CHEST

Clinical Implications of Low Absolute Blood Eosinophil Count in the SPIROMICS COPD Cohort

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BACKGROUND: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) considers blood eosinophil counts < 100 cells/μL ($BEC_{\leq 100}$) in people with COPD to predict poor inhaled corticosteroid (ICS) responsiveness. However, the $BEC_{\leq 100}$ phenotype is inadequately characterized, especially in advanced COPD.

RESEARCH QUESTION: Are there differences between GOLD group D patients with high BEC and those with low BEC regarding baseline characteristics and longitudinal outcomes?

STUDY DESIGN AND METHODS: We used multivariable mixed models and logistic regression to contrast clinical characteristics and outcomes of $BEC_{\leq 100}$ vs BEC > 100 (BEC_{100+}) in all subjects with COPD (n = 1,414) and GOLD group D subjects (n = 185) not receiving ICS.

RESULTS: We identified n = 485 with $BEC_{\leq 100}$ (n = 61 GOLD group D) and n = 929 people with BEC_{100+} (n = 124 GOLD group D). $BEC_{\leq 100}$ status was stable at 6 weeks and approximately 52 weeks (intraclass correlations of 0.78 and 0.71, respectively). Compared with BEC_{100+}, $BEC_{\leq 100}$ comprised more women, with greater current smoking, and less frequent childhood asthma. Among all analyzed participants, the two BEC-defined subsets showed similar rates of lung function decline (mean slope, $BEC_{\leq 100}$ vs BEC_{100+}, −50 vs −39 mL/y; P = .140), exacerbations (0.40 vs 0.36/y; P = .098), subsequent ICS initiation (2.5% vs 4.4%; P = .071), and mortality (7.8% vs 8.4%; P = .715). However, in GOLD group D, people with $BEC_{\leq 100}$ showed higher exacerbation rates within 365 days of enrollment (0.62 vs 0.33/y; P = .002) and total follow-up (1.16 vs 0.83/y; P = .014). They also had greater lung function decline (mean slope of −68 mL/y vs −23 mL/y; P = .036) and had greater emphysema at baseline (voxels < 950 Hounsfield units at total lung capacity of 7.46% vs 4.61%; P = .029).

INTERPRETATION: In non-ICS-treated GOLD group D COPD, people with $BEC_{\leq 100}$ had more baseline emphysema, prospective exacerbations, and lung function decline. Our analysis has identified a particularly vulnerable subpopulation of people with COPD, suggesting the need for studies focused specifically on their therapeutic treatment.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT01969344; URL: www.clinicaltrials.gov

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ABBREVIATIONS: 6MWD = 6-minute walk distance; AECOPD = acute exacerbation of the respiratory symptoms of COPD; BD = bronchodilator; BEC = blood eosinophil count; CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICC = intraclass correlation coefficient; ICS = inhaled corticosteroid; SGRQ = St. George's Respiratory Questionnaire; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study

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Take-home Points

Study Question: Do patients with group D COPD and low blood eosinophil counts (BECs) differ from those with high BEC regarding baseline characteristics and longitudinal outcomes?

Results: We found that group D COPD patients with low BEC had greater emphysema at baseline, had higher exacerbation rates in the first year and throughout the course of the study, and had greater lung function decline during the course of the study compared with their peers with high BEC.

Interpretation: Group D COPD patients with low BEC represent a distinct cohort characterized by greater emphysema, more exacerbations, and greater lung function decline as compared with those with high BEC.

The Global Initiative for Obstructive Lung Disease (GOLD) identifies patients with COPD in GOLD group D (GOLD D) as symptomatic people with at least one severe or two moderate acute exacerbations in the year before assessment. Current guidelines propose considering avoiding use of inhaled corticosteroids (ICS) in GOLD group D patients with blood eosinophil counts (BECs) $< 100/\mu L$ ($BEC_{\leq 100}$), with limited evidence to support this recommendation.[1] However, more recent results suggest that low BEC is associated with severity of emphysema[2-5] and is associated with worse survival and longer hospital stays in hospitalized patients with COPD exacerbations.[6,7]

To provide evidence to support management decisions in $BEC_{\leq 100}$, we performed a longitudinal analysis of people with COPD not receiving ICS, contrasting $BEC_{\leq 100}$ with normal or high blood eosinophil counts (BEC_{100+}). We hypothesized that differences that occurred in smaller, more defined subgroups, such as GOLD group D, might be hidden in larger cohorts of subjects with a broader range of COPD severity. Therefore, we analyzed data for both groups in the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), a large, observational cohort of people with or at risk of developing COPD.

Study Design and Methods

Study Design and Participants

SPIROMICS is an ongoing multicenter, observational study that between 2010 and 2015 enrolled 2,983 participants aged 40 to 80 years.[8] Participants included those who had either never ($\leq$ 1 pack-year) or had currently or previously smoked cigarettes ($\geq$ 20 pack-years); the latter two groups were with or without COPD as classified by GOLD guidelines.[9] All investigations were conducted according to the principles of the Declaration of Helsinki; institutional review boards at each participating site reviewed and approved protocols; and all participants provided written informed consent. SPIROMICS did not mandate uniform therapies.

Data Collection

We evaluated participants at baseline and annual in-person visits, with additional quarterly telephone surveys. Each patient was monitored for 3 years. Pulmonary function testing (based on 2005 American Thoracic Society/European Respiratory Society guidelines[10]) was done, and 6-min walk distance (6MWD) was determined, at enrollment and annual visits. Chest CT scans, at full inspiration (total lung capacity) and expiration (residual volume), were acquired at enrollment and 1-year follow-up. Using those scans, we performed parametric response mapping to assess functional small-airway disease quantitatively.[11] We assessed respiratory symptoms and disease-specific health status by self-report, using the modified Medical Research Council dyspnea score, COPD Assessment Test (CAT), and St. George's Respiratory Questionnaire (SGRQ). We elicited acute COPD exacerbation (AECOPD) data through quarterly telephone calls and yearly follow-up visits, defining AECOPD as symptom worsening requiring antibiotics and/or systemic corticosteroids (moderate) or treatment in ED or hospital settings (severe). BECs were obtained by differential blood counts from the clinical laboratories at visits 1, 2, and 4, which we dichotomized as $\leq 100/\mu L$ for $BEC_{\leq 100}$ and $> 100/\mu L$ for BEC_{100+} according to the baseline values.

The value of 100 was included in the low BEC cohort because many laboratories report blood eosinophils in intervals of 100.

Statistical Analyses

Demographic, comorbidity, and baseline clinical characteristics of participants were evaluated by χ^2 or Kruskal-Wallis test for

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categorical or continuous variables, respectively, and were stratified by $BEC_{\leq 100}$ vs BEC_{100+}. Using one-way analysis of variance to calculate the between-subject variation and within-subject variation, we performed repeatability analysis, using intraclass correlation coefficients (ICCs) between measures at enrollment and at 6-week and 1-year follow-up. ICC interpretations were as follows: < 0.50, poor; 0.50 to 0.75, moderate; 0.75 to 0.90, good; > 0.90, excellent.[12] To evaluate the relationship of some baseline characteristics with BEC among those not receiving ICS or oral steroids at baseline, we built multivariate regression models adjusted for age, race, sex, BMI, history of asthma, chronic bronchitis, smoking status, and pack-years. These characteristics were lung function, 6MWD, imaging variables, and symptoms measured by CAT or SGRQ. Because of the skewed distribution of some data including complement C3, C-reactive protein, fibrinogen, and various quantitative CT scan characteristics, those values were log-transformed and summarized as geometric means to facilitate interpretation.

We used mixed-effects linear regression models adjusted for age, race, sex, BMI, history of asthma, chronic bronchitis, smoking status, and pack-years to evaluate the relationship between baseline BEC groups and longitudinal changes in clinical measures (FEV_1, CAT, 6MWD, and SGRQ). Annual exacerbation rates were determined by dividing the number of reported exacerbations by the number of years in the study and were further analyzed using zero-inflated negative binomial regression models, adjusted as described above with the addition of exacerbations in the year before enrollment; in this analysis, we included only participants with complete 3-year follow-up data. $P < .05$ was considered statistically significant. All analyses were conducted with SAS 9.4 (SAS Institute).

Results

Study Cohort

From the entire SPIROMICS cohort, we identified n = 1,414 participants diagnosed with COPD who were taking neither ICS nor oral corticosteroids at enrollment, of whom n = 185 were classified as GOLD D. At the baseline visit of these participants with COPD who were not taking ICS/oral corticosteroids, $BEC_{\leq 100}$ was noted in a substantial fraction of both all (n = 485; 34.3%) and GOLD D participants (n = 61; 33.0%) (Fig 1).

Stability of $BEC_{\leq 100}$ Classification

To evaluate the stability of BEC classification on repeated testing, we analyzed data from the SPIROMICS repeatability substudy, in which a subset of participants underwent repeated assessment 6 weeks after enrollment.[13] Among 53 subjects who underwent repeated BEC analysis, BEC classifications were moderately repeatable (ICC, 0.78). To analyze longer-term stability, we compared the BEC values of all participants (n = 1,136) who underwent multiple analyses during the study and found similar repeatability (ICC, 0.71) of BEC classification.

Baseline Characteristics

$BEC_{\leq 100}$ participants with COPD were more frequently women and currently smoking, but without higher smoking burden by pack-years than BEC_{100+} participants (Table 1). $BEC_{\leq 100}$ participants had lower BMI and fibrinogen values, less frequently had a history of childhood asthma, and were less often prescribed a long-acting muscarinic antagonist or diagnosed with COPD before enrollment. However, there was no

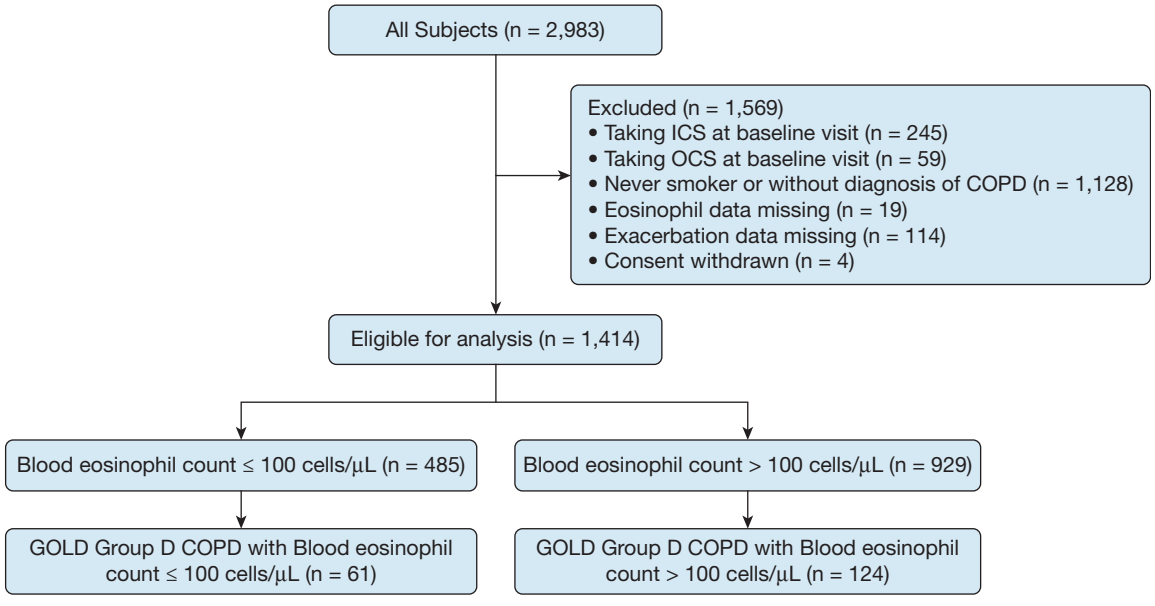

Figure 1 – *Enrollment and outcomes. GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; OCS = oral corticosteroids.*

TABLE 1] Baseline Univariate Analysis for Eligible Participants

	All Subjects With COPD					GOLD Group D Subjects				
	0 ≤ Eosinophils ≤ 100 (n = 485)		Eosinophils > 100 (n = 929)			0 ≤ Eosinophils ≤ 100 (n = 61)		Eosinophils > 100 (n = 124)		
Variable	No.	Value	No.	Value	*P* Value	No.	Value	No.	Value	*P* Value
Age, mean (SD), y	485	65.18 (8.32)	929	65.40 (7.79)	.6258	61	60.97 (8.74)	124	62.90 (8.32)	.145
Male, %	267	55	573	62	.0167	32	52	62	50	.7574
White, %	405	84	759	82	.3731	40	67	98	80	.0678
Hispanic, %	15	3	41	4	.2528	2	3	6	5	.7224
Current individuals who smoke, %	188	39	300	33	.0152	28	47	37	31	.0478
History of childhood asthma, %	29	6	91	10	.0118	5	9	13	12	.6063
BMI, mean (SD)	485	26.64 (5.05)	929	27.71 (5.23)	< .001	61	26.60 (5.65)	124	27.33 (5.45)	.4004
Smoking pack-years, mean (SD)	485	54.32 (29.83)	928	52.60 (25.06)	.2782	61	49.87 (21.03)	124	51.66 (22.43)	.6041
CRP, mean (SD), mg/dL	282	5.39 (11.00)	566	6.49 (9.69)	.1563	29	11.76 (22.78)	64	7.30 (8.75)	.3159
Fibrinogen, mean (SD), mg/dL	282	5.12 (1.29)	566	5.42 (1.50)	.0024	29	5.27 (1.62)	64	5.77 (1.70)	.1868
Ferritin, mean (SD), μg/L	282	165.18 (178.82)	566	164.55 (150.32)	.9594	29	192.72 (169.26)	64	128.66 (120.38)	.0732
IL-17, mean (SD), pg/mL	282	1.58 (0.44)	566	1.68 (0.83)	.0249	29	1.47 (0.04)	64	1.61 (0.73)	.1195
IL-6, mean (SD), pg/mL	282	9.84 (86.36)	566	4.39 (11.22)	.292	29	3.68 (1.87)	64	3.96 (5.46)	.719
TNF, mean (SD), pg/mL	282	13.15 (6.34)	566	14.61 (33.16)	.3128	29	13.47 (7.15)	64	13.30 (5.98)	.906
Post-FEV_1, mean (SD), L	485	1.81 (0.77)	928	1.83 (0.77)	.6729	61	1.42 (0.59)	124	1.40 (0.66)	.8578
Post-FVC, mean (SD), L	485	3.39 (1.05)	928	3.43 (1.04)	.5271	61	3.11 (0.99)	124	2.98 (0.92)	.3945
PRM^{fSAD}, mean (SD), %	424	25.89 (13.42)	832	25.99 (14.17)	.9019	50	29.74 (15.06)	107	29.97 (14.16)	.9258
Airway wall thickness, mean (SD), mm	477	1.24 (0.19)	907	1.26 (0.20)	.1805	59	1.24 (0.20)	120	1.23 (0.20)	.8194
Voxels < 865 HU at RV, mean (SD), %	479	32.68 (20.65)	921	31.88 (20.48)	.4881	58	40.08 (21.53)	123	39.25 (20.97)	.8056
Voxels < 950 HU at RV, mean (SD), %	479	5.80 (8.93)	921	5.40 (8.10)	.4197	58	8.90 (8.88)	123	7.96 (9.33)	.5182
6-Min walk distance, mean (SD), m	468	394.35 (112.04)	883	386.61 (112.76)	.2291	55	351.55 (133.68)	110	337.34 (109.80)	.468
Voxels < 865 HU at TLC, mean (SD), %	481	66.11 (14.48)	924	65.29 (14.37)	.3091	59	63.51 (17.79)	123	65.87 (16.08)	.3711
Voxels < 865 HU at RV, mean (SD), %	481	33.54 (17.36)	924	32.51 (16.71)	.2821	59	36.74 (18.81)	123	35.96 (17.75)	.7867
Voxels < 950 HU at TLC in LLL, mean (SD), %	481	8.38 (10.37)	924	7.88 (9.80)	.3712	59	12.40 (12.74)	123	9.75 (10.21)	.1657
Voxels < 950 HU at TLC in LUL, mean (SD), %	481	12.27 (13.64)	924	11.14 (12.14)	.1269	59	16.32 (13.69)	123	15.43 (14.68)	.6964
Voxels < 950 HU at TLC in RUL, mean (SD), %	481	13.46 (15.83)	924	12.45 (14.61)	.2436	59	18.26 (16.44)	123	17.22 (17.29)	.6981

(Continued)

TABLE 1] *(Continued)*

Variable	All Subjects With COPD					GOLD Group D Subjects				
	0 ≤ Eosinophils ≤ 100 (n = 485)		Eosinophils > 100 (n = 929)			0 ≤ Eosinophils ≤ 100 (n = 61)		Eosinophils > 100 (n = 124)		
	No.	Value	No.	Value	*P* Value	No.	Value	No.	Value	*P* Value
% Emphysema at TLC, mean (SD)	481	11.18 (11.63)	924	10.39 (10.78)	.191	59	15.36 (12.46)	123	13.84 (12.20)	.435
SGRQ, score (SD)	437	35.15 (20.40)	833	36.40 (19.21)	.2818	55	54.80 (15.12)	117	51.47 (13.83)	.1557
CAT, score (SD)	469	14.75 (8.01)	887	14.73 (7.90)	.9706	61	21.00 (6.67)	124	20.38 (6.33)	.5384
FEV_1 bronchodilator response, %	196	40	350	38	.357	18	30	36	29	1.000
Eosinophils (% of WBC count), mean (SD)	168	0.62 (1.59)	329	1.56 (5.01)	.0018	12	0.36 (0.58)	21	6.31 (17.01)	.1245
Eosinophils, mean (SD), cells/μL	485	82.80 (32.70)	929	275.76 (206.43)	< .001	61	76.36 (36.38)	124	269.51 (120.17)	< .001
History of exacerbations, %										
0	353	72.78	648	69.75	…	21	34.43	35	28.23	…
1	81	16.7	149	16.04	…	21	34.43	52	41.94	…
2	26	5.36	71	7.64	…	19	31.15	37	29.84	…
3	20	4.12	49	5.27	…	0	0	0	0	…
Missing	5	1.03	12	1.29	.411	0	0	0	0	.5693
GOLD stage, %										
1	125	25.77	214	23.04	…	4	6.56	12	9.68	…
2	217	44.74	437	47.04	…	23	37.7	45	36.29	…
3	107	22.06	203	21.85	…	26	42.62	43	34.68	…
4	36	7.42	75	8.07	…	8	13.11	24	19.35	…
Missing	0	0	0	0	.6735	0	0	0	0	.5529
mMRC, %										
0	125	25.77	230	24.76	…	0	0.0	2	1.61	…
1	219	45.15	422	45.43	…	3	4.92	10	8.06	…
2	85	17.53	166	17.87	…	23	37.70	49	39.52	…
3	42	8.66	80	8.61	…	23	37.70	32	25.81	…
4	12	2.47	26	2.8	…	8	13.11	24	19.35	…
Missing	2	0.41	5	0.54	.9957	4	6.56	7	5.65	.4773
GOLD group based on mMRC, %										
A	316	65.15	558	60.06	…	…	…	…	…	…
B	90	18.56	184	19.81	…	…	…	…	…	…

(Continued)

TABLE 1] *(Continued)*

Variable	All Subjects With COPD						GOLD Group D Subjects				
	0 ≤ Eosinophils ≤ 100 (n = 485)		Eosinophils > 100 (n = 929)		*P* Value		0 ≤ Eosinophils ≤ 100 (n = 61)		Eosinophils > 100 (n = 124)		*P* Value
	No.	Value	No.	Value			No.	Value	No.	Value	
C	32	6.6	84	9.04	…		…	…	…	…	…
D	35	7.22	68	7.32	…		…	…	…	…	…
Missing	12	2.47	35	3.77	.2379		…	…	…	…	…
GOLD group based on CAT, %											
A	136	28.04	232	24.97	…		…	…	…	…	…
B	254	52.37	479	51.56	…		…	…	…	…	…
C	6	1.24	20	2.15	…		…	…	…	…	…
D	61	12.58	124	13.35	…		…	…	…	…	…
Missing	28	5.77	74	7.97	.2963		…	…	…	…	…

Data are presented as mean (SD) or No. (%). CAT = COPD Assessment Test; CRP = C-reactive protein; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield unit; LLL = left lower lobe; LUL = left upper lobe; mMRC = modified Medical Research Council; PRM^{FSAD} = parametric response mapping functional small-airway disease; RUL = right upper lobe; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity; TNF = tumor necrosis factor.

significant difference in baseline FEV_1 ($BEC_{\leq 100}$, 1.81 vs 1.83 L; $P = .673$) or different distribution of GOLD A-D groups between the two eosinophil subsets. In adjusted multivariable analysis, $BEC_{\leq 100}$ participants had lower C-reactive protein than did BEC_{100+} participants (Table 2).

Among GOLD D participants, $BEC_{\leq 100}$ participants more often reported current smoking, without other differences between groups (Table 1).

Radiographic Characteristics

In univariable analysis of the overall group, we found no difference in airway wall thickness (Pi10; the average wall thickness of a hypothetical airway of 10-mm lumen perimeter on CT scan imaging) or percent emphysema (% voxels < 950 Hounsfield units [HU] at total lung capacity), but in multivariable analysis, $BEC_{\leq 100}$ participants had more air trapping defined by % voxels < 856 HU at expiration ($BEC_{\leq 100}$, 33.4% vs 31.1%; $P = .026$).

Among GOLD D participants not using ICS, multivariable analysis detected increased airway wall thickness ($P = .033$), and more emphysema ($P = .029$) in $BEC_{\leq 100}$ participants, without differences in air trapping (Table 2).

Exacerbations

In multivariable analysis of COPD participants not using ICS, there was no difference between BEC-defined subsets in AECOPD rate during follow-up (events per year, $BEC_{\leq 100}$ vs BEC_{100+}, 0.40 vs 0.36; $P = .098$), severe AECOPD (0.23 vs 0.19; $P = .097$), AECOPD over the first year (0.16 vs 0.13; $P = .138$), AECOPD requiring steroids (0.35 vs 0.32; $P = .365$), or AECOPD requiring antibiotics (0.34 vs 0.30; $P = .184$) (Table 2).

In contrast, in GOLD D participants multivariable analysis of prospective AECOPD revealed greater AECOPD rates in $BEC_{\leq 100}$ participants during both total follow-up ($BEC_{\leq 100}$ vs BEC_{100+}, 1.16 vs 0.83; $P = .014$) (Fig 2) and over the first year (0.62 vs 0.33; $P = .002$), as well as greater rates of AECOPD requiring antibiotics (0.71 vs 0.50; $P = .020$). However, the two BEC-defined subsets did not differ in rates of severe AECOPD ($BEC_{\leq 100}$ vs BEC_{100+}, 0.48 vs 0.39; $P = .258$) or AECOPD requiring steroids (0.92 vs 0.71; $P = .102$) (Table 2).

Initiation of ICS During the Follow-Up

To evaluate potential change in ICS use after baseline, we analyzed reported ICS use at the follow-up visits.

TABLE 2] Multivariate Analysis of Both All Analyzed Participants and Those With Group D COPD

Variable	COPD (n = 1,414)			Group D COPD (n = 185)		
	$BEC_{\leq 100}$ (n = 485)	BEC_{100+} (n = 929)	*P* Value[a]	$BEC_{\leq 100}$ (n = 61)	BEC_{100+} (n = 124)	*P* Value[a]
ICS initiation, No. (%)	12 (2.5)	41 (4.4)	.071	10 (16.4)	16 (12.9)	.917
Survival, No. (%)	447 (92.2)	851 (91.6)	.715	51 (83.6)	108 (87.0)	.521
6MWD, mean (95% CI), m	391.8 (381.7-401.9)	390.98 (383.4-398.6)	.901	343.90 (309.8-378.0)	346.2 (321.7-370.7)	.914
SGRQ score, mean (95% CI)	35.9 (34.3-37.3)	35.1 (33.9-36.3)	.419	54.6 (50.8-58.5)	51.14 (48.5-53.8)	.15
CAT score, mean (95% CI)	14.80 (14.2-15.5)	14.4 (13.9-14.9)	.36	20.52 (18.8-22.3)	20.4 (19.1-21.6)	.897
Voxels < 865 HU at RV, mean (95% CI), %	33.4 (31.8-35.0)	31.1 (29.9-32.3)	**.026**	43.5 (38-2-48.8)	38.8 (35.1-42.4)	.154
Voxels < 950 HU at TLC, mean (95% CI), %	3.9 (3.5-4.4)	3.6 (3.3-3.9)	.232	7.5 (5.3-10.6)	4.6 (3.6-5.9)	**.029**
Airway wall thickness (Pi10), mean (95% CI), mm	3.86 (3.8-3.9)	3.86 (3.85-3.87)	.438	3.91 (3.87-3.96)	3.85 (3.92-3.88)	**.033**
PRM^{fSAD}, mean (95% CI), %	26.27 (25.1-27.5)	25.54 (24.65-26.44)	.35	29.79 (25.66-33.92)	29.74 (26.89-32.58)	.983
CRP, mean (95% CI), mg/dL	2.56 (2.2-3.0)	3.12 (2.81-3.46)	**.032**	3.46 (1.97-6.1)	5.25 (3.55-7.76)	.238
Fibrinogen, mean (95% CI), g/L	5.02 (4.9-5.2)	5.21 (5.09-5.32)	.075	5.11 (4.54-5.75)	5.71 (5.26-6.2)	.132
Ferritin, mean (95% CI), μg/L	107.3 (95.4-120.7)	110.9 (101.83-120.78)	.657	142.22 (93.215.85)	96.95 (72.63-129.42)	.141
AEs, 1-y rate (95% CI)	0.16 (0.1-0.2)	0.13 (0.09-0.19)	.138	0.62 (0.35-1.11)	0.33 (0.18-0.59)	**.002**
AEs, total rate (95% CI)	0.40 (0.3-0.5)	0.36 (0.3-0.44)	.098	1.16 (0.72-1.86)	0.83 (0.51-1.34)	**.014**
Severe AEs, total rate (95% CI)	0.23 (0.16-0.37)	0.19 (0.13-0.27)	.097	0.48 (0.26-0.89)	0.39 (0.2-0.76)	.258
AEs requiring antibiotics, total rate (95% CI)	0.34 (0.27-0.43)	0.30 (0.24-0.37)	.184	0.71 (0.39-1.3)	0.50 (0.28-0.92)	**.020**
AEs requiring steroids, total rate (95% CI)	0.35 (0.27-0.45)	0.32 (0.25-0.41)	.365	0.93 (0.55-1.55)	0.71 (0.42-1.20)	.102

Multivariate regression analysis was adjusted for age, race, sex, BMI, history of asthma, chronic bronchitis, smoking status, and pack-years. 6MWD = 6-min walk distance (m); AE = acute exacerbation; BEC = blood eosinophil count; CAT = COPD Assessment Test; CRP = C-reactive protein; HU = Hounsfield unit; ICS = inhaled corticosteroids; Pi10 = average wall thickness for an airway of 10-mm lumen perimeter on CT scan imaging; PRM^{fSAD} = parametric response mapping functional small-airway disease; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity.

Data are presented as means (95% CI), No. (%), or rate (95% CI) as appropriate.

[a]Boldface entries indicate significance.

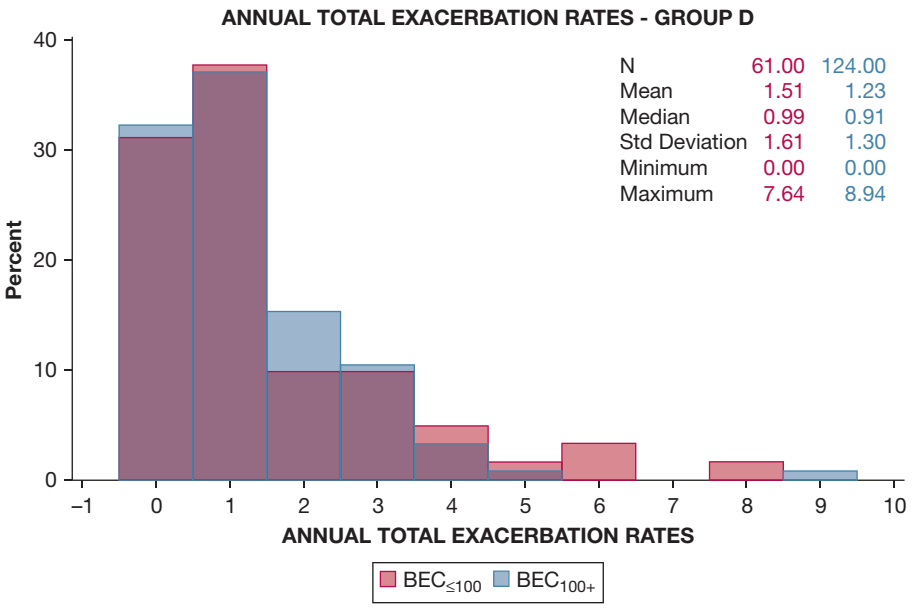

Figure 2 – *Annual exacerbation rates during the study in patients with group D COPD. Multivariate analysis of prospective acute exacerbation of the respiratory symptoms of COPD (AECOPD) in the GOLD D group revealed significant differences between BEC-defined subsets in AECOPD rates during the study follow-up period (1.16 vs. 0.83; P = .014). BEC = blood eosinophil count.*

Initiation of ICS was reported at some rate in both BEC-defined subsets without significant difference ($BEC_{\leq 100}$ vs BEC_{100+}, 12 [2.4%] vs 41 [4.4%]; $P = .07$).

Longitudinal Changes in Functional Status and Quality of Life

Excluding data from subjects with fewer than three outcome determinations, we identified n = 742 participants with COPD and n = 66 participants with GOLD group D COPD whose data we used for longitudinal analysis of functional performance, symptoms, and disease-specific health status. Using mixed-effects linear regression models to evaluate the changes in FEV_1, we found no difference in lung function decline between the two BEC-defined subsets among all COPD participants not using ICS. In contrast, $BEC_{\leq 100}$ GOLD D participants had greater decline of postbronchodilator FEV_1 than did BEC_{100+} GOLD D participants (mean slope, $BEC_{\leq 100}$ vs BEC_{100+}, −68 vs −23 mL/y; $P = .036$) (Fig 3, Table 3). However, there were no differences between BEC-defined subsets among all analyzed participants or those with group D COPD for changes in 6MWD, CAT score, or SGRQ score (Table 3). We performed this same analysis while taking

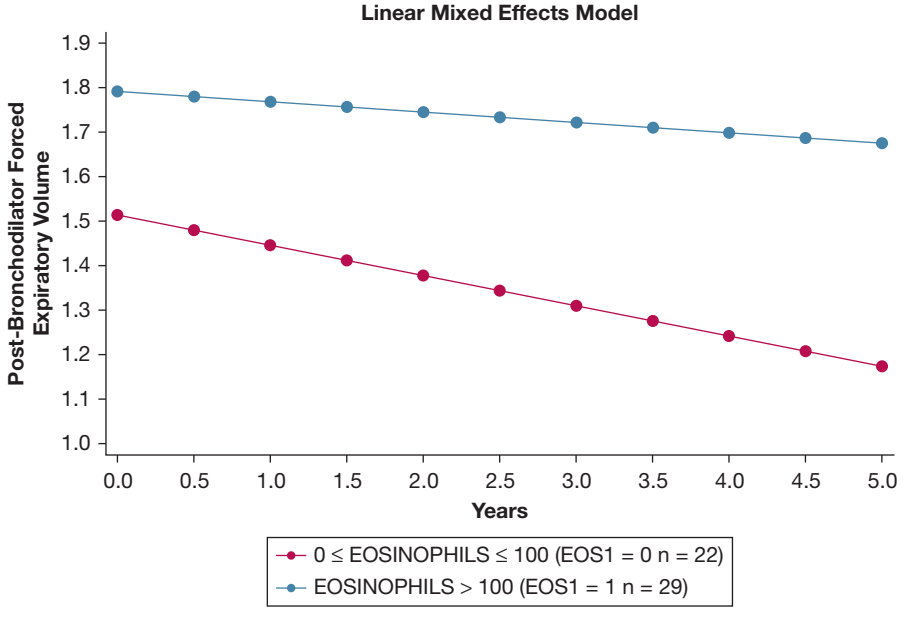

Figure 3 – *Longitudinal FEV_1 decline (in L) in group D COPD participants not using inhaled corticosteroids over the 3 years of the study, separated by baseline blood eosinophil count counts.*

TABLE 3] Longitudinal Changes in Lung Function, Functional Status, and Quality of Life

Variable	COPD (n = 742)				Group D COPD (n = 66)			
	$BEC_{\leq 100}$	BEC_{100+}	Difference (SE)	*P* Value	$BEC_{\leq 100}$	BEC_{100+}	Difference (SE)	*P* Value[a]
Postbronchodilator FEV_1, mL/y: mean slope (SE) [No.]	−50 (5.4) [248]	−39 (4.4) [404]	−10 (0.7)	.140	−68 (13.4) [22]	−23 (16.2) [29]	−45 (21)	**.036**
6MWD, m/y: mean slope (SE) [No.]	−12.681 (2.1) [238]	−13.002 (1.8) [368]	0.321 (2.71)	.906	−13.979 (5.6) [19]	−13.328 (4.9) [25]	−0.651 (7.404)	.930
CAT score, No./y: mean slope (SE) [No.]	0.091 (0.2) [227]	0.071 (0.1) [392]	0.020 (0.185)	.910	−0.558 (0.5) [21]	−0.468 (0.5) [28]	−0.091 (0.694)	.896
SGRQ score, No./y: mean slope (SE) [No.]	0.394 (0.3) [218]	0.124 (0.2) [362]	0.271 (0.352)	.442	−1.237 (1.1) [20]	−1.360 (0.9) [28]	0.122 (1.43)	.932

Mixed-effects linear regression models. Data are presented as the difference between mean slopes (SE) with [No.] where applicable. 6MWD = 6-min walk distance; BEC = blood eosinophil count; CAT = COPD Assessment Test; SGRQ = St. George's Respiratory Questionnaire.
[a]Boldface entry indicates significance.

into account changes in ICS use throughout the study, and the results were not significantly changed.

Predictors of Prospective Exacerbations

To identify independent predictors of AECOPD in $BEC_{\leq 100}$ participants, we used logistic regression to compare the two BEC-defined subsets among all participants with COPD not receiving ICS at enrollment. We limited this evaluation to the first 365 days from entry to avoid selection bias due to loss during follow-up. In both subsets, history of previous exacerbations was significantly associated with greater prospective exacerbations (Table 4), whereas postbronchodilator (BD) FEV_1 was significantly associated with fewer prospective exacerbations. Also in both subsets, White race was associated with increased AECOPD risk ($BEC_{\leq 100}$: OR, 2.34; 95% CI, 1.05-5.2; $P = .038$; BEC_{100+}: OR, 1.68; 95% CI, 1.02-2.79; $P = .043$). History of asthma was associated with exacerbations only in the BEC_{100+} subset (OR, 1.79; 95% CI, 1.1-2.91; $P = .02$). In group D participants, there were no significant associations of BEC status with race or exacerbations within 1 year.

Comparison With Those Using ICS at Enrollment

To investigate the effect of ICS on longitudinal outcomes in $BEC_{\leq 100}$ participants with GOLD group D COPD, we compared those participants in this analysis (n = 61) with $BEC_{\leq 100}$ GOLD D participants taking corticosteroids (oral or inhaled, n = 27) at baseline. As 81.5% of the 27 people taking corticosteroids at baseline did not report ICS continuation at all subsequent visits, we limited analysis to the first year of follow-up. We found no significant association between ICS use at baseline and AECOPD rate over the first year (ICS use vs no ICS use, 0.42 vs 0.41 exacerbation; $P = .914$) or initial lung function (1.15 vs 1.36 L; $P = .110$).

Discussion

Our analysis of a subset of the SPIROMICS cohort reveals several novel, clinically relevant findings about peripheral BEC in COPD. First, $BEC_{\leq 100}$ is prevalent in COPD participants not taking corticosteroids, being present in more than one-third of these participants with a similar percentage of low vs normal/high BEC across all GOLD A through D groups. Second, $BEC_{\leq 100}$ is stable over both short (6-week) and much longer intervals. Third, in GOLD D COPD, $BEC_{\leq 100}$ participants had more emphysema, greater airway wall thickness, more rapid FEV_1 decline, and more prospective AECOPD in the first year of follow-up. To

TABLE 4] Predictors of Prospective AECOPD Among All COPD Participants Not Receiving ICS at Enrollment

Predictor	COPD (n = 1,414)			
	$BEC_{\leq 100}$ (n = 485)	*P* Value[a]	BEC_{100+} (n = 929)	*P* Value[a]
Sex, male	0.7 (0.41-1.17)	.175	0.78 (0.53-1.13)	.186
Race, White	2.34 (1.05-5.2)	**.038**	1.68 (1.02-2.79)	**.043**
History of asthma	1.19 (0.57-2.47)	.643	1.79 (1.1-2.91)	**.020**
History of childhood asthma	1.11 (0.37-3.4)	.851	1.3 (0.66-2.55)	.455
Current individuals who smoke	0.55 (0.3-1.01)	.054	1.04 (0.68-1.6)	.845
BMI	0.98 (0.93-1.04)	.517	1 (0.96-1.03)	.773
Postbronchodilator FEV_1	0.98 (0.97-0.99)	**.002**	0.98 (0.97-0.99)	**< .001**
Exacerbations, year before enrollment	2.03 (1.47-2.8)	**< .001**	1.48 (1.21-1.81)	**< .001**
Age	0.97 (0.94-1.00)	.065	1 (0.97-1.02)	.717
Pack-years smoked	1.00 (0.99-1.01)	.652	1 (1-1.01)	.509

Analysis performed by logistic regression, limited to the first 365 days of follow-up. Data are presented as the OR of exacerbations (95% CI). AECOPD = acute exacerbation of the respiratory symptoms of COPD; BEC = blood eosinophil count; ICS = inhaled corticosteroid.
[a]Boldface entries indicate significance.

our knowledge, this is the first study to investigate clinical characteristics and longitudinal outcomes for symptomatic COPD exacerbators with low BEC who are not using corticosteroids. Collectively, these findings suggest that a categorical definition of BEC identifies a distinct and particularly vulnerable population with advanced COPD.

These results advance our understanding of BEC to guide ICS management in COPD patients with frequent exacerbations.[14] BECs are undoubtedly a useful biomarker in airway disease management. However, results of several analyses[15-17] raised concern that, rather than using explicit thresholds, BECs may be more appropriately used as a continuous value in the context of other clinical features. In addition, those analyses introduced controversy about the role of ICS in pauci-eosinophilic COPD. However, although $BEC_{\leq 100}$ has been associated with a less favorable response to ICS,[18] few published reports describe clinical outcomes in people with $BEC_{\leq 100}$ and with COPD not treated with ICS, a knowledge gap addressed by this analysis.

Nevertheless, BEC < 100 cells/μL has become a recommended criterion for avoiding ICS therapy in GOLD group D.[19] The IMPACT (Informing the Pathway of COPD Treatment) study observed benefit from adding ICS to long-acting β-agonist/long-acting muscarinic antagonist in terms of exacerbation reduction regardless of BEC level, although there was greater reduction in exacerbation rates among those with BEC ≥ 150/μL.[7] Subjects enrolled in the IMPACT trial all had a history of previous exacerbations as seen in group D.[7] In an analysis of the CHAIN (COPD History Assessment in Spain) and BODE (BMI, degree of airflow obstruction, functional dyspnea, and exercise capacity) cohorts, BEC varied significantly over 2 years, whereas clinical characteristics, including exacerbation rates, did not differ between COPD patients with BEC ≥ 300/μL and those with BEC < 300/μL.[20] Observed negative effects of ICS in $BEC_{\leq 100}$ COPD patients mostly relate to increased pneumonia incidence,[21] but studies suggest that this patient group is at increased risk of pneumonia even if untreated with ICS.[22,23] Our analysis indicates that the group excluded by this recommendation may experience worse outcomes when compared with their peers with higher BEC.

Our current report complements a published SPIROMICS analysis[24] that evaluated the relationship of blood and sputum eosinophilia, showing that BEC > 300/μL was associated with lower lung function and higher SGRQ score, but not increased history of exacerbations. Here, our current finding of worse outcomes in GOLD D participants with $BEC_{\leq 100}$ vs those with similar clinical characteristics but with a higher BEC suggests that future therapeutic guidelines may need to offer more data and a better-defined approach to those with low BEC.

Our demonstration of temporal BEC stability significantly extends previous evaluations.[20,25] One of the largest analyses[26] found less stable BEC in those with vs without COPD, and that COPD participants with BEC < 340/μL demonstrated greater stability than those with higher BEC. Both findings were likely confounded

by pharmacotherapy. By excluding those taking corticosteroids, we confirmed that $BEC_{\leq 100}$ is a sustainable trait both in short- and longer-term assessment, and hence a COPD phenotype.[27]

Among our entire $BEC_{\leq 100}$ COPD group, we confirm and extend several features that differ from those with higher BEC,[28] including predominance among women and those currently smoking.[18,29] Although a trend of increasing BEC has been recognized during smoking cessation,[30] its mechanism is undetermined. Because smoking cessation is associated with reduced risk of COPD exacerbations[31] and of hospital admission,[32] both smoking status and low BEC could affect the exacerbation rates among participants with COPD not receiving ICS therapy. Our finding of a less frequent history of childhood asthma in $BEC_{\leq 100}$ COPD is unsurprising. Eosinophilia characterizes subtypes of both asthma and COPD,[33] and BECs tend to be higher in those with an asthma diagnosis.[34]

Our findings in adjusted multivariate analysis of multiple adverse outcomes in $BEC_{\leq 100}$ GOLD D participants address an area of controversy. Previous data suggested an increased rate of emphysema progression in people with COPD and BEC < 2% but without observed differences in the extent of emphysema at baseline,[29,35] and greater airway wall thickness in people with COPD, at a cutoff of BEC > 150/μL.[36] With respect to emphysema, these data contrast with results from large cohort analyses,[4] which, similar to our findings, showed a negative correlation of emphysema extent with BEC, although the differing BEC thresholds preclude direct comparison. Two reports, although differing in BEC cut points from our study, appear to support our findings: first, a UK study of 26,675 people with COPD[37] found that the rate of change in FEV_1 did not differ when stratified by eosinophil level, similar to our findings of no significant difference in longitudinal change for post-BD FEV_1 in all SPIROMICS subjects; and second, the KOLD (Korean Obstructive Lung Disease) cohort study, which found that subjects with persistently high BEC (> 300/μL) had better survival than those with persistently low BEC (< 300/μL) over 6 years of follow-up,[38] which is consistent with the observation of greater decline in post-BD FEV_1 and more exacerbations in the low-BEC GOLD D group here. Collectively, the literature can be reconciled by recognizing that both higher-than-normal and lower-than-normal BEC may be associated with worsened disease progression if other conditions are present. Our data are compatible with data showing an association of decreasing eosinophil counts with higher mortality,[39] an outcome that we did not examine. As well, the finding that group D COPD patients with low eosinophils more often required antibiotics for exacerbations could potentially indicate greater infectious causes of exacerbations among those with low eosinophils.

Few $BEC_{\leq 100}$ COPD participants were started on ICS therapy during follow-up, and in participants in GOLD group D, the percentage did not differ from those with BEC_{100+}. Because much of our study period preceded the GOLD recommendation to consider withholding ICS in $BEC_{\leq 100}$ group D COPD,[9] we speculate that BEC numbers may not have contributed significantly to therapeutic decisions. Our finding that use of ICS in $BEC_{\leq 100}$ GOLD D COPD participants was not associated with greater total exacerbations in the first year, relative to $BEC_{\leq 100}$ GOLD D COPD participants not receiving ICS, should be interpreted with caution. Because of the small numbers of participants, inadequate capture of pneumonias, and the observational nature of the SPIROMICS cohort, these findings cannot argue for or against ICS use in this patient population. Studies have demonstrated a relationship between increasing BEC and the benefits of ICS in symptomatic COPD exacerbators; however, these studies have also shown benefits even in those with low BEC.[7,40] Our data instead argue for specifically investigating the role of ICS in group D $BEC_{\leq 100}$ COPD, and in particular those with greater emphysema. Our results are concordant with a prior analysis by Nishimura et al[3] that identified a group of "rapid decliners" characterized by greater radiographic emphysema as compared with lung function sustainers with higher levels of circulating eosinophils.

The analysis of risk of prospective AECOPD in BEC-defined subsets in GOLD group D made the novel observation that history of asthma was predictive only in BEC_{100+}, whereas current smoking was predictive only in $BEC_{\leq 100}$. The latter finding is compatible with the hypothesized effect of smoking to decrease both BEC numbers and AECOPD risk.[31] It suggests that as a biomarker, BEC may be significantly affected by behavioral (smoking) or therapeutic (corticosteroids) interventions, limiting its applicability without consideration of additional variables.

Strengths include use of data from a large cohort of participants with significant smoking histories, at

centers throughout the United States, with extensive baseline and longitudinal characterization, allowing adequate assessment of multiple clinical outcomes, particularly in smaller subgroups. Our design avoided treatment bias of BEC numbers by excluding those using any corticosteroid at enrollment. To interpret longitudinal changes adequately, we used mixed-effects models and assessed multiple testing points (minimum, three) over a period longer than 2 years.

Our study has several limitations. SPIROMICS was not designed specifically to examine the clinical implications of a low BEC. There are also clear limitations on our ability to evaluate the effect of therapeutic choices. This limitation was underscored by Harries et al,[41] who found differences in the usefulness of BEC to predict the ability of ICS to decrease exacerbations between subjects in observational vs randomized studies. In addition, the number of group D participants is relatively small, so that conclusions drawn from it warrant caution. Multiple biases cannot be excluded entirely. Selection bias in this non-population-based cohort may limit applicability of findings to the general population; recall bias and potential misreporting of ICS usage are acknowledged. Decisions to withhold or start ICS were made without the study team's involvement. Although limiting our analysis to those not receiving ICS at enrollment precluded evaluating the impact of that agent in treating $BEC_{\leq 100}$ patients with COPD, it allowed us to monitor the natural course of people with $BEC_{\leq 100}$ and to compare their outcomes with their BEC_{100+} counterparts.

Interpretation

Our data help to explain some of the discrepancies of prior analyses in examining the relationship between blood eosinophil level and patient outcomes in COPD. We demonstrate that both concomitant use of ICS and disease stage may modify these relationships. We found that GOLD D COPD participants with $BEC_{\leq 100}$ in the absence of ICS therapy are a distinct phenotype in our cohort, with higher prevalence of current smoking, greater emphysema, and worse prospective outcomes (higher rate of lung function decline and more prospective exacerbations) than their BEC_{100+} counterparts. However, such differences in outcomes between BEC-defined subsets were not observed outside of GOLD group D. Our analysis sheds light on a particularly vulnerable COPD phenotype, suggesting the need for further studies focused on their therapeutic treatment.

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