₁, 240.2 mL vs. 124.6 mL, p = 0.002; FVC, 304.8 mL vs. 150.2 mL; p = 0.030), and this beneficial effect was robust in the mild to moderate airflow limitation group.

Using five sets of diagnostic criteria in the KOCOSS cohort, ICS treatment decreased the risk for exacerbation in ACO of two sets of criteria (IRR, 0.55 and 0.69 in specialists’ diagnosis and GINA/GOLD criteria; p< 0.05 for both). The authors also suggested that, among COPD patients, the only factor associated with the reduction of exacerbation risk by ICS treatment was a high blood eosinophil count (≥ 300 cells/mL) (14).

Effect of LAMA add-on to ICS/LABA on prognosis

Recently, a multicenter randomized trial of 303 ACO patients who defined ACO as positive BDR or AHR and FEV₁/FVC < 0.7 and whose FEV₁ > 30% with moderate to high dose ICS/LABA treatment, was conducted. The times to first exacerbation between ACO with
ICS/LABA (n = 154) and LAMA added to ICS/LABA (n = 149) were analyzed (46). There was no significant difference in exacerbation events (HR 1.1, 95% CI 0.66–1.84); however, FEV$_1$ and FVC improved significantly in the LAMA add-on group (0.017 L vs. 0.108 L for FEV$_1$ and -0.004 L vs. 0.125 L for FVC; $p < 0.05$ for both).

**Conclusion**

In conclusion, despite the lack of consensus regarding the definition and recognition of ACO as a distinct disease entity with a distinct pathophysiological background, many Korean physicians have devoted attention to ACO. This may be due to the need for appropriate therapy for these patients because the clinical features and prognosis of ACO are somewhat different from those of asthma and COPD. In South Korea, ACO research has been conducted in various fields and has generally shown similar characteristics to the previously known group of ACO patients. This is important because an appropriate identification of patients with ACO may allow better targeted therapy, and could improve the clinical course. For prognosis, such as lung function changes and the effect of therapies, additional research using long-term data and consistent criteria for patient classification will be needed.

**Conflicts of Interest: None**


Table 1. Prevalence of ACO

<table>
<thead>
<tr>
<th>Citation</th>
<th>No. of patients</th>
<th>ACO definition</th>
<th>Prevalence of ACO</th>
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<tbody>
<tr>
<td>Lee et al. 2014</td>
<td>256 asthma patients</td>
<td>BDR &gt;200 mL and 12% or positive provocation test* AND Post BD FEV1/FVC &lt;0.70</td>
<td>97 (38%)</td>
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<tr>
<td>Park et al. 2019</td>
<td>959 asthma patients</td>
<td>BDR &gt;200 mL and 12% or positive provocation test* AND</td>
<td>228 (23.8%)</td>
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Table 2. The risk of exacerbation in ACO

<table>
<thead>
<tr>
<th>Citation</th>
<th>No. of patients</th>
<th>Definition of ACO</th>
<th>Duration of follow-up</th>
<th>Exacerbation risk statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 2021 (5)</td>
<td>482 severe asthma patients</td>
<td>Post BD FEV₁/FVC &lt;0.7 AND Specialist-diagnosed asthma-COPD overlap</td>
<td>10 years</td>
<td>Hospitalization than COPD-only group 31.3% vs 13.0%, p&lt;0.001</td>
</tr>
<tr>
<td>Kim et al. 2015 (32)</td>
<td>2933 COPD patients</td>
<td>Post BD FEV₁/FVC &lt;0.7 AND Asthma was diagnosed according to the GINA definition</td>
<td>1 year</td>
<td>Moderate to severe exacerbation compared to non-ACO COPD Adjusted HR - 1.97 (95% CI, 1.14-3.41) - 1.07 (95% CI, 0.2-5.82) - 1.35 (95% CI, 0.81-2.25) - 2.01 (95% CI, 0.97-4.15)</td>
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<tr>
<td>Park et al. 2017 (12)</td>
<td>1504 COPD patients</td>
<td>Post BD FEV₁/FVC &lt;0.7 AND BDR &gt;200 mL and 200 mL</td>
<td>2 years</td>
<td>Any AE required systemic corticosteroid, antibiotics or both in</td>
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Kim et al. 2018(15) 2269 of KNHANES database FEV₁/FVC <0.7 & FEV₁ ≥ 50% AND Self-reported wheezing (W⁺)
* Smoking (S+) was defined a current or an exsmoker who had smoked ≥100 cigarettes; W+S⁻ and W+S⁺ were asthma-predominant ACO and COPD-predominant ACO, respectively.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study design</th>
<th>Definition of ACO</th>
<th>Treatment</th>
<th>Results</th>
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<tbody>
<tr>
<td>Lim et al. (2014)(44)</td>
<td>Retrospective cohort study</td>
<td>Smoking PY ≥10 AND Post BD FEV₁/FVC &lt;0.7 AND BDR &gt;200 mL and 12% or positive provocation test*</td>
<td>ICS use (N=90) vs non-ICS use (N=35) in ACO patients</td>
<td>FEV₁ decline: No significant differences (9.61 ml/yr vs 15.68 mL/yr in ICS vs non-ICS group, p=0.598) Exacerbation: No reduction in severe exacerbation (adjusted incidence rate ratio 1.24, 95% CI, 0.44-3.46) Time to death: no differences</td>
</tr>
<tr>
<td>Lee et al. (2016)(45)</td>
<td>Retrospective cohort study</td>
<td>Smoking PY &gt;10 AND Post BD FEV₁/FVC &lt;0.70 AND History of asthma, and self-reported wheezing within 1 year &amp; BDR &gt;200 mL and 12%</td>
<td>ICS/LABA on ACO (N=45) vs COPD (N=107)</td>
<td>FEV₁ decline: favorable in ACO (240.2mL vs 124.6mL in ACO vs COPD, p=0.002) - mild to moderate AFL: 223 mL vs 84.6mL, p=0.005 - more than severe AFL: 268.2mL vs 197.1mL, p=0.209 Exacerbation: No significant differences (15.0% vs 12.2%, p=0.719)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Inclusion Criteria</td>
<td>Outcomes</td>
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| Jo et al. (2020)(14) | Retrospective cohort study | - GINA/GOLD guideline  
- ATS roundtable  
- Modified Spanish  
- Updated Spanish  
- Specialist’s judgement | ICS use vs non-ICS use in ACO  
- 81 vs 57 in GINA/GOLD  
- 21 vs 11 in ATS  
- 74 vs 97 in modified Spanish  
- 93 vs 128 in Updated Spanish  
- 152 vs 112 in specialists’ decision | Exacerbation: reduced moderate to severe exacerbation in ACO according to the specialists’ diagnoses and the GINA/GOLD criteria  
- adjusted IRR 0.34 (95% CI, 0.17-0.69) and 0.61 (0.39-0.95), respectively |
| Park et al. (2021)(46) | Randomized, noninferiority trial | Post BD FEV₁/FVC <0.7 AND BDR >200 mL and 12% or positive provocation test*  
Only ACO with FEV₁ >30% & moderate to high dose of ICS/LABA were enrolled | ICS/LABA (N=154) vs. ICS/LABA/LAMA (N=149) in ACO patients | Exacerbation: 18.8% (29/154) vs 18.8% (28/149) in ICS/LABA vs ICS/LABA/LAMA (HR 1.1; 95% CI 0.6-1.84)  
FEV₁ change: 0.017 L vs 0.108 L, p=0.023 in ICS/LABA vs ICS/LABA/LAMA |