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Clinical characteristic of patients with COPD-A

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Abstract

Background The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) document proposed the COPD-A subtype as a condition of COPD with asthma. We examined the characteristics of COPD-A patients and analyzed them according to smoking history and inhaled corticosteroid (ICS) use.

Methods Patients in the COPD cohort with a history of asthma were included. The patients were divided into two groups according to their smoking history (< 10 vs. ≥10 pack-years) and their clinical characteristics were compared. The association between patients' ICS use and the occurrence for exacerbations during 1 year follow-up period was analyzed.

Results Of the 970 patients included in the analysis, the group with a smoking history less than 10 pack-years ($n=158$) had a significantly higher BMI, FEV_1 (%), FEV_1/FVC (%), DLco, ESR, and prevalence of osteoporosis. Among 560 patients who were followed up for 1 year, the patients with ICS ($n=274$) had a higher exacerbation rate than without ICS ($n=286$) (54% vs. 44.1%, $p=0.018$). However, in multivariable analysis, ICS use was not significantly associated with exacerbation. In subgroup analysis of patients with blood eosinophil count ≥ 300 cells/μl, ICS use showed a trend to reduce the risk for exacerbation (IRR = 0.907, $p=0.708$). In patients with blood eosinophil count < 300 cells/μl, ICS use significantly increased the risk for exacerbation (IRR = 1.547, $p=0.005$).

Conclusions COPD-A patients with a smoking history of less than 10 pack-years had better pulmonary function test results, BMI, ESR, and prevalence of osteoporosis. The use of ICS did not decrease exacerbations in COPD-A.

Keywords COPD-A, Smoking, Inhaled corticosteroid, Exacerbation

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Introduction

Chronic obstructive pulmonary disease (COPD) is a complex condition characterized by chronic respiratory symptoms such as cough, sputum, and shortness of breath due to persistent airflow limitation caused by airway and alveoli abnormalities [1]. COPD caused about 3.3 million deaths in 2019 and was the eighth leading cause of death worldwide [2]. Many attempts have been made world widely to eradicate and prevent COPD, because a significant portion of the COPD burden is related to cigarette smoking, which is considered preventable [3]. However, about half of all COPD cases were caused by conditions unrelated to smoking [4]. Many risk factors for COPD have been revealed, including biomass smoke, air pollution, specific genes, airway hyperresponsiveness (AHR), and infections [3–5].

AHR is very common in asthma and plays an important role in disease progression [6]. AHR increases the risk for COPD and is responsible for about 15% of COPD cases [5]. A report from a longitudinal cohort study showed that people with a history of asthma had a 12-fold higher risk of developing COPD compared to those without asthma, after adjusting for the effect of cigarette smoking [7].

The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposed several subtypes of COPD that were categorized by etiology and COPD-A was introduced as a subtype describing patients with COPD and a history of asthma [8]. This reflected the fact that asthma is a major risk factor for COPD and that COPD-A patients might have distinct clinical characteristics compared to those with other COPD subtypes. Furthermore, there are significant pathological differences in the airways between asthmatics who smoke and those who do not [7, 9]. Thus, it is worth examining if COPD-A patients have different clinical features based on their smoking history.

No previous study has described the characteristics of patients with COPD-A. Therefore, we designed a study by utilizing large COPD cohort to assess the characteristics of COPD-A patients and analyze them according to smoking history. We also examined the association between exacerbation risk in patients with COPD-A and the use of inhaled corticosteroid (ICS), a general treatment for patients with asthma [10].

Methods

Study population

This was a descriptive study of patients enrolled from The Korea COPD Subgroup Study Team (KOCOSS; NCT02800499) cohort. The cohort includes adult COPD patients diagnosed and registered by pulmonologists from 60 referral medical centers, mostly tertiary hospitals, in South Korea. Patients were registered consecutively on their clinical visits, and their information were collected by case report forms documented by doctors or trained nurses [11, 12]. The main inclusion criteria were patients with age ≥ 40, diagnosed with COPD and had previously diagnosed as asthma by physicians. COPD was defined as a state of fixed airflow obstruction in pulmonary function tests (PFTs), showing a post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) less than 70% of the normal predicted value. The history of asthma was confirmed based on a self-reported medical history obtained during an interview. The exclusion criteria were patients with missing data on clinical history and test results crucial for the analysis.

Data collection

Clinical information and test results were collected from KOCOSS cohort data, including smoking history, comorbidities, body mass index (BMI), the results of pulmonary function tests and blood chemistry tests, COPD assessment test (CAT) scores, results from St. George's respiratory questionnaire for COPD patients (SGRQ-C), modified medical research council (mMRC) dyspnea scores, medications used for COPD, and frequency and severity of previous exacerbations. Furthermore, patients were followed prospectively and clinical parameters were recorded at the 1-year follow-up, including BMI, PFT results, CAT score, SGRQ-C results, and exacerbations during the year. PFTs were conducted following the protocol proposed in the ERS/ATS document [13], and the test results were calculated based on the reference values for the Korean population [14].

Study design

Enrolled patients were divided into two groups based on smoking history, with one group having smoked for more than 10 pack-years and the other having smoked for less than 10 pack-years, and their clinical characteristics were compared (Analysis 1). An additional analysis examined patients who participated in a 1-year follow-up (Analysis 2). In this analysis, the severity of the exacerbation events and frequency data for the 1-year follow-up period were gathered to investigate the relationship between baseline ICS use and exacerbation rates. Exacerbation severity was categorized as moderate or severe. Moderate exacerbation was defined as worsening of respiratory symptoms requiring outpatient treatment with antibiotics or steroids, and severe exacerbation was the worsening of respiratory symptoms requiring emergency department treatment or hospitalization [8, 15].

To assess the effectiveness of ICS use for preventing exacerbation events according to the eosinophil level, the subjects in Analysis 2 were subcategorized based on

their baseline blood eosinophil count (splitting subjects according to counts below/above 300 cells/μl) [8, 16, 17].

Ethics considerations

The study protocol was approved by the Institutional Review Board of Konkuk University Medical Center (IRB no. KHH1010338). All hospitals participated in the KOCOSS cohort obtained approval from their Institutional Review Boards and all participants provided informed consent.

Statistical analyses

All categorical variables are expressed as numbers (%) and continuous variables are given as means and standard deviations. Intergroup comparisons were made using Pearson's chi-square test for categorical variables and the independent *t*-test for continuous variables.

The association between ICS use and exacerbation, stratified by severity, was calculated using Pearson's chi-square test. To analyze the preventive effect of ICS on exacerbation risk after adjusting for confounders, logistic and negative binomial regression analyses were conducted. For the subgroup analysis according to blood eosinophil count, the incidence rate ratio (IRR) was calculated using negative binomial regression analysis. All statistical analyses were performed using SPSS for Windows ver. 28.0 (SPSS, Chicago, IL, USA).

Results

Between 2011 and 2022, 1,091 patients from the KOCOSS cohort with COPD-A were selected for the study. From these, 121 patients were excluded due to their missing data that were crucial for the analysis. Analysis 1 included 970 patients, with 158 having a smoking history of less than 10 pack-years and 812 with a history of 10 pack-years or more. Of these, 560 patients completed the 1-year follow-up were included in Analysis 2. Analysis 2 included 275 patients using ICS for COPD treatment (ICS group) and 286 patients not using them (non-ICS group) (Fig. 1).

Analysis 1

Table 1 summarizes the clinical characteristics of the patients enrolled in Analysis 1. There were no significant differences in age, the prevalence of most comorbidities, mMRC, CAT and SGRQ-C scores, eosinophil counts, percentage of ICS users, and exacerbation events in the previous year between the smoking history groups. The group that smoked less had significantly fewer males, lower FVC, and higher BMI, FEV_1, FEV_1/FVC, diffusing

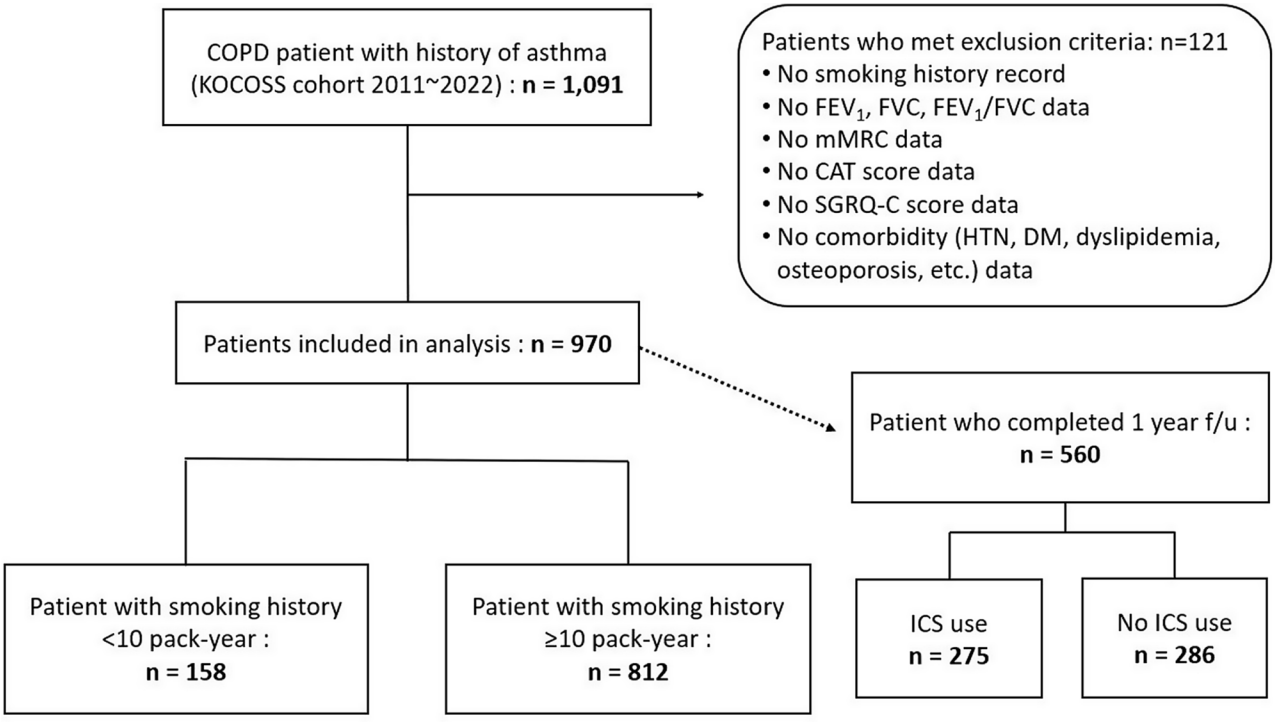

Fig. 1 Flowchart of the included participants. Analysis 1 included 970 patients; Analysis 2 included 560 patients. *COPD*, chronic obstructive pulmonary disease; *KOCOSS*, Korean COPD subgroup study; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *mMRC*, modified medical research council; *CAT*, COPD assessment test; *SGRQ-C*, St. George's respiratory questionnaire for COPD patients; *HTN*, hypertension; *DM*, diabetes mellitus; *ICS*, inhaled corticosteroid

Table 1 Characteristics of COPD-A patients by smoking history (Analysis 1)

	Smoking < 10 yrs	Smoking ≥ 10 yrs	*p*-value
N	158	812	-
Male (%)***	81 (51.3)	787 (96.9)	< 0.001
Age– years	68.42 ± 8.96	68.41 ± 7.94	0.983
BMI***	24.00 ± 3.60	22.97 ± 3.47	< 0.001
Currently on asthma treatment	45 (28.5)	180 (22.2)	0.085
FVC - % pred (post BD)**	73.84 ± 16.79	78.07 ± 15.91	0.003
FEV_1 - % pred (post BD)*	57.80 ± 18.58	54.53 ± 17.04	0.030
FEV_1/FVC - % (post BD)***	56.35 ± 10.95	49.60 ± 12.13	< 0.001
DLco - % pred ($n = 113$, $n = 634$)**	71.15 ± 21.21	64.85 ± 21.49	0.004
Smoking pack-years	1.40 ± 2.77	44.60 ± 25.86	-
Comorbidities			
MI (%)	9 (5.7)	34 (4.2)	0.399
HF (%)	7 (4.4)	32 (3.9)	0.774
PVD (%)	4 (2.5)	8 (1.0)	0.116
DM (%)	28 (17.7)	141 (17.4)	0.914
HTN (%)	62 (39.2)	286 (35.2)	0.335
GERD (%)	21 (13.3)	88 (10.8)	0.372
Osteoporosis (%)***	22 (13.9)	44 (5.4)	< 0.001
Dyslipidemia (%)	22 (13.9)	84 (10.3)	0.187
Thyroid diseases (%)	3 (1.9)	16 (2.0)	1.000
Inflammatory bowel disease (%)	0 (0)	7 (0.9)	0.377
Dementia (%)	4 (2.5)	15 (1.8)	0.533
Liver disease (%) ($n = 81$, $n = 366$)	2 (2.5)	5 (1.4)	0.615
Cancer (%) ($n = 81$, $n = 366$)	2 (2.5)	20 (5.5)	0.395
Chronic kidney disease (%) ($n = 81$, $n = 366$)	2 (2.5)	5 (1.4)	0.615
Cerebrovascular disease (%) ($n = 81$, $n = 366$)	1 (1.2)	13 (3.6)	0.482
Hemiplegia (%) ($n = 81$, $n = 366$)	0 (0)	0 (0)	-
Rheumatic disease (%) ($n = 81$, $n = 366$)	1 (1.2)	4 (1.1)	1.000
Gastric ulcer (%) ($n = 81$, $n = 366$)	2 (2.5)	5 (1.4)	0.615
AIDS (%) ($n = 81$, $n = 366$)	0 (0)	0 (0)	-
CCI score ($n = 81$, $n = 366$)			1.000
0 (%)	57 (70.4)	257 (70.2)	
1–2 (%)	22 (27.2)	97 (26.5)	
3–4 (%)	2 (2.5)	9 (2.5)	
≥ 5 (%)	0 (0)	3 (0.8)	
mMRC			0.759
0 ~ 2 (%)	135 (85.4)	686 (84.5)	
3 ~ 4 (%)	23 (14.6)	126 (15.5)	
CAT score	16.21 ± 9.55	15.16 ± 7.69	0.193
SGRQ-C score	35.38 ± 25.36	33.78 ± 21.41	0.459
ESR - mm/h ($n = 92$, $n = 429$)*	24.64 ± 23.45	17.96 ± 17.80	0.011
Blood eosinophil count (cells/μl) ($n = 137$, $n = 684$)	259.38 ± 285.90	249.35 ± 259.29	0.685
Eosinophil ≥ 150 cells/μl	75 (54.7)	371 (55.0)	0.949
Eosinophil ≥ 300 cells/μl	35 (25.5)	174 (25.8)	0.948
ICS user (%) ($n = 136$, $n = 711$)	84 (61.8)	389 (54.7)	0.129
ICS (%)	4 (2.9)	13 (1.8)	0.335
ICS + LABA (%)	80 (58.8)	377 (53.0)	0.214
ICS + LABA + LAMA (%)	49 (36.0)	236 (33.2)	0.521
Past 1 year exacerbation event ($n = 90$, $n = 547$)			
Moderate (%)	23 (25.6))	126 (23.0)	0.601

Table 1 (continued)

	Smoking < 10 yrs	Smoking ≥ 10 yrs	*p*-value
Severe (%)	13 (14.4)	69 (12.6)	0.631
Total (%)	25 (27.8)	135 (24.7)	0.530

BMI, body mass index; *FEV*$_1$, forced expiratory volume in 1 s; *FVC*, forced vital capacity; DLco, diffusing capacity for carbon monoxide; *MI*, myocardial infarction; *HF*, heart failure; *PVD*, peripheral vascular disease; *DM*, diabetes mellitus; *HTN*, hypertension; *GERD*, gastroesophageal reflux disease; *AIDS*, acquired immune deficiency syndrome; *CCI*, Charlson co-morbidity index; *mMRC*, modified medical research council; *CAT*, COPD assessment test; *SGRQ-C*, St. George's respiratory questionnaire for COPD patients; *ESR*, erythrocyte sedimentation rate; *ICS*, inhaled corticosteroid; *LABA*, long-acting beta agonist; *LAMA*, long-acting muscarinic antagonist. Plus-minus values are means ± SD; **p* < 0.05, ***p* < 0.01, ****p* < 0.001

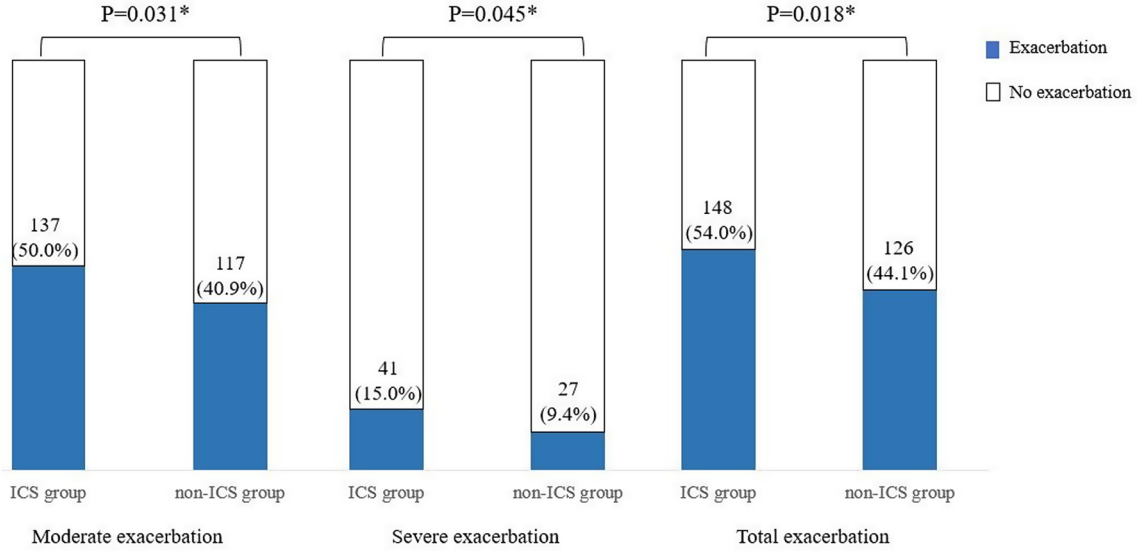

Fig. 2 Comparison of the exacerbation rate based on ICS use in COPD-A patients (Analysis 2). Moderate exacerbation was defined as worsening of respiratory symptoms requiring outpatient treatment with antibiotics or steroids. Severe exacerbation was defined as worsening of respiratory symptoms requiring emergency department treatment or hospitalization. *ICS*, inhaled corticosteroid; **p* < 0.05

Table 2 Covariates associated with exacerbation risk: logistic regression (Analysis 2)

	Adjusted OR[#]	95% CI	*p*-value
ICS use	1.177	[0.817, 1.695]	0.382
Male	1.043	[0.518, 2.098]	0.907
Age	0.998	[0.974, 1.022]	0.864
Smoking history ≥ 10 pack-years	1.677	[0.980, 2.870]	0.059
BMI	1.006	[0.955, 1.061]	0.814
FEV_1 (%, post BD)**	0.983	[0.971, 0.995]	0.005
CAT score***	1.056	[1.031, 1.081]	< 0.001
History for exacerbation in previous year**	1.768	[1.156, 2.704]	0.009

BMI, Body mass index; *FEV*$_1$, forced expiration volume in 1 s; *CAT*, COPD assessment test; *ICS*, inhaled corticosteroid; *OR*, odds ratio; *CI*, confidence interval; **p* < 0.05, ***p* < 0.01, ****p* < 0.001

[#]Adjusted OR of the ICS use on exacerbation was evaluated by multivariate logistic regression using sex, age, smoking history, BMI, post BD FEV_1(%), CAT score and history of exacerbation in previous year as covariates

capacity for carbon monoxide (DLco), erythrocyte sedimentation rate (ESR), and prevalence of osteoporosis.

Analysis 2

Figure 2 shows the association between ICS use and the rate for exacerbation in the 1-year follow-up period. The percentage of patients who experienced moderate exacerbation was significantly higher in the ICS group than in the non-ICS group (50.0% vs. 40.9%, $p = 0.031$). The same trend was seen between severe (15.0% vs. 9.4%, $p = 0.045$) and total (54.0% vs. 44.1%, $p = 0.018$) exacerbations.

Additional analyses were conducted to assess the relationship between ICS use and the exacerbation risk after adjusting for possible confounders. Table 2 shows the results of logistic regression analysis on covariates affecting the rate for exacerbation in the 1-year follow-up period: FEV_1, CAT score, and history of exacerbation in the previous year were associated with exacerbation whereas ICS use was not. Negative binomial regression analysis gave similar results (Table 3), except that ICS use was marginally associated with exacerbation.

The eosinophil count subgroups were analyzed via negative binomial regression to evaluate the association between ICS use and exacerbation risk (Fig. 3). In the group with blood eosinophil count ≥ 300 cells/μl, ICS use did not increase the risk for exacerbation (incidence rate

Table 3 Covariates associated with exacerbation risk: negative binomial regression (Analysis 2)

	Adjusted IRR[#]	95% CI	*p*-value
ICS use	1.259	[1.000, 1.586]	0.050
Male	1.171	[0.731, 1.876]	0.512
Age	0.999	[0.983, 1.015]	0.898
Smoking history ≥ 10 pack-year	1.421	[0.997, 2.024]	0.052
BMI	0.988	[0.954, 1.023]	0.483
FEV_1 (%, post BD)**	0.987	[0.979, 0.994]	0.001
CAT score***	1.044	[1.029, 1.059]	< 0.001
History for exacerbation in previous year**	1.540	[1.197, 1.981]	0.001

BMI, Body mass index; *FEV_1*, forced expiration volume in 1 s; *CAT*, COPD assessment test; *ICS*, inhaled corticosteroid; *IRR*, incidence rate ratio; *CI*, confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[#]Adjusted IRR of the ICS use on exacerbation was evaluated by negative binomial regression using sex, age, smoking history, BMI, post BD FEV_1(%), CAT score, and history of exacerbation in previous year as covariates

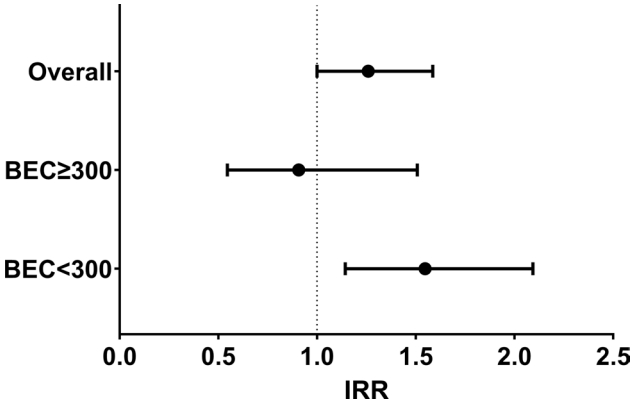

Fig. 3 Subgroup analysis based on eosinophil counts. The association between ICS use and exacerbation risk in each subgroup stratified by blood eosinophil count was analyzed using negative binomial regression. *BEC*, blood eosinophil count; *IRR*, incident rate ratio

ratio = 0.907, $p = 0.708$); in the other group, it did (incidence rate ratio = 1.547, $p = 0.005$).

Discussion

To the best of our knowledge, this is the first study to describe the clinical characteristics of patients with COPD-A. We compared their characteristics according to smoking history and evaluated the effects of ICS use on exacerbation risk.

We found that patients with COPD-A and a smoking history of less than 10 pack-years had a higher FEV_1, FEV_1/FVC, DLco, BMI, ESR, and prevalence of osteoporosis but lower FVC and percentage of male than those who smoked more. This result is generally consistent with previous studies of the clinical differences between COPD patients who smoke and those who do not. One study using the KOCOSS cohort reported that non-smoker COPD patients more often were females with higher BMIs and more comorbidities such as hypertension, osteoporosis, and gastroesophageal reflux disease [18]. Another study of a Korean cohort of male COPD patients showed that subjects with a smoking history of less than 5 pack-years were younger and had a higher BMI than those with a longer smoking history [19]. A study conducted in India reported that non-smoker COPD patients were more likely to be female, younger, have a lower FVC, higher BMI, higher DLco, and slower rate of lung function decline at the 2-year follow-up compared to COPD patients with a smoking history of 10 pack-years or more [20]. The significantly higher prevalence of osteoporosis that we observed in the shorter-smoking-history group may be explained by the higher proportion of elderly menopausal females in that group. Our results regarding ESR are not in line with a previous study, which reported no significant difference in ESR between groups with different smoking histories [21]. The reason for this discrepancy is not clear and requires additional research.

We also found that the exacerbation rate during the 1-year follow-up period was significantly higher in COPD-A patients using ICSs compared to those not using them. The same difference was observed for all types for exacerbation. However, this may be a biased finding, because the analysis did not consider the clinical setting of the patients using ICSs. Because the current guidelines recommend ICS as an add-on therapy for patients with persistent exacerbations while using a long-acting beta 2 agonist and a long-acting muscarinic antagonist [8], it is evident that COPD patients using ICS are in more severe disease course and are prone to more frequent exacerbations. Therefore, we analyzed the results again after adjusting for confounders and found that ICS use was not significantly associated with exacerbation risk. However, because this result was not consistent with previous reports [10, 22–24], an additional subgroup analysis based on the blood eosinophil count, which indicates a favorable response to ICS, was conducted [8]. In those whose baseline blood eosinophil counts were ≥ 300 cells/μl, ICS use tended to reduce exacerbation risk. By contrast, a significantly higher risk was noted in those with lower eosinophil counts, suggesting that ICS can be a possible harm to patients with COPD-A whose blood eosinophil count is low, even if they have a history of asthma.

These results are generally in line with previous studies of COPD and of asthma/COPD overlap (ACO) [25]. ACO has been used to describe patients with the clinical features of both COPD and asthma [6] since the 2015 GOLD and Global Initiative for Asthma (GINA) made a joint statement describing this as a distinct disease entity [26]. It shares most of the clinical aspects of COPD-A because the diagnostic criteria of ACO (based on ATS

roundtable criteria) include pulmonary function test results indicating persistent airflow limitation, age ≥ 40, smoking history of 10 pack-years (or exposure to air pollution ≥ 10 years), and a history of asthma (or bronchodilator response > 400 mL) [27]. Clinicians treat ACO using a strategy more similar to that for asthma than for COPD, which uses ICS as mainstream treatment [28]. A prospective cohort study of ACO reported that ICS treatment showed preventive effect on exacerbations in ACO patients, only in those with a high blood eosinophil count (≥ 300 cells/μl) [25].

Our contrasting results can be explained by the different proportion of asthmatic patients in the two disease groups. Being classified as a COPD-A patient does not guarantee that the patient still has the clinical features of asthma. By contrast, the definition of ACO includes clinical parameters that indicate active asthmatic features [10, 26, 29]. The difference in the composition of patients with asthmatic features in the two disease groups may have caused the discrepancy in the efficacy of ICS.

This study had some considerable limitations. First, since we used self-reported asthma history for the analysis, the disease could have been over diagnosed and could have caused biased result. Also, patients regardless of their age of asthma diagnosis were included in the analysis. Because the 2023 GOLD report defines COPD-A patients as those with a history of asthma, especially in childhood, we tried to extract patients who were diagnosed with asthma before the age of 40. However, the cohort data had few patients with information on the age of asthma diagnosis, making the sample size too small to expect a significant result. Third, because the patients were recruited mostly from tertiary medical centers, the subjects may not represent the general COPD population. Additionally, there was a significant difference in sample sizes between the groups classified by smoking history in Analysis 1. It was particularly challenging to obtain statistically significant results due to the very low prevalence of specific comorbidities in the group with less smoking. Finally, the 1-year follow-up period could have been too short to show a difference in the exacerbation rate and frequency between the study groups. Further research on a larger population with longer follow-up is needed.

In conclusion, COPD-A patients with a smoking history less than 10 pack-years had a higher FEV_1, FEV_1/FVC, DLco, BMI, ESR, and prevalence of osteoporosis than those with a longer history. The use of ICSs in patients with COPD-A did not decrease the exacerbation rate.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03731-9.

Supplementary Material 1

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Author contributions
Conceptualization: CKR; Methodology: JML and CKR; Investigation: JML, YK, JYC, SWR, DKK, THK, HKY, KHY, KSJ, and CKR.; Writing-Original Draft: JML and CKR; Writing-Review and Editing: JML, YK, JYC, SWR, DKK, THK, HKY, KHY, KSJ, and CKR; Formal analysis: JML and CKR; Data Curation and Visualization: JML, YK, and CKR; Funding acquisition: KHY and KSJ.

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Data availability
Data used in this analysis are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study protocol was approved by the Institutional Review Board of KONKUK university medical center and all participants in the cohorts provided written informed consent (IRB No. KHH1010338). All hospitals involved in the KOCOSS cohort obtained approval from the Institutional Review Board Committee and informed consent from their patients.

Consent for publication
No applicable.

Competing interests
CK Rhee received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer.

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