

Clinical implications of blood eosinophil count in patients with non-asthma–COPD overlap syndrome COPD

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Background: Recent studies that assessed the relevance of the blood eosinophil count as a biomarker in patients with COPD may have overestimated it because they included patients with asthma–COPD overlap syndrome (ACOS). We investigated the clinical implications of the blood eosinophil count in patients with non-ACOS COPD.

Patients and methods: From a Korean COPD Subtype Study (KOCOSS) cohort, we selected patients with non-ACOS COPD after excluding ACOS patients according to Spanish criteria. Clinical characteristics and the incidence of moderate-to-severe exacerbation were compared among the four groups stratified according to the quartiles of blood eosinophil percent and count.

Results: Of the KOCOSS cohort of 1,132 patients with COPD, 467 non-ACOS COPD patients (41.2%) with data of blood eosinophil count remained after excluding those with ACOS based on the Spanish definition. There was no difference in clinical characteristics among groups classified according to the quartiles of eosinophil percent and count. On multivariate logistic regression, eosinophil quartiles in percent and absolute count were not associated with the incidence of moderate-to-severe acute exacerbations of COPD (AECOPD). The eosinophil count did not affect the risk of AECOPD or forced expiratory volume in 1 second (FEV₁) changes according to exposure to inhaled corticosteroid (ICS). However, by increasing the cutoff value for the eosinophil count from 200/μL to 600/μL, the odds ratio for risk of exacerbation increased serially from 0.82 to 2.96 on trend analysis.

Conclusion: In patients with non-ACOS COPD, the blood eosinophil count and percent were not associated with FEV₁ changes, quality of life (QoL), AECOPD frequency, or response to ICS. The clinical implication of the blood eosinophil count should not be overestimated in patients with non-ACOS COPD.

Keywords: eosinophil, chronic obstructive lung disease, asthma, acute exacerbation, inhaled corticosteroid

Introduction

COPD is one of the leading causes of death and is associated with high medical costs in the USA.¹ Acute exacerbations of COPD (AECOPD) are associated with poor quality of life (QoL), decreased health status,² accelerated lung function decline,³ frequent hospitalization, and mortality⁴ of COPD patients. Current emerging concepts of biologic clusters in COPD exacerbations suggest that neutrophilic inflammation and eosinophilic inflammation are the main phenotypes of exacerbation.⁵ Several studies have reported the role of C-reactive protein (CRP)^{6,7} procalcitonin,⁷ and leukocyte counts⁶ in predicting AECOPD. Eosinophilic bronchial inflammation, reflected by the blood

eosinophil count,⁸ is the main target of inhaled corticosteroid (ICS) therapy.^{9–11} In addition, the blood eosinophil count is associated with an increased risk of moderate-to-severe exacerbations.^{8,9,12,13} According to previous studies that assessed the peripheral blood count, $>2\%$ or 200 cells/ μL is the cutoff value for the prediction of exacerbation¹⁴ and is associated with a better outcome in the hospital and intensive care unit.¹⁵

Asthma–COPD overlap syndrome (ACOS), defined by recent studies^{16–19} as a condition that includes clinical features of both asthma and COPD, affects 5%–55% of COPD patients.²⁰ In asthma, bronchial hyperresponsiveness is related to eosinophilic airway inflammation;²¹ both Spanish and ATS criteria included blood eosinophil level as a minor criterion for ACOS.^{17,19} Because previous studies of the eosinophil count in COPD did not exclude patients with ACOS,^{5,12,22} we assumed that the role of the peripheral eosinophil count may have been exaggerated.

In this study, we investigated whether the peripheral eosinophil count can predict clinical outcomes in cases of moderate-to-severe AECOPD, forced expiratory volume in 1 second (FEV_1) changes per year, and response to ICS/long-acting beta agonist (LABA) in patients with non-ACOS COPD.

Patients and methods

Patients and study design

The Korean COPD Subtype Study (KOCOSS) is an ongoing, prospective, observational COPD cohort study investigating the epidemiological characteristics and subtypes of

COPD. Nationwide, 28 hospitals are participating in South Korea (NCT02800499); a more detailed description of the cohort is available elsewhere.²³ Briefly, patients were eligible if they were aged >40 years, had post-bronchodilator FEV_1 /forced vital capacity <0.7 , and had smoked >10 years. Final data were assessed on June 28, 2016.

ACOS was defined according to Spanish criteria¹⁹ as follows: 1) previously treated or diagnosed with asthma; 2) strongly positive bronchodilator response: FEV_1 increase $>15\%$ and 400 mL compared with pre-bronchodilator values; 3) previous history of atopy, allergic rhinitis, or atopic dermatitis; 4) blood eosinophil percentage $>5\%$; and 5) a positive bronchodilator response: 12% and a 200-mL increase in FEV_1 . In this analysis, criterion (5) was defined for a single visit because KOCOSS data were collected at the annual visit. A diagnosis of ACOS required meeting at least one major or two minor criteria.

After excluding patients with ACOS and unavailable information on the eosinophil count in the initial cohort, patients with non-ACOS COPD were enrolled in the final analysis (Figure 1). The final study population was stratified into four groups based on the quartiles of eosinophil count and percent. The clinical variables were then compared among the groups. This study was approved by the Institutional Review Board (IRB) of each hospital (Seoul National University Hospital IRB, Catholic Medical Center Central IRB, Yonsei University Wonju College of Medicine IRB, Severance Hospital IRB, Ajou University IRB, Hallym University Sacred Heart hospital IRB, IRB of Konkuk University Hospital, IRB of Kangdong Sacred Heart Hospital, IRB of Seoul National

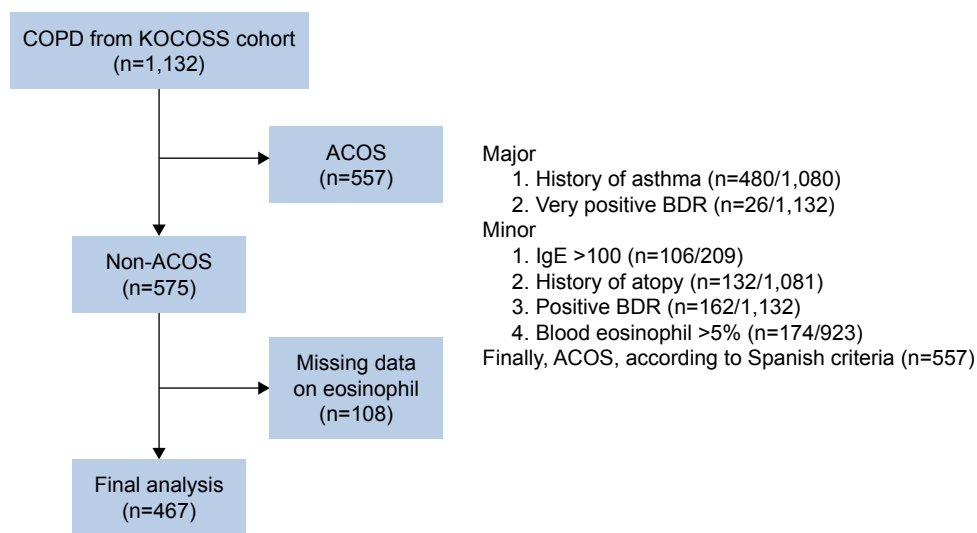


Figure 1 Patient selection flow.

Abbreviations: KOCOSS, Korean COPD Subtype Study; ACOS, asthma–COPD overlap syndrome; BDR, bronchodilator response; IgE, immunoglobulin E.

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Group A comprised patients with low risk and fewer symptoms (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2007 stage 1 or 2 and/or 0–1 exacerbations per year and Modified British Medical Research Council [mMRC] grade 0–1 or COPD Assessment Test [CAT] score 10). Group B (low risk, more symptoms) was characterized by GOLD 2007 stage 1 or 2 and/or 0–1 exacerbations per year and mMRC grade 2 or CAT score 10. Groups C and D were high-risk groups. Both were characterized by GOLD 2007 stage 3 or 4 and/or >2 exacerbations per year. Group C involved fewer symptoms (mMRC grade 0–1 or CAT score 10) than group D (mMRC grade 2 or CAT score 10).

Measurements

Demographic variables, including age, sex, body mass index (BMI), and smoking history, were collected. Laboratory data such as spirometric data and complete blood count (CBC) with differential count were collected. QoL was measured using St George's Respiratory Questionnaire (SGRQ) and the CAT. Information on inhaled respiratory medicine, including ICS/LABA and long-acting muscarinic antagonist (LAMA), was reported. We also measured the frequency of AECOPD with moderate-to-severe severity. Moderate-to-severe AECOPD was defined as COPD requiring antibiotics in outpatient clinics, emergency room admission or admission due to an increased quantity of sputum, purulent changes in sputum, or aggravation of dyspnea in the previous 12 months. To test the association between COPD subgroups or severity and eosinophil quartiles, the associations were

tested according to the COPD classification by the GOLD in 2007 and 2014.²⁴

Statistical analysis

The statistical analyses were performed using Stata 13.0 (StataCorp 2013, Stata Statistical Software: Release 13; StataCorp LP, College Station, TX, USA). Categorical variables were described as number (percentage), and continuous variables as mean \pm standard deviation (SD). The study population was stratified with the quartiles of eosinophil count and percent. The clinical characteristics of each group were compared using Pearson's chi-square test and Fisher's exact test for categorical variables and one-way ANOVA and Kruskal–Wallis tests for continuous variables. Multivariate logistic regression analysis was used to identify the role of eosinophil quartiles in predicting AECOPD. The prediction models were adjusted for age, sex, pack-years, BMI, ICS/LABA use, and initial FEV₁ predicted% acquired at the first visit.

Results

Among 1,132 patients with COPD, 557 (49.2%) were diagnosed with ACOS based on Spanish criteria. Of the patients with ACOS, 88.5% (n=480) had a history of asthma and 31.2% (n=174) had a blood eosinophil percentage >5% (Figure 1). Excluding patients with ACOS, 467 patients with non-ACOS were included in the final analyses. The median eosinophil percent in the study population was 2.4% (interquartile range [IQR] 1.3%–3.8%), and the median absolute count was 166.5 cells/ μ L (IQR 89.6–272.8 cells/ μ L). Blood eosinophil counts were distributed in the ranges of 0–89 cells/ μ L, 89–166 cells/ μ L, 167–273 cells/ μ L, and 263–2,213 cells/ μ L in each quartile. As shown in Figure 2, the majority of patients with non-ACOS COPD had an eosinophil count of <500 cells/ μ L, while the fourth quartile included relatively broad ranges for eosinophil percent and count.

Baseline characteristics of patients with non-ACOS COPD according to eosinophil count

The baseline characteristics of patients with non-ACOS COPD stratified by eosinophil quartiles are compared in Table 1. There were no statistically significant differences in age, sex, pack-years, or BMI among the groups. There was also no significant difference in spirometric data or QoL score, including SGRQ and CAT. Neither the white blood cell (WBC) nor the proportion of neutrophils showed any trends by increasing eosinophil quartiles, although the WBC counts

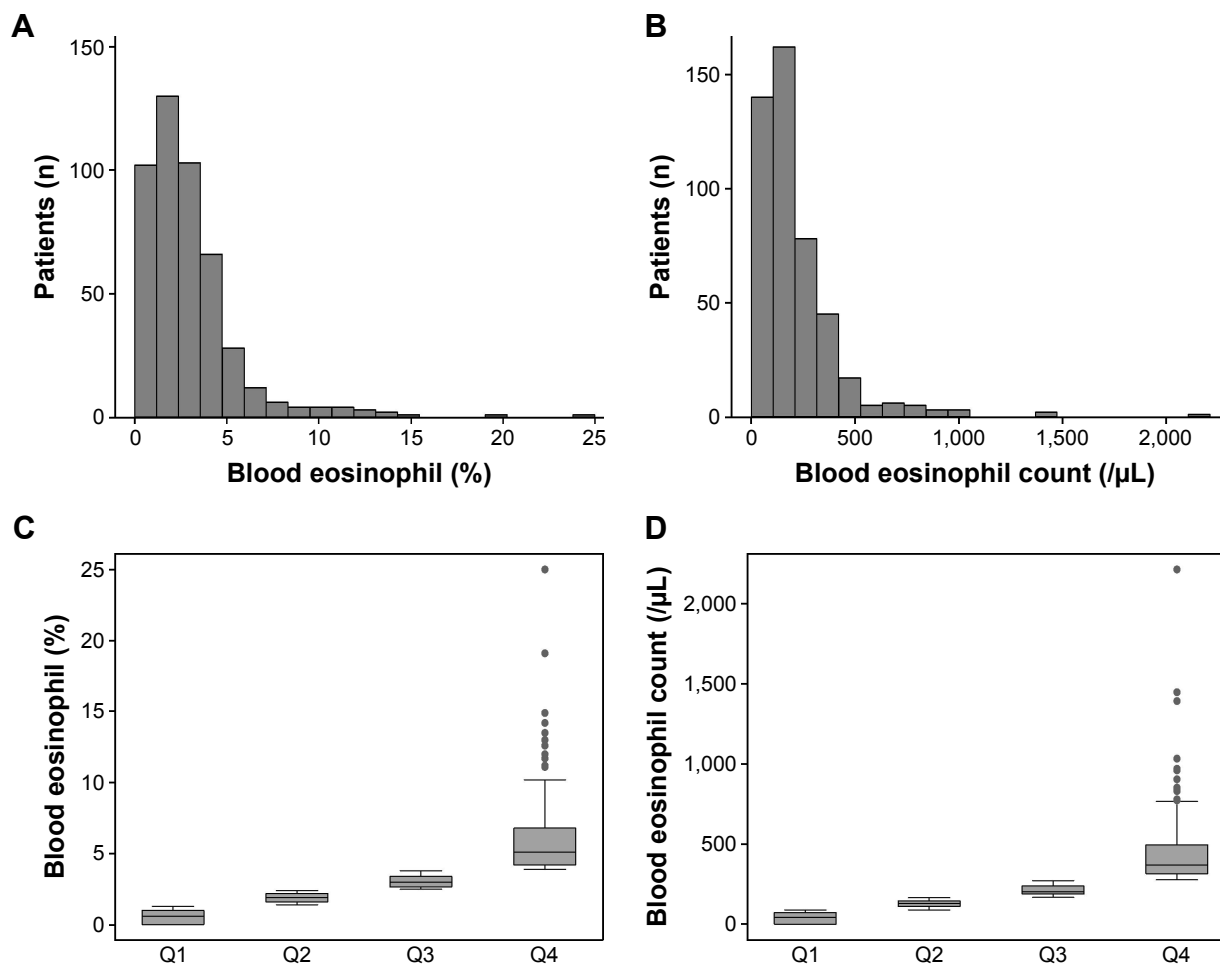


Figure 2 Distribution of eosinophil count in study population.

Notes: Histograms of eosinophil percentage (A) and absolute eosinophil count (B) in peripheral blood. (C) A box and whisker plot of the blood eosinophil percentages for the groups classified according to eosinophil percent quartiles. (D) A box and whisker plot of the absolute eosinophil count for the groups classified according to eosinophil count quartiles.

Abbreviation: Q, quartile.

were significantly higher in the first quartile than in the other groups (Q1: 8.4 ± 3.4 [$\times 10^3/L$], Q2: 7.2 ± 2.68 , Q3: 7.6 ± 2.0 , and Q4: 8.1 ± 2.1 , $P=0.003$). The proportion of moderate-to-severe exacerbations over the previous year was highest in the first quartile at 38/117 (41.4%; $P=0.007$). Although there was no linear trend in clinical characteristic variables according to quartiles, patients in the first and fourth quartiles showed more severe airflow limitation, higher neutrophil percentages, higher CRP, and a higher incidence of AECOPD than those in the second and third quartiles. Additionally, the use of bronchodilators, including LAMA, LABA, and ICS, did not differ among the groups.

Association between quartiles of eosinophil count and the severity or subgroups of COPD

Upon comparison of the quartiles in eosinophil count and percent according to the severity of airflow limitation

(FEV₁ % predicted) and subgroups of COPD defined by GOLD, we found no significant difference or association with previously suggested severity criteria ($P=0.297$ and $P=0.61$, respectively; Figure 3). The prevalence of patients with each eosinophil quartile was similar through stages I–IV as defined by GOLD 2007 ($P=0.757$; Table 2 and Figure 4).

Impact of eosinophil count on the risk of moderate-to-severe AECOPD

We analyzed patients who were followed up for 1 year to determine the association with acute exacerbations and blood eosinophil count. In univariate analysis of the effects of the blood eosinophil count on the risk of moderate-to-severe AECOPD, absolute eosinophil count and quartiles of blood eosinophil counts were not associated with a risk of acute exacerbation in this study group, whereas a lower FEV₁ (predicted%; odds ratio [OR] 0.97, 95% confidence interval

Table 1 Baseline characteristics of study population

Variables	Total (N=467)	Q1 (n=117)	Q2 (n=117)	Q3 (n=117)	Q4 (n=116)	P-value
Age (years)	69.5±7.4	69.2±7.6	69.5±7.6	69.2±7.2	70.0±7.3	0.784
Sex (male)	448 (95.9%)	111 (94.9%)	115 (98.3%)	109 (93.2%)	113 (97.4%)	0.175
Pack-year	47.5±25.1	50.1±27.6	46.7±22.1	45.3±25.9	47.8±24.8	0.532
BMI (kg/m ²)	22.7±3.4	22.3±3.3	22.7±3.2	23.3±3.6	22.6±3.3	0.148
Spirometry						
FEV ₁ % pred	55.5±18.0	53.5±16.7	56.3±17.7	56.8±18.7	55.3±18.7	0.488
FVC % pred	81.7±17.4	79.3±18.5	83.0±16.2	82.4±16.7	82.2±18.2	0.355
BDR % pred	5.97±8.78	6.5±10.3	5.7±7.3	6.7±8.2	4.9±9.1	0.390
RV/TLC%	47.0±16.4	49.1±17.0	45.0±14.7	46.4±16.3	47.6±17.9	0.417
WBC (×10 ³ /L)	7.8±2.6	8.4±3.4	7.2±2.6	7.6±2.0	8.1±2.1	0.003
Neutrophil%	60.3±33.8	61.7±20.5	59.3±10.9	57.4±9.2	63.0±62.9	0.603
CRP	2.2±7.4	2.7±5.7	2.1±6.5	1.1±1.8	2.8±11.4	0.590
SGRQ total	36.0±18.8	37.2±20.4	37.6±17.8	33.0±18.1	36.3±18.8	0.234
CAT total	16.4±7.7	17.8±8.3	16.5±7.5	15.0±7.4	16.4±7.3	0.055
AECOPD (Fr/year)	2.1±1.8	2.1±2.0	1.9±1.5	2.0±1.4	2.1±2.1	0.899
AECOPD in 1 year	148 (31.9%)	38 (41.4%)	30 (26.1%)	36 (30.8%)	34 (29.3%)	0.007
LAMA	275 (71.8%)	59 (68.6%)	73 (73.0%)	70 (71.4%)	73 (73.7%)	0.874
ICS/LABA	200 (53.6%)	56 (57.1%)	51 (54.8%)	50 (55.6%)	43 (46.7%)	0.488
LABA	89 (24.7%)	13 (16.3%)	27 (28.7%)	23 (25.6%)	26 (27.1%)	0.239

Note: Data are presented as mean ± SD or n (%).

Abbreviations: Q, quartile; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; % pred, % predicted; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; BDR, bronchodilator response; WBC, white blood cell; CRP, C-reactive protein; SGRQ, St George's Respiratory Questionnaire; CAT, COPD Assessment Test; AECOPD, acute exacerbation of COPD; LAMA, long acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; SD, standard deviation.

[CI] 0.95–0.99, *P*-value 0.001) and use of ICS/LABA at enrollment (OR 2.25, 95% CI 1.15–4.44, *P*-value 0.019) were associated with an increasing risk of acute exacerbation (Table 3).

After adjusting for age, sex, pack-years, BMI, and initial FEV₁, an eosinophil count of >600/μL was associated with moderate-to-severe AECOPD (OR 3.59, 95% CI 1.00–12.8, *P*-value 0.050). However, upon adjustment based on

ICS/LABA use, the statistical significance was lost (OR 1.66, 95% CI 0.43–6.40, *P*-value 0.460; Table 3).

When the risk of AECOPD was tested upon stratifying the absolute eosinophil count as 200, 300, 400, 500, or 600/μL, the eosinophil count was not a significant risk factor for AECOPD (Table 3). However, by increasing the cutoff value for the eosinophil count from 200/μL to 600/μL, the OR for risk of exacerbation increased serially from 0.82 to 2.96.

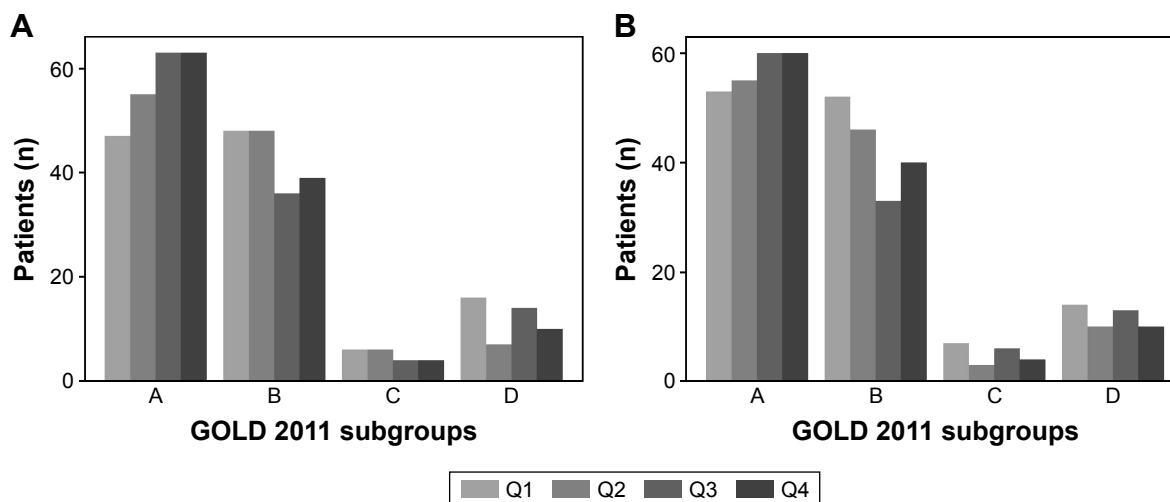


Figure 3 Distribution of eosinophil quartiles in GOLD subgroups of COPD.

Notes: (A) Distribution of blood eosinophil count quartile in each GOLD 2011 subgroup. (B) Distribution of blood eosinophil (%) quartile in each GOLD 2011 subgroup.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; Q, quartile.

Table 2 Distribution of eosinophil count quartiles in subgroups of GOLD stages

Blood eosinophil count quartile	GOLD stage I	GOLD stage II	GOLD stage III	GOLD stage IV	P-value
Q1 (n=117), n (%)	7 (15.6)	62 (25.9)	40 (25.5)	9 (30.8)	0.757
Q2 (n=117), n (%)	10 (22.2)	61 (25.5)	40 (25.5)	6 (23.1)	
Q3 (n=117), n (%)	17 (37.8)	58 (24.3)	37 (23.6)	5 (19.2)	
Q4 (n=116), n (%)	11 (24.4)	58 (24.3)	40 (25.5)	7 (26.9)	

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; Q, quartile.

Impact of eosinophil count on FEV₁ changes per year

Although the follow-up period was limited to 1 year, the FEV₁ change was measured according to the eosinophil quartiles. The absolute count of 200/ μ L had no impact on FEV₁ changes during the follow-up period (Table 4). Nevertheless, patients with an eosinophil count of >600/ μ L had a decreased FEV₁ (Table 4).

Association between eosinophil count and treatment response to ICS/LABA

The treatment response to ICS/LABA according to eosinophil count was assessed for the risk of AECOPD and FEV₁ changes for 1 year. The mean eosinophil count and percent were not different (user vs non-user 213.3 \pm 16.1 vs 204.4 \pm 14.9, $P=0.685$; 3.0 \pm 0.5 vs 2.8 \pm 0.2, $P=0.420$) according to the use of ICS/LABA at enrollment. While initial ICS/LABA use was associated with an increased risk of moderate-to-severe exacerbation of COPD (OR 2.25, 95%

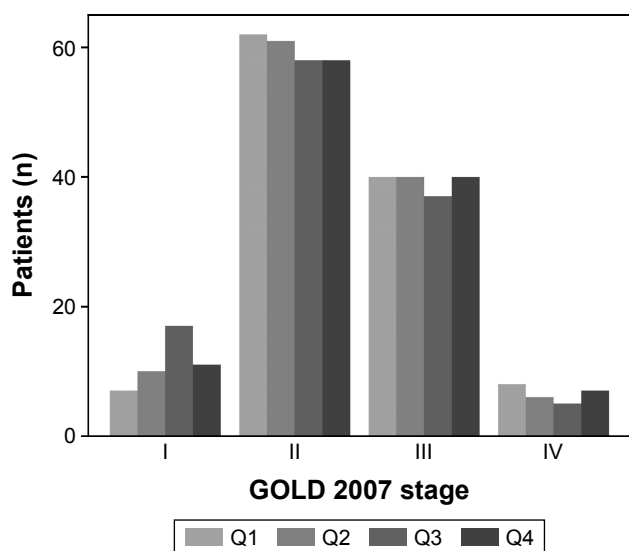
CI 1.15–4.44, P -value 0.019) on univariate analyses (Table 3), the statistical significance disappeared when the model was adjusted according to age, sex, BMI, pack-years, and initial FEV₁ (Table 5). When the population was stratified based on eosinophil counts' cutoff value of 200/ μ L and exposure to ICS/LABA, the FEV₁ change was not different among strata as in the test for risk of AECOPD (Table 6 and Figure 5). In patients with eosinophil counts >200/ μ L, incidence rate ratio (IRR) (95% CI) was not different between ICS/LABA

Table 3 The effects of blood eosinophil count on the moderate-to-severe acute exacerbation of non-ACOS COPD

Variables	OR (95% CI)	P-value
Univariate analysis		
Age (years)	1.00 (0.96–1.04)	0.972
Sex (male)	1.20 (0.25–5.87)	0.814
Pack-year	1.00 (0.98–1.01)	0.577
BMI (kg/m ²)	0.98 (0.90–1.07)	0.696
ICS/LABA use	2.25 (1.15–4.44)	0.019
FEV ₁ % pred	0.97 (0.95–0.99)	0.001
Eosinophil count (/ μ L)	1.00 (0.99–1.00)	0.948
Eosinophil count quartile*		
Q1	Reference	
Q2 versus Q1	0.94 (0.40–2.20)	0.882
Q3 versus Q1	0.57 (0.22–1.48)	0.253
Q4 versus Q1	1.11 (0.48–2.56)	0.809
Eosinophil >200/ μ L	0.82 (0.44–1.54)	0.544
Eosinophil >300/ μ L	1.18 (0.59–2.39)	0.633
Eosinophil >400/ μ L	1.34 (0.53–3.40)	0.538
Eosinophil >500/ μ L	2.19 (0.69–7.01)	0.185
Eosinophil >600/ μ L	2.96 (0.87–10.1)	0.083
Multivariate analysis		
Eosinophil >600/ μ L [#]	3.59 (1.00–12.8)	0.050
Eosinophil >600/ μ L [‡]	1.66 (0.43–6.40)	0.460
Eosinophil count (/ μ L) [#]	1.0 (0.99–1.00)	0.768
Eosinophil count (/ μ L) [‡]	1.0 (0.99–1.00)	0.815

Notes: *ORs and 95% CIs for patients in Q2, Q3, and Q4 of eosinophil count are presented, with patients in the lowest quartile serving as the reference. Q1 (n=42, median 47.2, IQR 7.2–71.0), Q2 (n=63, 129.2 [106.4–147.2]), Q3 (n=56, 202.7 [191.4–243.2]), and Q4 (n=63, 370.5 [320.8–481.1]). [#]ORs adjusted with age, sex, pack-year, BMI, and initial FEV₁% pred at enrollment. [‡]ORs adjusted with age, sex, pack-year, BMI, and ICS/LABA use at enrollment.

Abbreviations: ACOS, asthma–COPD overlap syndrome; OR, odds ratio; CI, confidence interval; BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; FEV₁, forced expiratory volume in 1 second; % pred, % predicted; IQR, interquartile range; Q, quartile.

**Figure 4** The association of eosinophil count (/ μ L) with FEV₁ in non-ACOS COPD.

Note: Distribution of eosinophil count quartile in each GOLD stages.

Abbreviations: FEV₁, forced expiratory volume in 1 second; ACOS, asthma–COPD overlap syndrome; GOLD, Global Initiative for Chronic Obstructive Lung Disease; Q, quartile.

Table 4 FEV₁ change in subgroups stratified according to blood eosinophil count

Blood eosinophil count quartile (μL)	FEV ₁ change (%)	P-value	FEV ₁ change (mL)	P-value
Eosinophil count $\leq 200/\mu\text{L}$ (n=107)	-0.2 \pm 11.8 (-2.5–2.1)	0.215	-10.4 \pm 386.0 (-84.4–63.6)	0.244
Eosinophil count $> 200/\mu\text{L}$ (n=77)	2.0 \pm 11.8 (-0.7–4.7)		52.2 \pm 316.3 (-19.6–124.0)	
Eosinophil count $\leq 600/\mu\text{L}$ (n=175)	0.3 \pm 11.2 (-1.4–1.9)	0.022	3.8 \pm 335.3 (-46.4–53.8)	0.044
Eosinophil count $> 600/\mu\text{L}$ (n=9)	9.5 \pm 19.2 (-5.2–24.2)		250.0 \pm 661.4 (-258.4–758.4)	

Note: Data presented as FEV₁ change per year-mean \pm standard deviation (95% confidence interval).

Abbreviation: FEV₁, forced expiratory volume in 1 second.

user and non-user (1.12 [0.66–1.91] vs 0.32 [0.00–20.88], $P=0.657$) and lower than 200/ μL (0.86 [0.48–1.56] vs 3.26 [0.36–290.9], $P=0.623$).

Discussion

Against the background of an increasing focus being placed on blood eosinophils and their significance in COPD, this study elucidated the clinical significance of the blood eosinophil count in patients with non-ACOS COPD. Our results indicated that neither the absolute blood eosinophil count nor the quartiles were associated with the risk of AECOPD, FEV₁ changes, or therapeutic response to ICS in patients with non-ACOS COPD.

To the best of our knowledge, this was the first analysis of the clinical implication of the blood eosinophil count in non-ACOS COPD patients from a nationwide cohort. We believe that the results are relevant to clinical practice. Generally, eosinophilic inflammation is regarded as a pivotal etiological factor in the asthmatic component of COPD.^{25,26} Additionally, multiple reports have suggested the usefulness of the eosinophil count in predicting the therapeutic response to ICS.^{9,13,27} However, before generalization of these results, we should consider the following points. COPD includes various phenotypes or endotypes and blood eosinophil count is not the only important biomarker; the reports referenced earlier

did not discuss the phenotypes in which blood eosinophilia may be useful.^{10,11,22} To date, among the various phenotypes of COPD, ACOS has been regarded as a COPD phenotype that is characterized by asthmatic components, such as a high eosinophil count, an increased IgE level, a positive bronchodilator response, and a history of allergic disease.²⁸ COPD is a precise phenotype that can be diagnosed clinically, and the criteria for ACOS include the components that indicate responsiveness to ICS. Therefore, to generalize the usefulness of the blood eosinophil count as a biomarker in COPD, it is necessary to verify that this count is also a useful biomarker in other patients, excluding ICS-susceptible patients such as those with ACOS. However, when we analyzed only patients with non-ACOS COPD, the alleged clinically significant role of the blood eosinophil count was absent. Therefore, the usefulness of the blood eosinophil count should not be overestimated in these patients.

Since the eosinophil count and related allergic components are included in the diagnosis of ACOS and the more predictable factors for a specific phenotype have not been confirmed, there may be controversy over the exclusion of ACOS patients from our analysis. Nevertheless, the distributions of blood eosinophil percent (median value 2.4%, IQR 2.3%–3.8%) and absolute count (167/ μL , range 90–273/ μL) in South Korean non-ACOS COPD patients

Table 5 FEV₁ change in subgroups stratified according to blood eosinophil counts and use of ICS/LABA

	FEV ₁ change (%)	P-value	FEV ₁ change (mL)	P-value
Eosinophil count $\leq 200/\mu\text{L}$				
ICS/LABA use (n=60)	-0.8 \pm 11.5 (-3.8–2.2)	0.745	-33.3 \pm 459.7 (-182.3–115.7)	0.769
No use of ICS/LABA (n=39)	0.01 \pm 12.4 (-4.0–4.0)		-9.2 \pm 352.7 (-100.3–81.9)	
Eosinophil count $> 200/\mu\text{L}$				
ICS/LABA use (n=34)	0.7 \pm 11.2 (-3.1–4.6)	0.290	100.6 \pm 385.2 (-33.8–235.0)	0.339
No use of ICS/LABA (n=35)	3.9 \pm 13.3 (-0.8–8.5)	0.290	24.3 \pm 263.8 (-66.3–114.9)	
Eosinophil count $\leq 600/\mu\text{L}$				
ICS/LABA use (n=71)	1.2 \pm 11.7 (-1.6–4.0)	0.3022	6.3 \pm 379.0 (-83.4–96.0)	0.864
No use of ICS/LABA (n=88)	-0.7 \pm 11.2 (-3.0–1.7)		-3.2 \pm 320.2 (-71.0–64.7)	
Eosinophil count $> 600/\mu\text{L}$				
ICS/LABA use (n=2)	5.5 \pm 13.1 (-6.6–17.6)	0.558	835 \pm 1,364.7 (-11,426.5–13,096.5)	0.558
No use of ICS/LABA (n=7)	23.5 \pm 37.5 (-313.2–360.2)		134.2 \pm 355.1 (-245.6–411.3)	

Note: Data presented as FEV₁ change per year-mean \pm standard deviation (95% confidence interval).

Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist.

Table 6 Impact of eosinophil count on moderate-to-severe acute exacerbation rates in COPD patients according to the exposure to ICS/LABA

	IRR (95% CI) ^a	P-value for interaction
Eosinophil count ≤200/μL		
ICS/LABA use (n=60)	1.12 (0.66–1.91)	0.657
No use of ICS/LABA (n=39)	0.32 (0.00–20.88)	
Eosinophil count >200/μL		
ICS/LABA use (n=34)	0.86 (0.48–1.56)	0.623
No use of ICS/LABA (n=35)	3.26 (0.36–290.9)	

Note: ^aModels adjusted for age, sex, BMI, pack-year, and FEV₁% pred at enrollment. **Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; IRR, incidence rate ratio; CI, confidence interval.

were similar to those in previous Copenhagen cohort studies that included ACOS patients (median blood eosinophil 2.6%, IQR 1.6%–3.7%; blood eosinophil count 200/μL, range 120–300/μL)¹² and a US-based cohort (median blood eosinophil 2.6%, IQR 1.8%–4.0%).²⁶ Additionally, although there were more patients with a blood eosinophil count >3%–5% than in previous reports that included patients with non-ACOS COPD in the COPD History Assessment in Spain (CHAIN) cohort (35.8% vs 26.7% for an eosinophil count >3%; 12.6% vs 5.2% for an eosinophil count >5%),¹⁹ the blood eosinophil count was not associated with COPD subgroups, the risk of

AECOPD, FEV₁ changes per year, or responsiveness to ICS in the non-ACOS COPD patients.

This finding implies that the eosinophilic activity of patients with non-ACOS COPD may be different from that of patients with asthma or ACOS. In patients with allergic asthma, the eosinophilic activity may be altered by the enhanced production of spontaneous reactive oxygen species, increased chemotaxis, and diminished apoptosis,²⁹ while the eosinophilic activity in COPD is not reported. Recently, a patient-level meta-analysis reported that patients with an eosinophil count of <2% had a higher risk of pneumonia,³⁰ which may reflect the importance of other inflammatory cells such as neutrophils, which has a key role in immune reaction of COPD,³¹ in this subpopulation.

Although we were unable to confirm the blood eosinophil count as an essential biomarker in non-ACOS COPD, when the cutoff value of the eosinophil count was changed from 200 to 600 cells/μL, the risk of AECOPD showed a tendency to increase gradually without statistical significance. This finding suggests that the cutoff value of the eosinophil count should be changed if it is used as a biomarker in patients with non-ACOS COPD.

Despite its clinically important and interesting findings, this study had some limitations. First, the final sample size

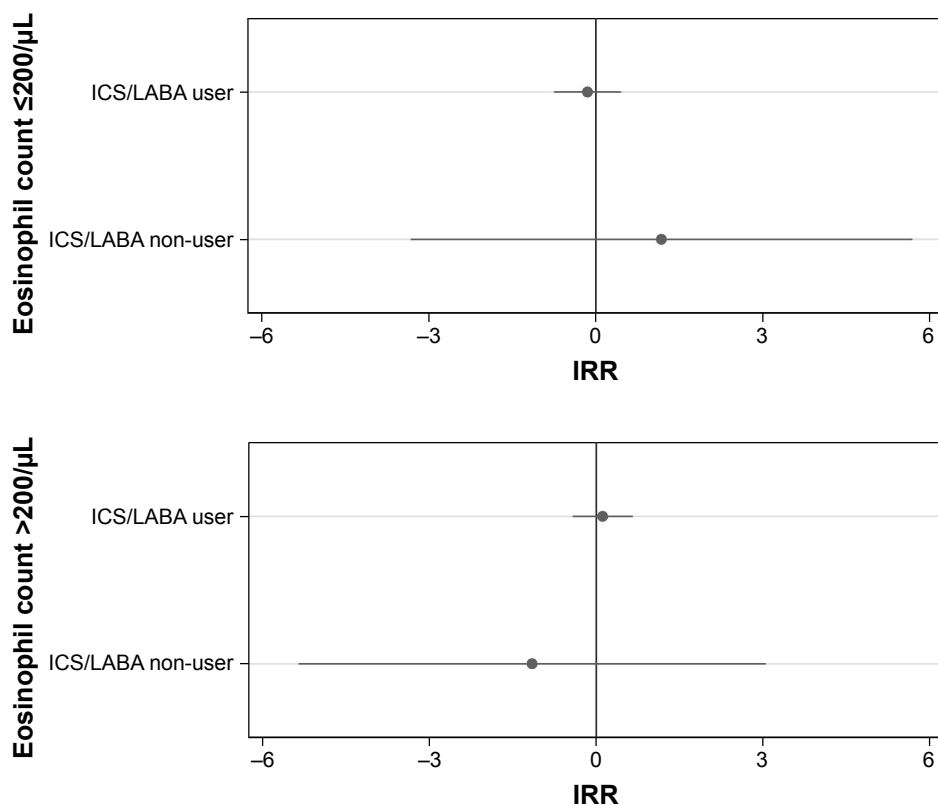


Figure 5 Impact of eosinophil count on moderate-to-severe acute exacerbation rates in COPD patients according to the exposure to ICS/LABA. **Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; IRR, incidence rate ratio.

was diminished by excluding a large proportion of ACOS patients, although the prevalence of ACOS varies based on the qualifying criteria of each region.³² Second, this cohort did not have an ICS washout period before enrollment. As a result, approximately half of the patients had been exposed to ICS, which could have decreased the blood eosinophil count at enrollment.²⁷ Third, the one-year evaluation period of the FEV₁ changes may have been too short to assess the decline of lung function. Fourth, the analysis did not include adjustment for seasonal variation of eosinophil, which was described in a previous study.³³

Conclusion

In patients with non-ACOS COPD, the blood eosinophil count and percent were not associated with FEV₁ changes, QoL, frequency of AECOPD, or responsiveness to ICS. Therefore, the clinical implications of the blood eosinophil count should not be overestimated in patients with non-ACOS COPD. Further studies are needed to identify the proper phenotypes and relevant biomarkers in this group.

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Disclosure

The authors report no conflicts of interest in this work.

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