

# Combination therapy of inhaled steroids and long-acting beta2-agonists in asthma–COPD overlap syndrome

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**Background:** The efficacy of inhaled corticosteroids (ICSs)/long-acting beta2-agonist (LABA) treatment in patients with asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) compared to patients with COPD alone has rarely been examined. This study aimed to evaluate the clinical efficacy for the improvement of lung function after ICS/LABA treatment in patients with ACOS compared to COPD alone patients.

**Methods:** Patients with stable COPD were selected from the Korean Obstructive Lung Disease (KOLD) cohort. Subjects began a 3-month ICS/LABA treatment after a washout period. ACOS was defined when the patients had 1) a personal history of asthma, irrespective of age, and wheezing in the last 12 months in a self-reported survey and 2) a positive bronchodilator response.

**Results:** Among 152 eligible COPD patients, 45 (29.6%) fulfilled the criteria for ACOS. After a 3-month treatment with ICS/LABA, the increase in forced expiratory volume in 1 second (FEV<sub>1</sub>) was significantly greater in ACOS patients than in those with COPD alone (240.2±33.5 vs 124.6±19.8 mL,  $P=0.002$ ). This increase in FEV<sub>1</sub> persisted even after adjustment for confounding factors (adjusted  $P=0.002$ ). According to severity of baseline FEV<sub>1</sub>, the ACOS group showed a significantly greater increase in FEV<sub>1</sub> than the COPD-alone group in patients with mild-to-moderate airflow limitation (223.2±42.9 vs 84.6±25.3 mL,  $P=0.005$ ), whereas there was no statistically significant difference in patients with severe to very severe airflow limitation.

**Conclusion:** This study provides clinical evidence that ACOS patients with mild-to-moderate airflow limitation showed a greater response in lung function after 3 months of ICS/LABA combination treatment.

**Keywords:** pulmonary disease, chronic obstructive, asthma, respiratory function tests

## Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are two major pulmonary diseases characterized by chronic airway inflammation; the features of both the diseases are often shared in substantial patients who present with chronic respiratory symptoms and airflow limitation. Recently, the disease entity of asthma–COPD overlap syndrome (ACOS) has been described and identified by global guidelines,<sup>1,2</sup> and 13%–55% of COPD patients are estimated to have characteristics of ACOS depending on the diagnostic criteria applied.<sup>3–5</sup> Despite inconsistent ACOS diagnosis criteria or definition, numerous studies have consistently reported that patients with ACOS experience more respiratory symptoms, severe and frequent exacerbations, comorbidities, and healthcare utilization compared to those with COPD alone.<sup>6–8</sup>

Treatment in ACOS patients is poorly implemented because pharmacological clinical trials have excluded either asthma patients from COPD studies or COPD patients from

asthma studies.<sup>9</sup> The key difference in treatment between the two diseases is the use of inhaled corticosteroids (ICSs). ICS is the principal treatment of choice for asthma, while its usage is recommended only for those COPD patients with severe-to-very severe airflow limitation and frequent exacerbations that are not adequately controlled by long-acting bronchodilators, according to current guidelines.<sup>1</sup> Recently, patients with ACOS have been suggested to be more responsive to ICS compared to those with COPD alone;<sup>10</sup> however, the benefits of ICS has rarely been examined in patients with ACOS.

In the current guidelines, long-acting beta2-agonist (LABA) monotherapy is considered as first-line therapy in COPD patients, but LABA monotherapy without ICS is never considered to be acceptable in asthma patients.<sup>2</sup> In addition, ICS monotherapy is not recommended in COPD patients.<sup>1</sup> Thus, this study aimed to evaluate the clinical efficacy for lung function improvement after a 3-month combined inhalation of ICS and a long-acting  $\beta$ 2-agonist (LABA) in ACOS patients compared with those with COPD alone.

## Methods

### Subjects

This study retrospectively analyzed data from patients with stable COPD selected from the Korean Obstructive Lung Disease (KOLD) cohort, which is prospectively recruited from the pulmonary clinics of 14 hospitals in South Korea between June 2005 and December 2012.<sup>11</sup> The criteria for COPD patients to be enrolled in KOLD are as follows: age  $\geq 40$  years, presence of airflow limitation that was not fully reversible (post-bronchodilator forced expiratory volume in 1 second/forced vital capacity [FEV<sub>1</sub>/FVC] <70%), smoking history >10 pack-years, and no or minimal abnormality on chest radiography. After enrollment in the KOLD cohort, some subjects underwent a 2-week washout period and then received treatment including a fixed-dose combination inhaler of ICS and LABA. However, subjects whose condition did not allow cessation of medications did not undergo a washout period and maintained their original treatment. This decision was made at the discretion of the treating physicians. Baseline clinical data including Charlson comorbidity score, extent of dyspnea (modified Medical Research Council [mMRC] dyspnea score), blood eosinophil count, lung function, and chest CT scan were obtained after cessation of the following respiratory medications: an ICS for 2 weeks, an inhaled LABA or long-acting muscarinic antagonist for 2 days, and an inhaled short-acting  $\beta$ 2-agonist or inhaled short-acting anticholinergic for 12 hours. Spirometry and lung volumes were again measured following the 3-month treatment. Subjects who underwent a washout period were treated with a fixed-dose combination inhaler

of ICS and LABA (50  $\mu$ g salmeterol/500  $\mu$ g fluticasone or 9  $\mu$ g formoterol/320  $\mu$ g budesonide, twice daily) for the following 3 months after the washout period. After exclusion of 30 subjects using tiotropium in addition to ICS and LABA during the 3 months, a total of 152 subjects remained eligible for this study. The institutional review boards of all participating hospitals (Ajou Institutional Review Board; Asan Medical Center Institutional Review Board; CHA Bundang Medical Center, CHA University Institutional Review Board; Ewha Womans University Mokdong Hospital Institutional Review Board; Hanyang University Guri Hospital Institutional Review Board; Inje University Ilsan Paik Hospital Institutional Review Board; Kangbuk Samsung Hospital Institutional Review Board; Kangnam Sacred Heart Hospital Institutional Review Board; Kangwon National University Hospital Institutional Review Board; Korea University Anam Hospital Institutional Review Board; National Medical Center Institutional Review Board; Seoul National University Bundang Hospital Institutional Review Board; Seoul National University Hospital Institutional Review Board; Yeouido St Mary's Hospital, Institutional Review Board) approved the study protocol, and written informed consent was obtained from all the patients.

### Pulmonary function tests

Spirometry was performed using a Vmax 22 instrument (Sensor-Medics; Yorba Linda, CA, USA) or a PFDX machine (MedGraphics, St Paul, MN, USA), as recommended by the American Thoracic Society/European Respiratory Society.<sup>12</sup> FVC, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC were evaluated both before and 15 min after inhalation of 400  $\mu$ g albuterol. Lung volume was measured by body plethysmography (V600, Sensor-Medics, or PFDX). DL<sub>CO</sub> was assessed by the single-breath method using a Vmax229D (Sensor-Medics) or a Masterlab Body (Jaeger AB, Wurzburg, Germany) instrument. Absolute values of FVC and FEV<sub>1</sub> were obtained, and the percentage of the predicted value (% predicted) for FEV<sub>1</sub> and FVC was calculated from equations formulated using data from a population of healthy non-smoking Koreans.<sup>13</sup> Spirometry was conducted at baseline and after 12 weeks of treatment.

### Computed tomography (CT)

Volumetric CT scans were performed using 16-slice multi-detector CT scanners as previously described.<sup>14</sup> The extent of emphysema (emphysema index) was estimated using the threshold technique quantifying the percentage ratio of low attenuation areas (an apparent X-ray attenuation value below -950 HU) to the corresponding lung areas.<sup>15</sup> Airway wall areas were measured near the origin of the right apical

and left apico-posterior segmental bronchi as selected by the consensus of two radiologists.<sup>16</sup>

### Definition of ACOS, the severity of airflow limitation, and FEV<sub>1</sub> responders

ACOS was defined when patients had 1) a personal history of asthma irrespective of age and wheezing in the last 12 months in a self-reported survey and 2) a positive bronchodilator response defined as a >12% and 200 mL post-bronchodilator increase in FEV<sub>1</sub> from baseline values.<sup>8</sup> COPD severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grading system: mild-to-moderate, FEV<sub>1</sub> ≥50% predicted; and severe to very severe, FEV<sub>1</sub> <50% predicted.<sup>1</sup> Subjects were classified as FEV<sub>1</sub> responders or FEV<sub>1</sub> non-responders based on an FEV<sub>1</sub> improvement of at least 12% and 200 mL from baseline after 3 months of combined treatment with ICS/LABA.<sup>17</sup>

### Statistical analysis

The baseline characteristic data are presented as mean ± standard deviation if normally distributed or as median (interquartile range [IQR]) if non-normally distributed for continuous variables as appropriate. Categorical variables were presented as frequency with percentage. Continuous

variables were analyzed using a *t*-test or Mann–Whitney *U*-test based on normality, and categorical data were compared using Pearson's  $\chi^2$  test or Fisher's exact test. A multiple linear regression for FEV<sub>1</sub> changes following a 3-month ICS/LABA treatment, and a logistic regression analysis for FEV<sub>1</sub> responders were performed with adjustment for the following variables: Model 1 contained demographic variables of age (continuous), body mass index (BMI, continuous), and smoking pack-years; Model 2 additionally included pulmonary-related variables of baseline FEV<sub>1</sub>, baseline mMRC, baseline CT-determined emphysema index, and peripheral blood eosinophils (≥260/μL).<sup>17</sup> Sex was excluded as a covariate because 97.4% of the population was male. We used the Hosmer–Lemeshow test to verify the goodness of the model fit. A two-sided *P*-value <0.05 was considered significant. All statistical tests were performed using SPSS Statistics, version 22.0 (IBM, Armonk, NY, USA).

## Results

### Patient characteristics

As shown in Table 1, 45 subjects (29.6%) fulfilled the definition of ACOS. There were no significant differences in age, sex, BMI, smoking history, initial Charlson comorbidity score, and dyspnea score (mMRC) between the ACOS and COPD-alone

**Table 1** Baseline characteristics of ACOS and COPD-alone patients

	ACOS (N=45)	COPD alone (N=107)	P-value
Age, years	64 (61–70)	68 (61–71)	0.440
Male (n)	44 (97.8)	104 (97.2)	1.000
Body mass index, kg/m <sup>2</sup>	23.9 (22.3–25.6)	23.1 (20.4–25.4)	0.131
Smoking status			
Current smoker	17 (37.8)	44 (41.1)	0.721
Pack-years	44.0 (36.6–55.0)	45.0 (30.0–55.0)	0.729
Charlson comorbidity score	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.684
mMRC dyspnea score	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.366
Severity of airflow limitation			
Severe to very severe	17 (37.8)	38 (35.5)	0.854
Pulmonary function test			
FVC, L	3.34 (2.62–3.66)	3.25 (2.65–3.87)	0.715
FVC, % predicted	82.0 (73.2–95.5)	87.0 (73.0–99.0)	0.323
FEV <sub>1</sub> , L	1.53 (1.19–1.81)	1.52 (1.09–1.91)	0.569
FEV <sub>1</sub> , % predicted	54.9 (44.5–65.5)	56.0 (43.0–72.0)	0.339
TLC, L	6.17 (5.62–7.11)	6.78 (5.63–7.48)	0.319
RV, L	3.03 (2.41–3.51)	2.93 (2.15–4.00)	0.192
IC, L	2.05 (1.67–2.39)	1.92 (1.56–2.52)	0.718
DL <sub>CO</sub> , %	85.0 (66.0–96.0)	83.0 (71.0–101.3)	0.848
CT determined			
Emphysema index, %	15.6 (7.6–27.0)	15.7 (7.3–33.5)	0.240
Mean wall area, %	66.5 (62.4–70.2)	65.7 (62.0–69.4)	0.545
Peripheral eosinophil count			
Eosinophil count, /μL	213.3 (134.2–339.5)	197.1 (108.3–360.4)	0.251
Eosinophil count ≥260, %	20 (44.4)	43 (40.2)	0.719

**Note:** The data are presented as number (%) or as median and interquartile range.

**Abbreviations:** ACOS, asthma–COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DL<sub>CO</sub>, diffusing capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; mMRC, modified Medical Research Council; RV, residual volume; TLC, total lung capacity.

**Table 2** Changes of pulmonary function and symptom score, and the rate of acute exacerbation after 3 months of treatment in ACOS and COPD-alone patients

	ACOS (N=45)	COPD alone (N=107)	P-value
Changes of pulmonary function and symptom score			
Δ FEV <sub>1</sub> , mL	240.2±33.5	124.6±19.8	0.002
Δ FVC, mL	304.8±59.0	150.2±38.1	0.030
Δ TLC, mL	435.3±264.0	888.3±247.7	0.213
Δ RV, mL	-93.3±156.0	102.8±129.5	0.380
Δ IC, mL	166.9±84.9	141.5±62.6	0.820
Δ mMRC	-0.05±0.17	-0.39±0.08	0.126
Acute exacerbation, %	15.0	12.2	0.719

**Note:** The baseline PFT data are presented as median and interquartile range, and lung function changes are presented as mean ± standard error.

**Abbreviations:** ACOS, asthma-COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; mMRC, modified Medical Research Council; RV, residual volume; TLC, total lung capacity.

groups. In addition, 37.8% (17/45) of the ACOS group and 35.5% (38/107) of the COPD-alone patients had severe to very severe airflow limitation. Initial FEV<sub>1</sub>, FVC, total lung capacity (TLC), residual volume (RV), inspiratory capacity (IC), DL<sub>CO</sub>, CT-determined emphysema index, and mean wall area were not different between the two groups. Blood eosinophil count was 213.3/μL (IQR, 134.2–339.5/μL) in the ACOS group and 197.6/μL (IQR, 113.2–364.0/μL) in the COPD-alone group, which were not significantly different.

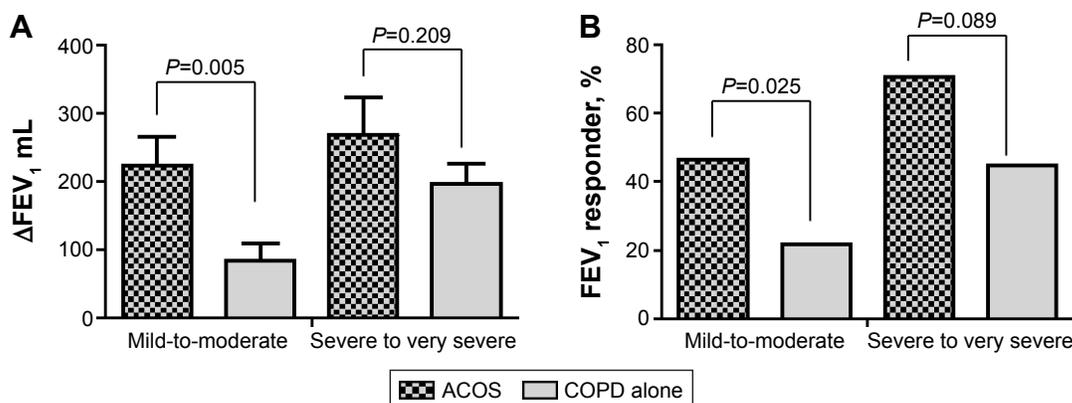
#### Changes of pulmonary function and symptom score following 3 months of ICS/LABA treatment

The changes of TLC, RV, and IC during the 3 months were not different between the ACOS and COPD-alone groups, while FEV<sub>1</sub> (240.2±33.5 vs 124.6±19.8 mL,  $P=0.002$ ) and FVC (304.8±59.0 vs 150.2±38.1 mL,  $P=0.030$ ) significantly

increased with 3 months of ICS/LABA treatment in the ACOS group compared with the COPD-alone group (Table 2). The change of mMRC score and the rate of acute exacerbations during 3 months did not show significant differences between ACOS and COPD-alone groups (Table 2). When comparing FEV<sub>1</sub> increase based on the severity of airflow limitation, the ACOS group showed greater improvement than the COPD-alone group in patients with mild-to-moderate airflow limitation (223.2±42.9 vs 84.6±25.3 mL,  $P=0.005$ ), but the FEV<sub>1</sub> increase did not reach statistical significance in those with severe to very severe airflow limitation (268.2±54.5 vs 197.1±28.4 mL,  $P=0.209$ ) (Figure 1A). The percentage of FEV<sub>1</sub> responders was also higher in the ACOS group than the COPD-alone group in patients with mild-to-moderate airflow limitation (46.4% vs 12.7%,  $P=0.025$ ) but not in those with severe to very severe airway obstruction (70.6% vs 44.6%  $P=0.089$ ; Figure 1B).

#### ACOS as a predictor of FEV<sub>1</sub> increase following 3 months of ICS/LABA treatment

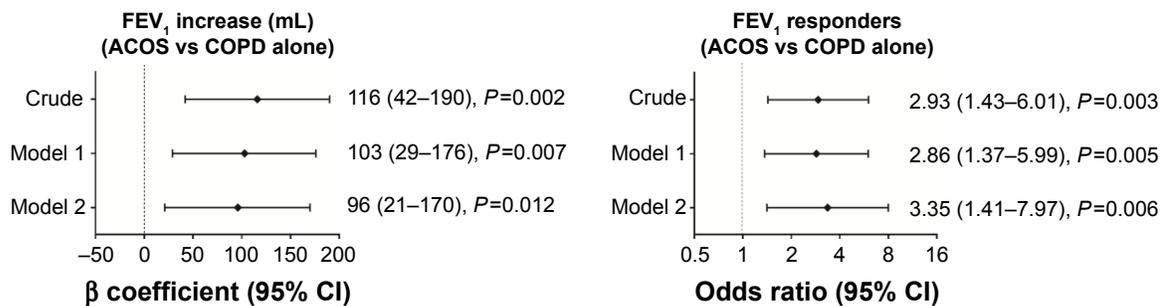
The presence of ACOS was independently associated with FEV<sub>1</sub> (mL) increase ( $P=0.002$ ) and FEV<sub>1</sub> responders ( $P=0.003$ ), which persisted even after adjustment for age, BMI, smoking history, initial mMRC dyspnea score, initial FEV<sub>1</sub>, emphysema index, and high eosinophil count (>260/μL) (FEV<sub>1</sub> [mL] increased [adjusted  $P=0.012$ ] and FEV<sub>1</sub> responders [adjusted  $P=0.006$ , model 2]; Figure 2). In addition, model 2 showed that age (adjusted  $P=0.009$  and adjusted  $P=0.006$ ), baseline FEV<sub>1</sub> (adjusted  $P=0.002$  and adjusted  $P=0.003$ ), and blood eosinophil count >260/μL (adjusted  $P=0.034$  and adjusted  $P=0.004$ ) were correlated with both FEV<sub>1</sub> (mL) increase and FEV<sub>1</sub> responders (Table S1).



**Figure 1** Comparison of change in FEV<sub>1</sub> between ACOS and COPD-alone patients.

**Note:** The ACOS group showed a significantly greater increase in FEV<sub>1</sub> than the COPD-alone group in patients with mild-to-moderate airflow limitation but not in patients with severe to very severe airflow limitation. (A) ΔFEV<sub>1</sub> (mL); (B) FEV<sub>1</sub> responders (%).

**Abbreviations:** ACOS, asthma-COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second.



**Figure 2** Independent associations of ACOS with FEV<sub>1</sub> increase and FEV<sub>1</sub> responders.

**Note:** The presence of ACOS was independently associated with FEV<sub>1</sub> increase and FEV<sub>1</sub> responders compared with COPD alone.

**Abbreviations:** ACOS, asthma–COPD overlap syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second.

## Discussion

In the present study, it was found that the FEV<sub>1</sub> increment following 3 months of ICS/LABA treatment was significantly higher in the ACOS group compared with COPD-alone group, which persisted after adjustment for baseline characteristics, baseline FEV<sub>1</sub>, emphysema index, and eosinophil count. Moreover, the difference in FEV<sub>1</sub> increment was definite in patients with mild-to-moderate airflow limitation.

Contrary to treatment for asthma, the beneficial effects of ICS treatment for COPD have been debated. ICS reduces the risk of exacerbations,<sup>18,19</sup> but the effect of ICS monotherapy is weaker in improving lung function than that of long-acting bronchodilators, and it does not affect mortality or the rate of decline in lung function.<sup>20–22</sup> Moreover, long-term high-dose exposure to ICS increases the risk of pneumonia.<sup>23</sup> On the basis of clinical trials, current guidelines recommend ICS not as monotherapy but as a combination with long-acting bronchodilators in patients with severe airflow limitation and frequent exacerbations, despite regular bronchodilator treatment.<sup>1</sup> However, in real clinical practice, ICSs are widely used in combination with long-acting bronchodilators, even in COPD patients with mild-to-moderate airflow limitation.<sup>24,25</sup> This discrepancy with current guidelines requires the identification of features associated with ICS responsiveness in COPD patients. The present study showed a significant increase in FEV<sub>1</sub> following 3 months of treatment with ICS/LABA in the ACOS group compared with COPD alone, especially in those with the mild-to-moderate airflow limitation. In addition, due to various modifications in defining ACOS, this study also analyzed the data with other ACOS criteria<sup>9</sup> proposed by experts (replaced “documented history of asthma before 40 years of age” with “history of asthma” due to absence of age at diagnosis) and found still significant increase in FEV<sub>1</sub> following 3 months of treatment with ICS/LABA in the new defined ACOS group (Figure S1).

Previous studies have shown that patients with ACOS are younger, more likely to be female, and have more symptoms and poorer health status than those with COPD alone,<sup>4,7,26</sup> however, these observations could not be reproduced. This might be explained by the predominantly male patients in the study population, due to a high smoking prevalence and medical service utilization by men in Korea,<sup>27,28</sup> and another reason is that the recruitment of patients was mostly from secondary and tertiary hospitals, who often had more symptoms than those from primary clinics. Regarding eosinophils, previous studies have reported a higher eosinophil count in the sputum of patients with ACOS than in that of those with COPD alone,<sup>10</sup> and sputum eosinophilia is considered as a predictor of clinical benefits of ICS in COPD.<sup>10,29,30</sup> Although the previous<sup>17</sup> and present studies showed that high eosinophil blood count was a significant predictor of increase in FEV<sub>1</sub> following a 3-month ICS/LABA treatment, eosinophil blood count per se, was not different between patients with ACOS and COPD alone, which is consistent with data from ECLIPSE.<sup>26</sup>

This study had some limitations. First, it focused on lung function improvement following 3 months of ICS/LABA treatment between ACOS and COPD-alone groups. Further studies with long-term clinical outcomes such as lung function decline, exacerbations, and mortality are necessary. Second, all patients enrolled in this study received ICS/LABA combination therapy; thus, the single effects of ICS or LABA could not be compared. Third, personal history of asthma irrespective of age was based on patient recall, which might have under- or overestimated the proportion of asthma patients in this study. To reduce recall bias, a history of wheezing in the last 12 months and bronchodilator response to the ACOS criteria was added.

In conclusion, this study showed that ICS/LABA treatment is more effective for FEV<sub>1</sub> improvement in patients with ACOS than in those with COPD alone, which was significant in patients with mild-to-moderate airflow limitation.

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## Disclosure

The authors report no conflicts of interest in this work.

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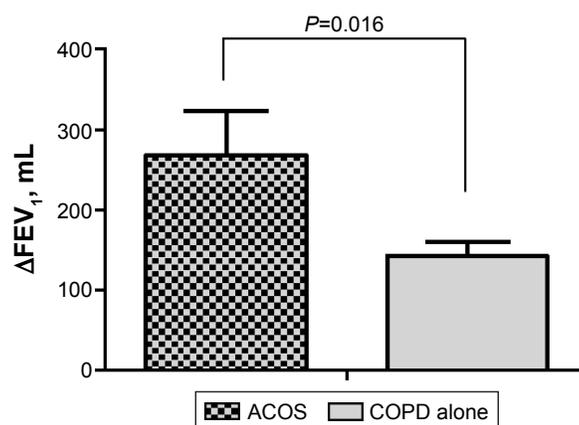
## Supplementary materials

**Table S1** Multiple logistic regression analysis of clinical factors associated with FEV<sub>1</sub> (mL) change after 3 months of ICS/LABA treatment

Variables	FEV <sub>1</sub> (mL) change			FEV <sub>1</sub> responder*		
	$\beta$ coefficient	95% CI	P-value	OR	95% CI	P-value
ACOS	95.82	21.383–170.258	0.012	3.352	1.409–7.972	0.006
Age	-6.232	-10.894–1.570	0.009	0.921	0.868–0.977	0.006
BMI	11.680	0.380–22.979	0.043	1.033	0.908–1.176	0.621
Smoking status, pack-years	-0.226	-1.707–1.256	0.764	0.995	0.977–1.013	0.605
mMRC	24.973	-10.491–60.437	0.166	1.217	0.798–1.857	0.362
Baseline FEV <sub>1</sub>	-122.788	-198.469–47.107	0.002	0.223	0.083–0.600	0.003
Emphysema index on CT	-3.607	-6.257–0.957	0.008	0.979	0.948–1.010	0.177
Blood eosinophil count >260/L	72.931	5.758–140.103	0.034	3.292	1.476–7.346	0.004

**Note:** \*Defined by an FEV<sub>1</sub> improvement of at least 12% and 200 mL from baseline after 3 months of combined treatment with ICS/LABA.

**Abbreviations:** ACOS, asthma–COPD overlap syndrome; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ICS, inhaled corticosteroid; FEV<sub>1</sub>, forced expiratory volume in 1 second; LABA, long-acting beta2-agonist; mMRC, modified Medical Research Council; OR, odds ratio.



**Figure S1** Comparison of change in FEV<sub>1</sub> (mL) between ACOS and COPD-alone patients.

**Note:** ACOS patients, classified with other criteria<sup>1</sup> proposed by experts, showed a significantly greater increase in FEV<sub>1</sub> than those with COPD alone.

**Abbreviations:** ACOS, asthma–COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second.

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