

Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease



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Background: Eosinophilic airway inflammation in patients with chronic obstructive pulmonary disease (COPD) is associated with exacerbations and responsivity to steroids, suggesting potential shared mechanisms with eosinophilic asthma.

However, there is no consistent blood eosinophil count that has been used to define the increased exacerbation risk.

Objective: We sought to investigate blood eosinophil counts associated with exacerbation risk in patients with COPD.

Methods: Blood eosinophil counts and exacerbation risk were analyzed in patients with moderate-to-severe COPD by using 2 independent studies of former and current smokers with longitudinal data. The Genetic Epidemiology of COPD (COPDGene) study was analyzed for discovery (n = 1,553), and the Evaluation of COPD Longitudinally to Identify Predictive

Surrogate Endpoints (ECLIPSE) study was analyzed for validation (n = 1,895). A subset of the ECLIPSE study subjects were used to assess the stability of blood eosinophil counts over time.

Results: COPD exacerbation risk increased with higher eosinophil counts. An eosinophil count threshold of 300 cells/ μ L or greater showed adjusted incidence rate ratios for exacerbations of 1.32 in the COPDGene study (95% CI, 1.10-1.63). The cutoff of 300 cells/ μ L or greater was validated for prospective risk of exacerbation in the ECLIPSE study, with adjusted incidence rate ratios of 1.22 (95% CI, 1.06-1.41) using 3-year follow-up data. Stratified analysis confirmed that the increased exacerbation risk associated with an eosinophil count of 300 cells/ μ L or greater was driven by subjects with a history of frequent exacerbations in both the COPDGene and ECLIPSE studies.

Conclusions: Patients with moderate-to-severe COPD and blood eosinophil counts of 300 cells/ μ L or greater had an increased risk exacerbations in the COPDGene study, which was prospectively validated in the ECLIPSE study. (J Allergy Clin Immunol 2018;141:2037-47.)

Key words: Chronic obstructive pulmonary disease, asthma, eosinophil, exacerbation

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Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation and has limited therapeutic options. Patients with COPD are prone to exacerbations, which are associated with decreased lung function and increased morbidity and mortality. In patients with COPD, respiratory tract inflammation is thought to be driven by lymphocytes and neutrophils¹ compared with inflammation in asthmatic patients, which is mediated by T_H2 cells and eosinophils.² In patients with asthma, eosinophilic inflammation is associated with an increased exacerbation risk and loss of disease control on inhaled corticosteroid (ICS) withdrawal.³ Similarly, increasing evidence suggests that 20% to 40% of patients with stable COPD have eosinophilic airway inflammation, as measured based on sputum eosinophil counts,⁴ that is associated with exacerbations^{5,6} and response to steroids.⁷⁻⁹

Because blood eosinophil counts are more easily assessed than sputum eosinophil counts, associations between blood eosinophil counts and COPD phenotypes have been investigated. Prior studies have reported that a blood eosinophil count of 2% can serve as a surrogate for sputum eosinophilia during a COPD exacerbation,¹⁰ whereas other studies have reported a lack of correlation between sputum and blood eosinophil counts.¹¹⁻¹⁴

Abbreviations used

ACO:	Asthma-COPD overlap
CBC:	Complete blood count
COPD:	Chronic obstructive pulmonary disease
COPDGene:	Genetic Epidemiology of COPD
CT:	Computed tomography
ECLIPSE:	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
FVC:	Forced vital capacity
GERD:	Gastroesophageal reflux disease
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
ICS:	Inhaled corticosteroid
IRR:	Incidence rate ratio
ROC:	Receiver operating characteristic
SGRQ:	Saint George's Respiratory Questionnaire
WBC:	White blood cell

Furthermore, there is conflicting evidence about whether increased blood eosinophil counts are associated with increased exacerbations. Some studies reported increased COPD exacerbation risk, with varying blood eosinophil counts in general and clinical populations¹⁵⁻¹⁷ and *post hoc* analyses of clinical trials,¹⁸⁻²¹ whereas other studies have reported lack of associations between blood eosinophil counts and COPD exacerbations.^{11-13,22,23} Recently, a clinical trial showed that mepolizumab, an anti-IL-5 mAb, reduced moderate or severe exacerbations in patients with COPD with high blood eosinophil counts,²⁴ demonstrating that blood eosinophil counts are a useful biomarker to identify eosinophilic inflammation that can be targeted for therapy.

In this study we aimed to evaluate the relation between blood eosinophil counts and COPD exacerbation risk in 2 well-phenotyped COPD cohorts: the Genetic Epidemiology of COPD (COPDGene)²⁵ and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)²⁶ studies. We determined blood eosinophil counts associated with COPD exacerbations in the COPDGene study and validated the findings prospectively in the ECLIPSE study.

METHODS**Study populations**

The COPDGene and ECLIPSE studies have been described previously.^{25,26} Briefly, the COPDGene study is a multicenter observational study that enrolled 10,192 smokers with and without COPD in phase 1. Complete blood counts (CBCs) were measured at the phase 2 visit, which was approximately 5 years later. Subjects were clinically stable, with at least 30 days since their last exacerbation. The current analysis included 1,553 phase 2 subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry grade 2 to 4 COPD (postbronchodilator FEV₁/forced vital capacity [FVC] ratio <0.7 with FEV₁ <80% of predicted value)²⁷ who had available CBC and clinical data. Of these subjects, 1,113 (71%) participated in a longitudinal follow-up program to prospectively assess exacerbations after the phase 2 visit.

The ECLIPSE study was a multicenter, multinational, 3-year longitudinal study that enrolled 3,291 subjects. We analyzed 1,895 subjects with GOLD spirometry grade 2 to 4 with complete CBC and 3-year follow-up data. Subjects with an exacerbation within 3 weeks of enrollment were excluded. We also analyzed 243 smokers as control subjects with repeated CBC measurements to measure eosinophil stability. Subjects taking oral corticosteroids were excluded from both the COPDGene and ECLIPSE analyses (see Fig E1 in this article's Online Repository at www.jacionline.org).

Exacerbation ascertainment

In the COPDGene and ECLIPSE studies exacerbations were self-reported and defined as an episode of increased dyspnea, cough, and/or sputum production that required antibiotic and/or systemic steroid treatment. Severe exacerbations were defined as exacerbations requiring emergency department visits or hospitalization.^{14,28} In the longitudinal follow-up program for COPDGene study participants, exacerbation information was collected by means of telephone call or Web-based survey every 6 months.

Statistical analysis

Descriptive analysis was performed with the *t* test, Fisher exact test, and Kruskal-Wallis test, as appropriate. Negative binomial multivariate regression was performed for exacerbation analysis, and incidence rate ratios (IRRs) were calculated with 95% CIs. Nested models with and without eosinophil counts were compared by using a likelihood ratio test. Logistic regression was performed for binary variables (frequent exacerbations and severe exacerbations). Linear regression was performed for continuous variables, and the residuals were plotted to check normality assumption. Receiver operating characteristic (ROC) curves for multivariate models with different eosinophil counts were plotted for no exacerbations versus 1 or more exacerbations to evaluate eosinophil cutoffs. Statistical analyses were performed with R version 3.3.1 software.

RESULTS**Eosinophil count thresholds and exacerbation risk in a cross-sectional analysis of the COPDGene study**

Of the 1,765 COPDGene subjects with GOLD grade 2 to 4 COPD and CBC data, subjects taking chronic oral steroids or with incomplete information were excluded, leaving 1,553 subjects for analysis (see Fig E1). Because there is no consensus definition for eosinophilic COPD, we evaluated a range of thresholds ranging from 2% to 5% and from 100 to 400 cells/ μ L for association with exacerbations. We also included an eosinophil count cutoff of 340 cells/ μ L based on a recent publication.¹⁵ In negative binomial regression analysis adjusting for known COPD exacerbation risk factors, including gastroesophageal reflux disease (GERD), Saint George's Respiratory Questionnaire (SGRQ) total score, baseline smoking status, postbronchodilator FEV₁ percent predicted, and white blood cell (WBC) count, we observed increasing IRRs for exacerbation frequency as the eosinophil count cutoff increased (Fig 1). Eosinophil counts showed a consistent linear relationship with exacerbation risk, which was not clearly seen with eosinophil percentages. Multivariable logistic regression models using different eosinophil count cutoffs found that a threshold of 300 cells/ μ L produced the maximal area under the ROC curve, with the highest sensitivity and specificity (see Fig E2 in this article's Online Repository at www.jacionline.org). Compared with the nested model without eosinophil counts, inclusion of an eosinophil count threshold of 300 cells/ μ L was statistically significant ($P = .006$, likelihood ratio test).

Patients with eosinophilic COPD were more likely to be male and non-Hispanic white and had a greater number of exacerbations per year. Subjects with eosinophil counts of 300 cells/ μ L or greater had higher WBC counts with lower neutrophil percentages. There was no difference in reported ICS use between patients with eosinophil counts of greater than or less than 300 cells/ μ L (Table I). In multivariable analysis eosinophilic COPD was associated with higher SGRQ score (total, impact, and activity) and less emphysema measured by using quantitative analysis of chest computed tomographic (CT) scans

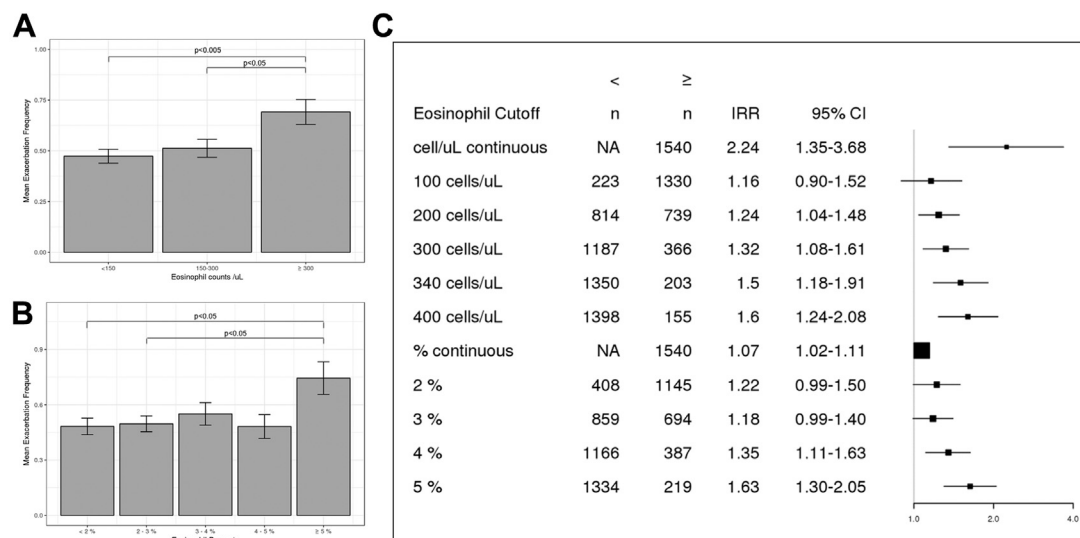


FIG 1. Risk of COPD exacerbations with increasing blood eosinophil counts in the COPDGene study. **A**, Mean 1-year exacerbation frequency reported at phase 2 visit per blood eosinophil count range in patients with moderate-to-severe COPD. Error bars indicate SEs. Differences between group means were determined by using 1-way ANOVA and the Tukey honestly significant difference test. **B**, Mean 1-year exacerbation frequency reported at phase 2 visit per blood eosinophil percentage range in patients with moderate-to-severe COPD. Error bars indicate SEs. Differences between group means were determined by using 1-way ANOVA and the Tukey honestly significant difference test. **C**, Adjusted IRRs for COPD exacerbations with different eosinophil cutoff values. Risk estimates are derived from negative binomial regression models adjusted for age, sex, race, GERD, SGRQ score, postbronchodilator FEV₁ percent predicted, and WBC count. NA, Not available.

(low-attenuation area at -950 Hounsfield units and the 15th percentile of the lung density histogram; see Table E1 in this article's Online Repository at www.jacionline.org). There was no difference in spirometric measures (FEV₁, FVC, and FEV₁/FVC ratio) or 6-minute walk distance.

In a multivariable model exacerbation frequency was associated significantly with female sex, white race, GERD, higher SGRQ total score, lower postbronchodilator FEV₁ percent predicted, and eosinophil counts of 300 cells/ μ L or greater (Table II). Eosinophil counts of 300 cells/ μ L or greater had an IRR of 1.32 (95% CI, 1.10-1.61; Table II). Furthermore, eosinophilic COPD was associated with frequent exacerbations (≥ 2 per year) in a logistic regression analysis (odds ratio, 1.58; 95% CI, 1.07-2.30; Table II).

Prospective analysis of the COPDGene study

Of the 1,553 patients in the cross-sectional analysis, 1,113 (71.6%) had at least 1 follow-up contact after the COPDGene phase 2 visit, for a total of 1,561 person-years (mean, 512 days). There was no difference in follow-up duration or proportion lost to follow-up between patients with eosinophilic and those with noneosinophilic COPD. The same covariates as in the cross-sectional multivariable model were used, with the addition of prior exacerbation history. Subjects with eosinophil counts of 300 cells/ μ L or greater at the phase 2 visit had an increased prospective exacerbation rate, with a similar risk estimate as the cross-sectional analysis (IRR, 1.33; 95% CI, 0.91-1.95); however, eosinophilic COPD was not statistically significant in multivariable regression (Table II).

When we performed stratified analysis based on exacerbation frequency in the prior year, we found that the predictive ability of eosinophilic COPD for future exacerbations was driven by

the subset of subjects with a history of frequent exacerbations (≥ 2 per year; IRR, 1.96; 95% CI, 1.21-3.21; $P = .008$). In subjects with 2 or more exacerbations in the prior year, the annual exacerbation rate during follow-up was 2.39 in those with increased eosinophil counts compared with 1.42 in those without increased eosinophil counts (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). A high eosinophil count was not significantly associated with future exacerbations in subjects with a history of 1 or fewer exacerbations in the previous year (Table III and see Table E2).

Validation in the ECLIPSE study

We prospectively validated the increased exacerbation risk with increased eosinophil counts in the ECLIPSE study. Among 2,303 subjects with GOLD grade 2 to 4 COPD, 1,895 with baseline CBC data and complete covariate information were included in the analysis. There were 133 subjects who participated in the screening visit but did not have follow-up visits or had missing laboratory information. There was no difference in the proportion of eosinophilic and noneosinophilic COPD among these subjects compared with the overall study population. Similar to the COPDGene study, those with eosinophil counts of 300 cells/ μ L or greater at the screening visit were more likely to be male. WBC counts were increased, and neutrophil percentages were decreased (Table I). There was no difference in quantitative CT measurements of emphysema and SGRQ scores in the ECLIPSE study in contrast to the COPDGene study (see Table E1). As in the COPDGene study, there was no association between eosinophil counts of 300 cells/ μ L or greater and spirometric measures or 6-minute walk distance.

We calculated exacerbation rates by dividing the total number of moderate-to-severe exacerbations by observed time at 2 different

TABLE I. Baseline characteristics of subjects with high versus low blood eosinophil counts

	COPDGene study			ECLIPSE study		
	Eosinophil count <300 cells/ μ L (n = 1,187)	Eosinophil count $\geq$ 300 cells/ μ L (n = 366)	P value	Eosinophil count <300 cells/ μ L (n = 1,477)	Eosinophil count $\geq$ 300 cells/ μ L (n = 418)	P value
Age (y), mean (SD)	67.88 (8.19)	68.27 (8.29)	.43	63.23 (7.1)	63.86 (6.8)	.11
Female sex, no. (%)	567 (47.8)	130 (35.5)	<.001	542 (36.7)	114 (27.3)	<.001
White race, no. (%)	911 (76.7)	305 (83.3)	.009	1,446 (97.9)	407 (97.4)	.64
Postbronchodilator FEV ₁ (% predicted), mean (SD)	53.11 (17.0)	51.43 (17.2)	.10	47.96 (15.5)	48.72 (15.9)	.38
GOLD grade, no. (%)			.55			.77
2	695 (58.6)	204 (55.7)		644 (43.6)	179 (42.8)	
3	360 (30.3)	115 (31.4)		631 (42.7)	186 (44.5)	
4	132 (11.1)	47 (12.8)		202 (13.7)	53 (12.7)	
FEV ₁ decrease (mL/y), mean (SD)	NA	NA	NA	34.12 (45.0)	30.0 (50.0)	.18
DLCO (mL/min/mmHg)*†	14.70 (6.4)	15.17 (6.4)	.26	NA	NA	NA
CT emphysema (% at -950 HU),† mean (SD)	12.59 (12.8)	11.69 (11.7)	.31	17.77 (12.4)	17.43 (11.8)	.65
CT lung density 15th percentile,† mean (SD)	-936.30 (27.3)	-933.32 (29.9)	.13	-948.37 (27.07)	-949.35 (25.41)	.54
SGRQ total score, mean (SD)	35.21 (20.3)	37.41 (21.8)	.07	49.97 (20.26)	47.98 (20.23)	.08
Six-minute walk distance (m), mean (SD)†	345.9 (128)	340.5 (138)	.50	370.9 (120)	372.2 (122.8)	.85
Any asthma history, no. (%)	299 (25.2)	101 (27.6)	.51	326 (24.0)	102 (26.3)	.39
ACO, no. (%)	130 (11.3)	54 (15.3)	.06	120 (9.4)	47 (12.7)	.09
Bronchodilator reversibility,‡ no. (%)	189 (15.9)	65 (17.8)	.46	318 (21.5)	120 (28.7)	.003
Exacerbations/y,§ mean (SD)	0.49 (0.9)	0.69 (1.2)	<.001	1.15 (1.3)	1.37 (1.6)	.004
Severe exacerbations, (%)	190 (16)	69 (18.9)	.23	0.27 (0.6)	0.29 (0.7)	.55
BMI (kg/m ²), mean (SD)	28.06 (6.4)	28.52 (6.4)	.22	26.42 (5.7)	26.65 (5.5)	.45
Pack-years of smoking, mean (SD)	51.96 (24.3)	51.43 (25.8)	.72	47.91 (26.6)	50.53 (28.0)	.08
Current smokers, no. (%)	404 (34.0)	116 (31.7)	.44	926 (62.7)	266 (63.6)	.77
ICS use, no. (%)†	568 (48.4)	187 (51.1)	.40	1047 (70.9)	310 (74.2)	.21
WBC count, mean (SD)	7.32 (2.2)	8.32 (1.9)	<.001	7.70 (2.3)	8.76 (2.4)	<.001
Eosinophils (%), mean (SD)	2.01 (1.1)	5.15 (2.3)	<.001	2.10 (1.2)	5.56 (2.7)	<.001
Neutrophils (%), mean (SD)	62.06 (10.2)	59.61 (9.7)	<.001	65.29 (8.9)	62.99 (8.4)	<.001
Lymphocytes (%), mean (SD)	27.08 (9.3)	26.30 (8.9)	.16	26.06 (8.1)	24.91 (7.3)	.009
Monocytes (%), mean (SD)	8.26 (2.5)	8.26 (2.2)	1.00	6.22 (2.3)	6.15 (2.2)	.57
Basophils (%), mean (SD)	0.60 (0.6)	0.68 (0.6)	.02	0.33 (0.2)	0.38 (0.2)	<.001

Statistically significant values are shown in boldface.

BMI, Body mass index; DLCO, diffusion capacity of the lung for carbon monoxide; HU, Hounsfield units.

*Adjusted for altitude and hemoglobin level.

†Subsets of subjects with complete information were used as follows: DLCO—eosinophil count <300 cells/ μ L (n = 1,003), eosinophil count $\geq$ 300 cells/ μ L (n = 304). Chest CT data—COPDGene study (eosinophil count <300 cells/ μ L [n = 863], eosinophil count $\geq$ 300 cells/ μ L [n = 256]), ECLIPSE study (eosinophil count <300 cells/ μ L [n = 1,263], eosinophil count $\geq$ 300 cells/ μ L [n = 347]). Six-minute walk distance—COPDGene study (eosinophil count <300 cells/ μ L [n = 1,166], eosinophil count $\geq$ 300 cells/ μ L [n = 355]), ECLIPSE study (eosinophil count <300 cells/ μ L [n = 1,457], eosinophil count $\geq$ 300 cells/ μ L [n = 414]). Asthma—COPDGene study (eosinophil count <300 cells/ μ L [n = 1,322], eosinophil count $\geq$ 300 cells/ μ L [n = 184]), ECLIPSE study (eosinophil count <300 cells/ μ L [n = 1,170], eosinophil count $\geq$ 300 cells/ μ L [n = 370]).

‡Defined as change in FEV₁ of at least 200 mL and 12% after bronchodilator. Two subjects from the COPDGene study had missing data.

§Number of exacerbations in the prior year to phase 2 study visit is reported for the COPDGene study, and exacerbation rate during the overall study period is reported for the ECLIPSE study.

||Severe exacerbations defined by emergency department visits or hospitalizations was a binary variable in the COPDGene study. In the ECLIPSE study the severe exacerbation rate during the overall study period is reported.

time points: 1-year follow-up and overall study period (4,981 person-years total; mean, 959 days). Models were adjusted for age, sex, race, and known risk factors for COPD exacerbations (ie, prior history of exacerbations, GERD, SGRQ total score, baseline smoking status, postbronchodilator FEV₁ percent predicted, and WBC count). There was no difference in risk estimates when we accounted for subjects with a change in smoking status, and therefore we only included baseline smoking status in the model. An eosinophil count of 300 cells/ μ L or greater at screening was consistently predictive of future exacerbations (IRR, 1.20 [95% CI, 1.05-1.36] at 1 year; IRR, 1.22 [95% CI, 1.06-1.42] for the overall study period; Table IV). Comparable with the COPDGene study, increasing eosinophil counts were associated with greater risk of exacerbation (Fig 2). Addition of eosinophil counts was statistically significant based on the likelihood ratio test ($P < .001$ for 1-year follow-up

and overall study period). The area under the curve in ROC analyses did not differ with different eosinophil count cutoffs (see Fig E3 in this article's Online Repository at www.jacionline.org). Similar to the COPDGene longitudinal follow-up study, the exacerbation risk associated with increased eosinophil counts was driven by the frequent exacerbators with 2 or more exacerbations before study entry in the stratified analysis (IRR, 1.40; 95% CI, 1.15-1.70; $P < .001$; Table V). Subjects with frequent exacerbation history and eosinophil counts of 300 cells/ μ L or greater had a higher annual exacerbation rate (overall, 2.41 per year) than those with frequent exacerbation history and lower eosinophil counts (overall, 1.61 per year; see Table E3). In the longitudinal analysis patients with eosinophilic and noneosinophilic COPD had similar changes in FEV₁, FVC, SGRQ score, and 6-minute walk distance.

TABLE II. Multivariable models of blood eosinophil counts of 300 cells/ μ L or greater and exacerbation risk in the COPDGene study

Factors	COPDGene: Year before visit 2 (cross-sectional)				COPDGene: Longitudinal follow-up	
	Exacerbation frequency* (n = 1,553)		Frequent exacerbation† (n = 1,281)		Exacerbation rate* (n = 1,113)	
	IRR* (95% CI)	P value	OR† (95% CI)	P value	IRR* (95% CI)	P value
Age	0.98 (0.97-1.00)	.007	0.96 (0.94-0.99)	.003	0.99 (0.97-1.01)	.48
Female sex	1.43 (1.20-1.71)	<.001	1.83 (1.30-2.58)	<.001	0.87 (0.65-1.15)	.31
Nonwhite race	0.73 (0.57-0.92)	.008	0.63 (0.40-0.99)	.05	1.73 (1.19-2.55)	.005
SGRQ total score‡	1.02 (1.02-1.03)	<.001	1.04 (1.03-1.05)	<.001	1.02 (1.01-1.03)	<.001
Postbronchodilator FEV ₁ (% predicted)§	0.98 (0.98-0.99)	<.001	0.97 (0.96-0.98)	<.001	0.99 (0.98-1.00)	.003
GERD	1.33 (1.11-1.59)	.002	1.35 (0.95-1.91)	.09	1.08 (0.81-1.45)	.57
Current smoking	0.71 (0.57-0.89)	.002	0.56 (0.37-0.84)	.006	0.63 (0.45-0.90)	.01
Previous exacerbations	NA	NA	NA	NA	2.51 (1.87-3.37)	<.001
WBC count	1.00 (0.96-1.04)	.97	1.02 (0.94-1.10)	.66	1.03 (0.96-1.10)	.44
Eosinophil count $\geq$ 300 cells/ μ L	1.32 (1.08-1.61)	.006	1.58 (1.07-2.30)	.019	1.33 (0.92-1.95)	.13

Statistically significant values are shown in boldface.

NA, Not available; OR, odds ratio.

*Risk estimate from negative binomial regression.

†Odds ratio from logistic regression comparing subjects with 2 or more exacerbations per year to subjects with less than 1 exacerbation per year.

‡Per 1-point increase in score.

§Per percentage point increase in FEV₁.**TABLE III.** Risk of increased blood eosinophil counts on future exacerbations stratified by prior exacerbation history: IRRs associated with eosinophil counts of 300 cells/ μ L or greater derived from multivariable analysis for exacerbation rate in the COPDGene longitudinal follow-up study

Noneosinophilic vs eosinophilic	COPDGene longitudinal follow-up stratified analysis					
	No exacerbations in the prior year (666 vs 98)		One exacerbation in the prior year (165 vs 28)		Two or more exacerbations in the prior year (125 vs 31)	
	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
Eosinophil count $\geq$ 300 cells/ μ L at phase 2 visit	1.12 (0.57-2.28)	.73	1.02 (0.48-2.20)	.97	1.96 (1.21-3.21)	.008

Multivariable model adjusted for age, sex, race, SGRQ score, GERD, current smoking, and WBC count. Statistically significant values are shown in boldface.

We also analyzed the subset of subjects (1,839 patients with COPD and 243 control subjects) with repeated eosinophil measurements over the course of the ECLIPSE study. Eosinophil counts were relatively stable over time, with an interclass correlation coefficient of 0.57. There was no significant difference in interclass correlation coefficient between patients with COPD and control subjects (0.57 and 0.56, respectively). For a subset of 1,345 (71%) patients with COPD with 4 CBC measurements over the study (0, 1, 2, and 3 years), 90 (6.7%) had persistently increased eosinophil counts of greater than 300/ μ L. The majority (784 [58%]) had eosinophil counts of less than 300/ μ L for the entire study. The exacerbation risk in patients with persistently increased eosinophil counts was greater compared with that in patients with persistently low eosinophil counts and those with fluctuating eosinophil counts (see Table E4 in this article's Online Repository at www.jacionline.org), suggesting that although baseline eosinophil count was predictive of exacerbation risk up to 3 years, patients with persistent eosinophilia are at the greatest risk of exacerbation.

Sensitivity analysis

To evaluate for confounding by ICS use, we included use of ICSs as a covariate in the multivariable model. The association between eosinophilic COPD and exacerbations in the COPDGene and ECLIPSE studies remained (COPDGene IRR, 1.34 [95% CI, 1.01-1.63]; ECLIPSE 1-year follow-up IRR, 1.18, [95% CI, 1.04-1.34]; and overall study period IRR, 1.21 [95%

CI, 1.05-1.39]). In addition, we performed a sensitivity analysis focusing on the subgroup of subjects not taking ICSs. Although increasing eosinophil counts were associated with increased exacerbation risk, the cutoff of 300 cells/ μ L was no longer statistically significant. This is likely related to the reduced sample size (see Fig E4 in this article's Online Repository at www.jacionline.org) because previously validated risk factors for COPD exacerbations, including GERD and WBC,¹⁴ were no longer significant in the subgroup analysis (data not shown).

Epidemiologic relationship between eosinophilic COPD and asthma-COPD overlap

We analyzed the relationship between eosinophilic COPD, asthma-COPD overlap (ACO), and exacerbation risk. ACO has been shown previously to be associated with increased exacerbation risk in the COPDGene^{29,30} and ECLIPSE³¹ studies. Patients with COPD with eosinophil counts of 300 cells/ μ L or greater were more likely to have ACO by using the COPDGene study's definition of self-report of a doctor's diagnosis of asthma before age 40 years (odds ratio, 1.51 for the COPDGene study and 1.69 for the ECLIPSE study; see Table E5 in this article's Online Repository at www.jacionline.org).^{30,32} However, the overall concordance between eosinophilic COPD and asthma was low (n = 54 in the COPDGene study and n = 47 in the ECLIPSE study, Fig 3). In negative binomial regression ACO and

TABLE IV. Multivariable models of blood eosinophil counts of 300 cells/ μ L or greater and exacerbation risk in the ECLIPSE study

Factors associated with exacerbation rate	ECLIPSE study			
	1 y		Overall study period	
	IRR (95% CI)	P value	IRR (95% CI)	P value
Age	1.01 (1.00-1.02)	.008	1.01 (1.00-1.02)	.01
Female sex	1.23 (1.10-1.38)	<.001	1.31 (1.15-1.49)	<.001
Nonwhite race	0.82 (0.56-1.18)	.29	0.71 (0.45-1.08)	.12
SGRQ total score*	1.01 (1.01-1.01)	<.001	1.01 (1.01-1.01)	<.001
Postbronchodilator FEV ₁ (% predicted)†	0.99 (0.98-0.99)	<.001	0.98 (0.97-0.98)	<.001
GERD	1.39 (1.24-1.56)	<.001	1.36 (1.19-1.56)	<.001
Current smoking	1.10 (0.98-1.24)	.11	1.21 (1.06-1.39)	.005
previous exacerbations	2.45 (2.18-2.74)	<.001	2.87 (2.51-3.29)	<.001
WBC count	1.04 (1.01-1.06)	.001	1.04 (1.02-1.07)	<.001
Eosinophil count $\geq$ 300 cells/ μ L at screening	1.20 (1.05-1.36)	.005	1.22 (1.06-1.42)	.006

Risk estimates from negative binomial regression are shown. Statistically significant values are shown in boldface.

*Per 1-point increase in score.

†Per percentage point increase in FEV₁.

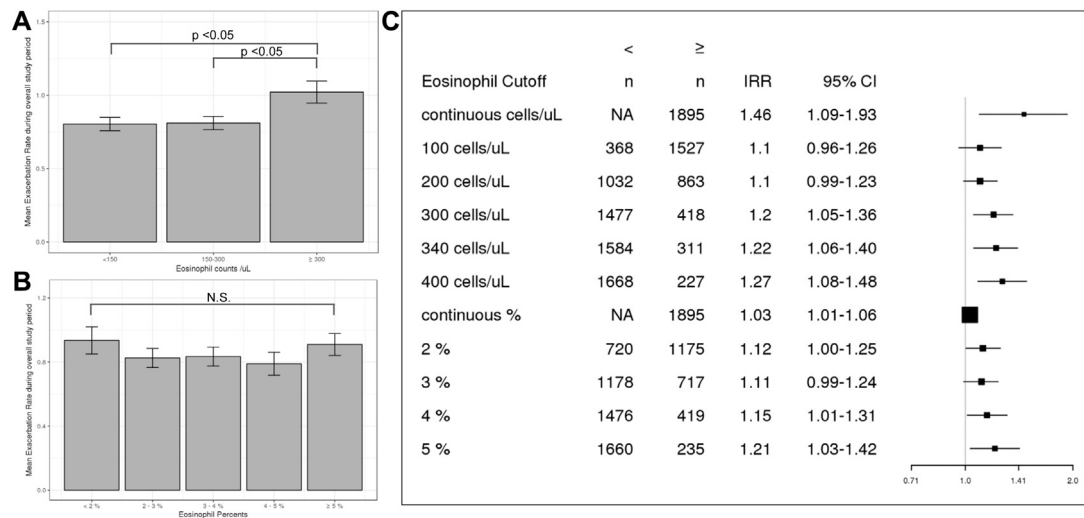


FIG 2. Risk of prospective COPD exacerbations with increasing blood eosinophil counts in the ECLIPSE study. **A**, Mean exacerbation rate during the overall study period per blood eosinophil count range in patients with moderate-to-severe COPD. Error bars indicate SEs. Differences between group means were determined by using 1-way ANOVA and the Tukey honestly significant difference test. **B**, Mean exacerbation rate during the overall study period per blood eosinophil percentage range in patients with moderate-to-severe COPD. Error bars indicate SEs. Differences between group means were determined by using 1-way ANOVA and the Tukey honestly significant difference test. **C**, Adjusted IRRs for COPD exacerbations with different eosinophil cutoffs. Risk estimates are derived from negative binomial regression models adjusted for age, sex, race, previous exacerbations, GERD, SGRQ score, postbronchodilator FEV₁ percent predicted, and WBC count.

eosinophilic COPD were associated independently with exacerbation risk in the COPDGene and ECLIPSE studies (Table VI).

DISCUSSION

In this study of 2 multicenter longitudinal cohorts of patients with moderate-to-severe COPD, we found that exacerbation risk increased linearly with greater blood eosinophil counts. We identified a threshold blood eosinophil count of 300 cells/ μ L or greater to be associated with exacerbations and then validated this cutoff as a predictor of future exacerbations using prospective data from the ECLIPSE study. We showed further that the increased COPD exacerbation risk associated with increased

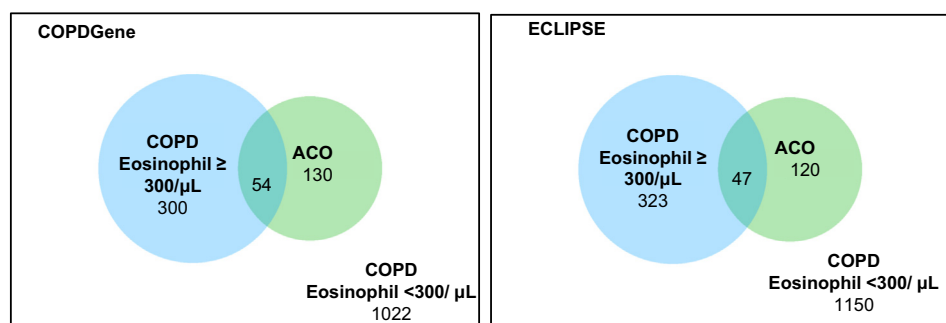
eosinophil counts was driven by subjects in both studies with a history of frequent exacerbations, which was defined as 2 or more exacerbations per year.

The most commonly used cutoff to define eosinophilic COPD is 2%, which originates from a sentinel study describing increased exacerbation risk with blood eosinophil counts of 2% or greater that was predictive of sputum eosinophilia ($\geq 3\%$) at the time of exacerbation.¹⁰ A previous analysis in the ECLIPSE study showed 88% concordance between blood eosinophil count thresholds of 2% and 150 cells/ μ L.³³ Many subsequent studies have used these lower thresholds.^{11,34-38} In our study we found that higher baseline eosinophil counts were associated with future exacerbation risk up to 3 years and that absolute eosinophil counts were consistently

TABLE V. Risk of increased blood eosinophil counts on future exacerbations stratified by prior exacerbation history: IRRs associated with eosinophil counts of 300 cells/ μ L or greater derived from multivariable analysis for exacerbation rate in the ECLIPSE overall study period

ECLIPSE stratified analysis on overall study period						
Noneosinophilic vs eosinophilic	No exacerbations in the prior year (788 vs 223)		One exacerbation in the prior year (373 vs 99)		Two or more exacerbations in the prior year (316 vs 96)	
	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
Eosinophil count ≥ 300 cells/ μ L at screening	1.03 (0.85-1.24)	.77	1.15 (0.87-1.51)	.33	1.40 (1.15-1.70)	<.001

Multivariable model adjusted for age, sex, race, SGRQ score, GERD, current smoking, and WBC count. Statistically significant values are shown in boldface.

**FIG 3.** Venn diagrams of the number of subjects with ACO (defined by asthma diagnosis before the age of 40 years)³⁰ and patients with COPD with blood eosinophil counts of 300 cells/ μ L or greater in the COPDGene and ECLIPSE studies.**TABLE VI.** ACO, which was defined by asthma diagnosis before age 40 years, and increased eosinophil counts (≥ 300 cells/ μ L) independently predict exacerbations

Factors	COPDGene study		ECLIPSE study			
	Cross-sectional exacerbation frequency		Prospective exacerbation rate			
	IRR (95% CI)	P value	1 y	Overall study period		
	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
Age	0.99 (0.97-1.00)	.02	1.01 (1.00-1.02)	.006	1.01 (1.00-1.02)	.009
Nonwhite race	0.69 (0.54-0.88)	.003	0.83 (0.54-1.25)	.37	0.69 (0.41-1.12)	.15
Female sex	1.39 (1.16-1.66)	<.001	1.20 (1.06-1.36)	.004	1.29 (1.11-1.49)	<.001
SGRQ score*	1.02 (1.02-1.03)	<.001	1.01 (1.01-1.01)	<.001	1.01 (1.01-1.01)	<.001
Postbronchodilator FEV ₁ (% predicted) [†]	0.98 (0.98-0.99)	<.001	0.99 (0.98-0.99)	<.001	0.98 (0.98-0.99)	<.001
GERD	1.37 (1.14-1.64)	<.001	1.40 (1.23-1.59)	<.001	1.39 (1.20-1.61)	<.001
Current smoking	0.73 (0.58-0.90)	.004	1.10 (0.97-1.25)	.12	1.25 (1.08-1.44)	.003
Previous exacerbations	NA	NA	2.35 (2.08-2.65)	<.001	2.77 (2.40-3.21)	<.001
WBC count	1.01 (0.97-1.05)	.70	1.03 (1.01-1.06)	.006	1.04 (1.01-1.07)	.004
ACO	1.33 (1.04-1.71)	.02	1.29 (1.08-1.54)	.005	1.33 (1.08-1.63)	.006
Eosinophil count ≥ 300 cells/ μ L	1.26 (1.03-1.54)	.02	1.21 (1.06-1.39)	.005	1.22 (1.04-1.42)	.01

Results from negative binomial regression analysis are shown. Statistically significant values are shown in boldface.

NA, Not available.

*Per 1-point increase in score.

[†]Per percentage point increase in FEV₁.

associated with increased exacerbations, whereas the eosinophil percentage did not show a linear relationship in either the COPDGene or ECLIPSE study. The absolute eosinophil count might be more relevant biologically because WBC counts can vary widely and single percentage values might not capture the entire range of blood eosinophils. In contrast, a percentage cutoff has been used for sputum because the sputum differential count is typically based on counting a fixed number of cells (400-600 cells) on a cytospin slide.^{13,39-42}

Our finding is in line with the recently published Copenhagen General Population Study, in which an eosinophil cutoff of

340 cells/ μ L was associated with COPD exacerbations.¹⁵ Two studies based on health care use data also demonstrated increased exacerbation risk with blood eosinophil counts of 300 cells/ μ L or greater¹⁷ and 450 cells/ μ L or greater.¹⁶ In common with our study, these studies included large numbers of patients with moderate-to-severe COPD (FEV₁ <80% or GOLD classification C and D) and applied higher eosinophil count cutoffs defined by absolute counts. Other studies reporting a lack of association between blood eosinophil counts and COPD exacerbations had differences compared with our study. Most of these studies were smaller.^{11,12,22,23} Acute Exacerbation and

Respiratory InfectionS in COPD (AERIS),¹¹ Initiatives BPCO,²² and a recent meta-analysis used only percentage cutoffs for eosinophil counts.³⁸ The importance of a higher count-based eosinophil cutoff is demonstrated by the lack of association between an eosinophil cutoff of 2% and exacerbation risk in a subset of the ECLIPSE study.³³ No association was found in Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), which included GOLD 0 subjects (37% of the study population), whereas 22% of the subjects had moderate-to-severe COPD.¹³ Because low lung function is a risk factor for COPD exacerbations, selection of patients with moderate-to-severe COPD can enrich for subjects prone to exacerbations. These observations suggest that patient population, disease severity, and eosinophil count cutoffs all matter in understanding the significance of eosinophils in patients with COPD.

Our findings highlight the utility of measuring eosinophil counts in patients with frequent exacerbations because eosinophilic COPD is a significant risk factor for future exacerbations in this subgroup. In the prospective follow-up in both the COPDGene and ECLIPSE studies, frequent exacerbators with eosinophil counts of 300 cells/ μ L or greater had an average of 1 additional exacerbation episode per year compared with frequent exacerbators with lower eosinophil counts. Although the most significant predictive factor for future exacerbation is a prior history of exacerbation in patients with COPD,¹⁴ we showed that measurement of eosinophil counts in a high-risk group can serve as a biomarker for additional risk stratification. Measurements of eosinophil counts might not have much utility in patients with COPD with few exacerbations. Furthermore, eosinophil measurements in patients with frequent exacerbations might identify subjects who can be treated with antieosinophilic therapy based on recent mepolizumab trials.²⁴ METREX and METREO were phase 3, randomized, placebo-controlled, double-blind trials that enrolled patients with 2 or more moderate exacerbations or 1 or more severe exacerbations receiving triple inhaled therapy.²⁴ The eosinophilic COPD phenotype based on blood eosinophil counts was part of the enrollment criteria in METREO but not for METREX.²⁴ In line with our study, these parallel trials also showed that exacerbation risk can be further stratified based on blood eosinophil counts, even in patients with a significant prior exacerbation history.²⁴

Subjects with a history of 2 or more exacerbations in the past year included 14% of patients with moderate-to-severe COPD in the COPDGene study and 22% in the ECLIPSE study. Based on the current guidelines, frequent exacerbators receiving maximal inhaled therapy would be considered for long-term azithromycin or roflumilast to prevent future exacerbations.^{43,44} Eosinophilic frequent exacerbators comprised 2.8% of patients with moderate-to-severe COPD in the COPDGene study and 5% of patients in the ECLIPSE study, corresponding to 20% of the frequent exacerbator group. Further studies are required to determine the effects of anti-inflammatory therapy versus antieosinophilic therapy in eosinophilic and noneosinophilic exacerbation-prone subjects.

At a single time point, both the COPDGene and ECLIPSE studies had approximately 20% of patients with moderate-to-severe COPD with eosinophil counts of 300 cells/ μ L or greater. However, in the ECLIPSE study only 6.7% had persistently increased eosinophil counts of greater than 300 cells/ μ L, which carried the greatest risk of exacerbation. A recent study of the UK Clinical Practice Research Datalink showed that blood eosinophil

counts are more variable in patients with COPD, particularly for patients with higher baseline eosinophil counts.⁴⁵ Although we did not observe differences in eosinophil stability between patients with COPD and control subjects, we found that about 60% of patients with COPD never had eosinophil counts of 300 cells/ μ L or greater.

In the COPDGene study eosinophilic COPD was associated with an approximately 30% increased risk of exacerbations in both cross-sectional and prospective data. However, eosinophil counts were not statistically significant in the prospective analysis. Data collection for the longitudinal follow-up program was different than for the main COPDGene study because exacerbations were assessed every 6 months with a Web- and telephone-based telecommunication system.⁴⁶ It is possible that the longitudinal follow-up data might not represent the same type of exacerbation information collected in person at the study visits.

We have also found differences between the COPDGene and ECLIPSE studies. For example, current smoking was negatively associated with exacerbation frequency in the COPDGene study, whereas it was associated with an increased exacerbation rate in the ECLIPSE study. This likely reflects indication bias in the COPDGene population; subjects with more severe disease might preferentially quit smoking.⁴⁷ Subjects in the ECLIPSE study had a higher proportion of bronchodilator reversibility, which might be due to withdrawal of bronchodilators before assessment, which was not performed in the COPDGene study. Patients with COPD and blood eosinophil counts of 300 cells/ μ L or greater had higher SGRQ scores in the COPDGene study but not in the ECLIPSE study.

Because eosinophilic inflammation is classically regarded as a feature of allergic asthma,⁴⁸ we examined the relationship between eosinophilic COPD and asthma. Neither the COPDGene study nor the ECLIPSE study excluded patients with an asthma history. In univariate analysis there were no significant associations between eosinophilic COPD and ACO, which was defined as an asthma diagnosis before the age of 40 years in the COPDGene study.³⁰ The limited concordance between eosinophilic COPD and asthma could be due to the incomplete definition of ACO because we relied on patient report of a diagnosis of asthma or because of the heterogeneous nature of ACO itself. ACO can include asthmatic patients with fixed obstruction or smokers with COPD and features of asthma or a T_H2 immune response that can develop independent of asthma.⁴⁹

A count-response relation between blood eosinophil counts and asthma-related outcomes has well been described in patients with asthma; blood eosinophil counts of 290 to 400 cells/ μ L have been associated with increased asthma exacerbations.⁵⁰⁻⁵³ However, patients with eosinophilic COPD in our study had an average smoking history of 50 pack-years, whereas studies of eosinophilic asthma typically exclude smokers with a greater than 10 pack-year history or patients with COPD. Therefore, even if a subset of patients with COPD had prior asthma that progressed to COPD in our cohorts, these subjects still had significant cigarette smoke exposure that is much greater than that seen in populations in asthma studies. Despite the differences in smoking exposure, patients with eosinophilic asthma and those with eosinophilic COPD have similar relationships between blood eosinophil counts and frequent exacerbations, which points to a shared role of eosinophilic inflammation. This is in line with a recently published study demonstrating asthma-like airway

remodeling and inflammation in patients with eosinophilic COPD without allergies or asthma history.⁵⁴

Response to therapeutics in patients with eosinophilic COPD also provides clues to a potential shared mechanism with eosinophilic asthma. Previous studies have shown that increased blood eosinophil counts in patients with COPD predict a favorable response to oral corticosteroids^{55,56} and ICSs,^{18-20,57} which have been cornerstones for asthma therapy. In a recent trial benralizumab (an anti-IL-5 receptor α mAb) reduced exacerbations in patients with COPD with blood eosinophil counts of greater than 300 cells/ μ L.⁵⁸ As mentioned above, mepolizumab reduced exacerbations in patients with COPD with increased blood eosinophil counts.²⁴ The blood eosinophil count threshold for targeting intervention requires additional investigation and is an effort in the COPD Biomarker Qualification Consortium.⁵⁹

The strength of our study is the inclusion of 2 large cohorts of well-characterized patients with COPD who were prospectively analyzed as discovery and validation populations to identify an eosinophil threshold count increasing exacerbation risk.

We are also aware of the limitations of this study. We measured blood eosinophil counts and not sputum or lung tissue eosinophil counts, which might be more closely related to the disease process. We excluded patients taking oral steroids; however, approximately 50% of the COPDGene subjects and 70% of the ECLIPSE subjects were using ICSs. Although ICS use has a minimal effect on blood eosinophil counts,⁶⁰ patients with eosinophilic COPD are known to be more responsive to ICS therapy and have less exacerbations on ICSs, which might reduce the effect of the exacerbation risk. The analysis restricted to nonusers of ICSs showed increasing eosinophil counts were associated with increased risk of exacerbation, but the cutoff of 300 cells/ μ L was no longer significant, likely because of the reduced number of subjects. In the COPDGene study CBC data were obtained only at the phase 2 visit, and therefore we could not assess changes in eosinophil counts over time or use the full longitudinal data from phase 1 to phase 2. Self-report of exacerbation history might be a limitation, although this definition has been used in multiple prior studies in both the COPDGene²⁸ and ECLIPSE¹⁴ studies. Finally, because patients with asthma history were enrolled in the cohorts, there could be misclassification between patients with eosinophilic COPD and those with asthma. We did not have skin test results or IgE measurements to independently assess the allergic component. However, because there is no gold standard definition of ACO, we aimed to assess the relationship of ACO and eosinophilic asthma using this data set.

In conclusion, we showed that blood eosinophil counts of 300 cells/ μ L or greater were associated with increased exacerbation frequency in 2 large COPD studies. This threshold identified an eosinophilic subgroup of 20% of patients with moderate-to-severe COPD and 20% of patients with frequent exacerbations in whom blood eosinophils could further stratify exacerbation risk.

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Key messages

- Patients with moderate-to-severe COPD and increased blood eosinophil counts have increased exacerbation risk compared with those with blood eosinophil counts of less than 300 cells/ μ L.
- Our study supports measurement of eosinophil counts in patients with frequent COPD exacerbations, which might have utility in identifying a population for treatments targeting eosinophilic inflammation.

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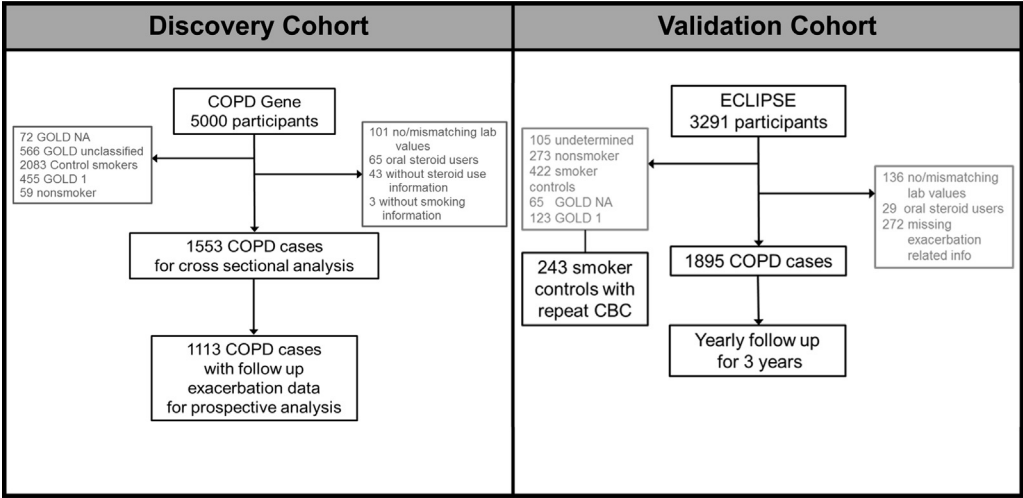


FIG E1. Study design and populations. NA, Not available.

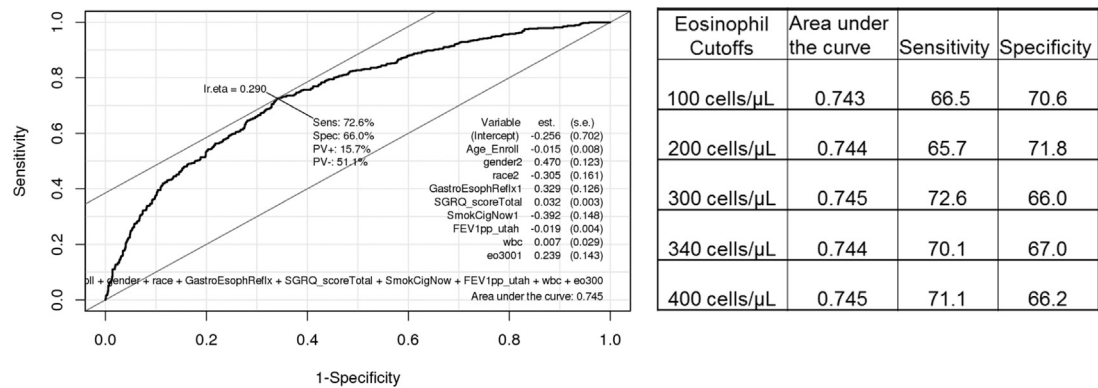


FIG E2. ROC curve for eosinophil cutoff of 300 cells/μL in the COPDGene study. ROC analysis was based on logistic regression models (0 vs any exacerbation history) adjusted for age, sex, race, GERD, SGRQ score, current smoking, postbronchodilator FEV₁, percent predicted (*pp*), WBC count, and eosinophil count ranging from 100 to 400 cells/μL. *PV+*, Predictive value for a positive result; *PV-*, predictive value for a negative value; *Sens*, sensitivity; *Spec*, specificity.

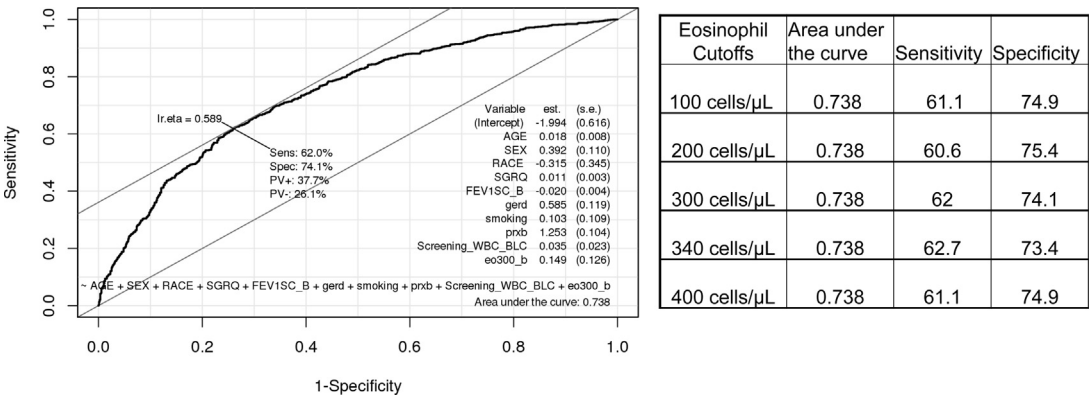


FIG E3. ROC curve for eosinophil cutoff of 300 cells/μL in the ECLIPSE study. ROC analysis was based on logistic regression models (exacerbation rate ≥ 1 during overall study period vs <1) adjusted for age, sex, race, previous exacerbation, GERD, SGRQ score, current smoking, postbronchodilator FEV₁ (*pp*), WBC count, and eosinophil count ranging from 100 to 400 cells/μL. *PV+*, Predictive value for a positive result; *PV-*, predictive value for a negative value; *Sens*, sensitivity; *Spec*, specificity.

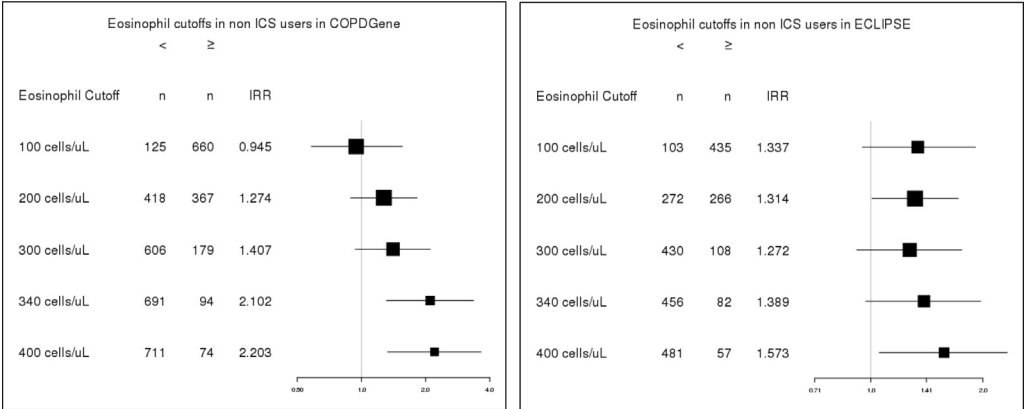


FIG E4. Eosinophil count cutoffs in patients with COPD not using ICSs. Risk estimates are derived from negative binomial regression models adjusted for age, sex, race, GERD, SGRQ score, current smoking, postbronchodilator FEV₁ percent predicted, and WBC count.

TABLE E1. Quantitative chest CT emphysema results and SGRQ total scores in patients with COPD with eosinophil counts of 300 cells/ μ L or greater

Factor	COPDGene study		ECLIPSE study	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
log(LAA950)	−0.26 (−0.43 to −0.08)	.005	−0.07 (−0.17 to −0.03)	.19
Perc15	4.68 (1.53 to 7.82)	.004	1.55 (−1.22 to 4.32)	.27
SGRQ	3.00 (0.61 to 5.38)	.014	−1.99 (−4.19 to 0.21)	.07

For log(LAA950) and Perc15, a subset of subjects with quantitative CT data were analyzed (COPDGene study, n = 1,119; ECLIPSE study, n = 1,610). Linear regression models are adjusted for age, sex, race, smoking status, body mass index, CT scanner model, and WBC. For SGRQ scores, linear regression models are adjusted for age, sex, race, and pack-years smoking history. Statistically significant values are shown in boldface.

LAA950, Low-attenuation area at less than 950 Hounsfield units; Perc15, 15th percentile of the lung density histogram.

TABLE E2. Annual exacerbation rate in subgroups stratified by prior exacerbation frequency and blood eosinophil count: COPDGene longitudinal follow-up study

No. of exacerbations in prior year	Annual exacerbation rate during longitudinal follow-up	
	Eosinophil count <300 cells/ μ L	Eosinophil count $\geq$ 300 cells/ μ L
0	0.29	0.35
1	0.81	0.79
$\geq$ 2	1.42	2.39

TABLE E3. Annual exacerbation rate in subgroups stratified by prior exacerbation frequency and blood eosinophil count: ECLIPSE 1-year and overall study period

No. of exacerbations in prior year	Annual exacerbation rate			
	1 y		Overall study period	
	Eosinophil count <300 cells/ μ L	Eosinophil count $\geq$ 300 cells/ μ L	Eosinophil count <300 cells/ μ L	Eosinophil count $\geq$ 300 cells/ μ L
0	0.62	0.63	0.40	0.38
1	1.40	1.51	1.00	1.12
$\geq$ 2	2.05	2.97	1.61	2.41

TABLE E4. Persistent eosinophilia and exacerbation risk in the ECLIPSE study

Factors associated with exacerbation rate	ECLIPSE overall study period			
	Persistently increased vs low eosinophil counts (n = 90 vs n = 784)		Persistently increased vs fluctuating eosinophil counts (n = 90 vs n = 471)	
	IRR (95% CI)	P value	IRR (95% CI)	P value
Age	1.00 (0.99-1.02)	.75	1.00 (0.99-1.02)	.89
Nonwhite race	0.76 (0.41-1.34)	.36	0.90 (0.36-1.90)	.80
Female sex	1.29 (1.06-1.57)	.009	1.38 (1.10-1.73)	.004
SGRQ total score*	1.01 (1.01-1.02)	<.001	1.01 (1.00-1.01)	.02
Postbronchodilator FEV ₁ (% predicted)†	0.98 (0.97-0.98)	<.001	0.99 (0.98-0.99)	<.001
GERD	1.32 (1.07-1.62)	.008	1.43 (1.14-1.79)	.002
Current smoking	1.10 (0.89-1.35)	.39	1.19 (0.94-1.52)	.16
Previous exacerbations	2.77 (2.27-3.39)	<.001	3.00 (2.38-3.82)	<.001
WBC count	1.00 (0.95-1.05)	.99	1.04 (0.99-1.09)	.1
Persistent eosinophil count ≥300 cells/μL	1.48 (1.11-1.96)	.007	1.39 (1.07-1.80)	.01

Risk of exacerbation in subjects with persistently increased eosinophil counts compared with persistently low eosinophil counts and in subjects with persistently increased eosinophil counts compared with fluctuating eosinophil counts. Statistically significant values are shown in boldface.

*Per 1-point increase in score.

†Per percentage point increase in FEV₁.

TABLE E5. Association between ACO and eosinophilic COPD defined as a blood eosinophil count of 300 cells/ μ L or greater

Factor	COPDGene study		ECLIPSE study	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age	0.95 (0.93-0.97)	<.001	0.94 (0.92-0.96)	<.001
Female sex	1.68 (1.22-2.32)	.001	2.16 (1.54-3.03)	<.001
Nonwhite race	1.37 (0.93-1.99)	.11	2.69 (1.10-6.08)	.02
BMI	1.03 (1.00-1.05)	.03	1.04 (1.01-1.07)	.007
Smoking (pack-years)	0.99 (0.98-0.99)	.01	0.99 (0.98-0.99)	.03
Eosinophil count $\geq$ 300 cells/ μ L	1.51 (1.04-2.18)	.03	1.69 (1.15-2.48)	.007

Odds ratios were derived from logistic regression. ACO was defined based on a doctor's diagnosis of asthma before age 40 years.^{E1} Statistically significant values are shown in boldface.

BMI, Body mass index.