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Correlation Between Blood Eosinophil Count and Response to Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: A Prospective Observational Cohort Study.

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Abstract

Background: Inhaled corticosteroids (ICS) reduce exacerbations in a subset of patients with chronic obstructive pulmonary disease (COPD) but expose all recipients to pneumonia and other adverse effects. Blood eosinophil count (BEC) has emerged as an accessible biomarker of type 2 airway inflammation and is now embedded in international treatment algorithms, yet prospective data from routine practice in South Asian populations remain limited. Objectives: To determine whether baseline BEC correlates with clinical response to ICS-containing therapy in patients with COPD, as measured by exacerbation frequency, lung function and symptom burden over 12 months.***Methods:*** A prospective observational cohort study was conducted in the Department of Biochemistry and Respiratory Medicine, tertiary care hospital. Patients aged ≥40 years with spirometrically confirmed COPD (post-bronchodilator FEV_1/FVC <0.70), at least one moderate or severe exacerbation in the preceding year, and no prior regular ICS use were enrolled and commenced on LABA/LAMA/ICS triple therapy. Participants were stratified a priori by baseline BEC into three groups (<100, 100–299 and ≥300 cells/µL) and followed for 12 months. The primary outcome was the change in annualised moderate or severe exacerbation rate; secondary outcomes were change in trough FEV_1, COPD Assessment Test (CAT) score and mMRC dyspnoea grade. Response was defined a priori as a ≥50% reduction in exacerbation rate. ***Results:*** Of 120 patients (mean age 62.8 ± 8.4 years; 98 male, 81.7%), 34 (28.3%) had BEC <100, 52 (43.3%) 100–299 and 34 (28.3%) ≥300 cells/µL. The annualised exacerbation rate fell by 10.2% (p=0.284), 27.7% (p=0.008) and 45.2% (p<0.001) across ascending eosinophil strata (p for trend <0.001). Mean trough FEV_1 improved by 38 ± 96, 82 ± 104 and 141 ± 118 mL respectively (p=0.002), and mean CAT score by 1.2 ± 2.8, 2.6 ± 3.1 and 4.1 ± 3.4 points (p<0.001). Responders comprised 23.5%, 40.4% and 61.8% of each stratum (p=0.006). Baseline BEC correlated positively with proportional exacerbation reduction (ρ=0.512, p<0.001) and with ΔFEV_1 (ρ=0.436, p<0.001). On multivariable analysis, BEC ≥300 cells/µL independently predicted response (adjusted OR 5.25, 95% CI 1.86–14.82; p=0.002). ***Conclusion:*** Baseline blood eosinophil count showed a graded, independent association with clinical response to ICS-containing therapy in COPD. Patients with counts ≥300 cells/µL derived substantial benefit, while those below 100 cells/µL showed no significant improvement in exacerbation rate, supporting eosinophil-guided prescribing in routine practice.

Keywords: COPD; blood eosinophil count; inhaled corticosteroids; exacerbations; biomarker; treatable traits.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the leading causes of morbidity and mortality worldwide, accounting for over three million deaths annually, with the greatest burden concentrated in low- and middle-income countries where tobacco smoking, biomass fuel exposure and ambient air pollution coexist.[1] Exacerbations drive much of this burden: each event accelerates lung function decline, impairs health status and independently predicts mortality, and preventing exacerbations is therefore a central objective of pharmacological management.[2]

Inhaled corticosteroids (ICS), given in combination with long-acting bronchodilators, reduce exacerbation frequency in COPD. The benefit, however, is neither universal nor free of cost. ICS use is associated with an increased risk of pneumonia, oral candidiasis, dysphonia, mycobacterial infection and, at higher doses, systemic corticosteroid effects.[3] For much of the past two decades ICS were prescribed empirically to broad populations of patients with COPD, with the

consequence that many were exposed to harm without prospect of benefit. The clinical problem has therefore shifted from whether ICS work to identifying, in advance, the patients in whom they will.[4]

Blood eosinophil count (BEC) has emerged as the most practicable candidate biomarker for this purpose. Eosinophilic airway inflammation is present in a substantial minority of patients with COPD, and although the concordance between blood and airway eosinophilia is imperfect, higher blood counts are associated with greater sputum eosinophilia and with elevated markers of type 2 inflammation in the airway wall.[5,6] Bafadhel and colleagues first demonstrated that sputum eosinophilia predicted corticosteroid responsiveness at exacerbation,[7] and subsequent secondary analyses of large randomised trials established the same relationship for the more accessible blood measurement. Pascoe et al. found, in a pooled analysis of two fluticasone furoate/vilanterol trials, that exacerbations were reduced by 29% in patients with eosinophils ≥2% but by only 10% in those below that threshold.[8] Comparable gradients were reported for extrafine beclometasone/formoterol[9] and for budesonide-containing regimens.[10]

The relationship has since been confirmed prospectively. Modelling of the IMPACT trial showed that the magnitude of benefit from ICS-containing regimens increased continuously in proportion to baseline eosinophil count,[11,12] and the ETHOS trial demonstrated similar effect modification with budesonide-containing triple therapy.[13] Conversely, withdrawal studies point in the same direction: in the WISDOM trial, patients with higher eosinophil counts experienced the greatest increase in exacerbations after ICS were removed,[14,15] and in SUNSET, de-escalation was safe except in those with counts ≥300 cells/µL.[16] The FLAME study, in which dual bronchodilation outperformed LABA/ICS overall, reinforced that ICS benefit is confined to a subgroup rather than being general.[17]

These data have been translated into guideline recommendations. The Global Initiative for Chronic Obstructive Lung Disease now advises that BEC be measured before adding or withdrawing ICS, with counts ≥300 cells/µL favouring their use and counts <100 cells/µL indicating a low likelihood of benefit.[18] Reservations persist, however. Eosinophil counts vary within individuals over time, particularly at higher values,[19,20] the thresholds are pragmatic rather than biologically derived, and most supporting evidence derives from post hoc analyses of trials conducted in predominantly European and North American populations whose participants are typically younger and healthier than patients seen in routine care.[21] Prospective data from South Asian settings, where biomass exposure and a high burden of pulmonary tuberculosis shape the COPD phenotype, are scarce.

The present study was therefore undertaken to examine, prospectively and in routine clinical practice, whether baseline blood eosinophil count correlates with clinical response to ICS-containing therapy in patients with COPD.

MATERIALS AND METHODS

This was a prospective, observational cohort study conducted in the Department of Biochemistry and Respiratory Medicine, Basweshwar teaching tertiary care hospital, over a period of 24 months (12 months of recruitment followed by 12 months of follow-up for each participant).

Participants. Consecutive patients attending the outpatient department were screened. Eligible participants were aged ≥40 years with a physician diagnosis of COPD confirmed by post-bronchodilator spirometry showing an FEV_1/FVC ratio <0.70, who had experienced at least one moderate or severe exacerbation in the preceding 12 months, and who were judged by the treating physician to require ICS-containing therapy.

Exclusion criteria. A physician diagnosis of asthma or documented asthma–COPD overlap; regular ICS use within the preceding six months; blood eosinophil count ≥1,500 cells/µL or any diagnosis of eosinophilic granulomatosis, hypereosinophilic syndrome or allergic bronchopulmonary aspergillosis; active pulmonary tuberculosis or treatment for tuberculosis within the preceding 12 months; bronchiectasis on imaging as the dominant pathology; known parasitic infestation; systemic corticosteroid or immunosuppressive therapy; malignancy; and a life expectancy of less than 12 months. Baseline assessment. After written informed consent, demographic details, smoking and biomass exposure history, comorbidities and the number of moderate and severe exacerbations in the preceding 12 months were recorded using a structured proforma. A moderate exacerbation was defined as one requiring systemic corticosteroids and/or antibiotics, and a severe exacerbation as one requiring hospitalisation or emergency department attendance. Post-bronchodilator spirometry was performed in accordance with ATS/ERS standards.[22] Symptom burden was quantified with the COPD Assessment Test (CAT)[23] and the modified Medical Research Council (mMRC) dyspnoea scale.[24] Blood eosinophil measurement. A venous sample was drawn during clinical stability, at least four weeks after any exacerbation, and analysed on an automated haematology analyser within two hours of collection. Absolute eosinophil count was derived from the total leucocyte count and differential. A second count at three months assessed stability. Participants were stratified a priori into three groups according to baseline count: <100, 100–299 and ≥300 cells/µL, corresponding to current guideline thresholds.[18]

Intervention and follow-up. All participants were commenced on fixed-dose LABA/LAMA/ICS triple therapy delivered by a single inhaler, with inhaler technique demonstrated at each visit. Treatment allocation was not randomised; all participants received the same regimen, and the exposure of interest was baseline eosinophil stratum. Participants were reviewed at 3, 6, 9 and 12 months. Adherence was assessed by canister count and self-report. Exacerbations during follow-up were recorded prospectively and verified against prescription and admission records.

Outcomes. The primary outcome was the change in annualised rate of moderate or severe exacerbations between the 12 months preceding and the 12 months following initiation of therapy. Secondary outcomes were change in trough FEV_1, change in CAT score, proportion achieving a ≥1-grade improvement in mMRC, and the incidence of physician-diagnosed pneumonia. Response was defined a priori as a ≥50% reduction in exacerbation rate.

Statistical analysis. Data were analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies and percentages. Within-group changes were tested by paired t-test, between-group differences by one-way ANOVA with Tukey correction, and categorical associations by chi-square or Fisher's exact test. A test for linear trend was applied across the ordered strata. Associations between baseline eosinophil count as a continuous variable and each outcome were quantified by Spearman rank correlation. Multivariable logistic regression, adjusted for age, sex, FEV_1 % predicted, pack-years, biomass exposure and prior exacerbation count, identified independent predictors of response. Receiver operating characteristic (ROC) analysis assessed the discriminatory performance of eosinophil count, with the optimal cut-off determined by the Youden index. A two-sided p-value <0.05 was considered significant.

RESULTS

Table 1. Baseline characteristics by blood eosinophil stratum (n=120)

Characteristic	BEC <100 cells/µL (n=34)	BEC 100–299 cells/µL (n=52)	BEC ≥300 cells/µL (n=34)	Total (n=120)	p-value
Age, years (mean ± SD)	63.9 ± 8.1	62.4 ± 8.7	62.2 ± 8.3	62.8 ± 8.4	0.612
Male, n (%)	28 (82.4)	42 (80.8)	28 (82.4)	98 (81.7)	0.976
Current smoker, n (%)	13 (38.2)	19 (36.5)	11 (32.4)	43 (35.8)	0.878
Smoking, pack-years	32.6 ± 14.2	30.9 ± 13.8	29.4 ± 15.1	31.0 ± 14.2	0.678
Biomass exposure, n (%)	9 (26.5)	14 (26.9)	8 (23.5)	31 (25.8)	0.937
BMI, kg/m²	21.8 ± 4.1	22.3 ± 4.4	22.6 ± 4.0	22.2 ± 4.2	0.712
Post-BD FEV_1, % predicted	47.2 ± 13.6	48.9 ± 14.1	46.8 ± 13.2	47.8 ± 13.7	0.744
GOLD grade 3–4, n (%)	21 (61.8)	30 (57.7)	22 (64.7)	73 (60.8)	0.804
CAT score	19.4 ± 5.8	20.1 ± 6.2	20.8 ± 5.9	20.1 ± 6.0	0.596
mMRC grade ≥2, n (%)	25 (73.5)	39 (75.0)	27 (79.4)	91 (75.8)	0.845
Exacerbations in prior year	2.06 ± 1.12	2.13 ± 1.18	2.21 ± 1.24	2.13 ± 1.18	0.874
Blood eosinophils, cells/µL	68 ± 21	186 ± 54	428 ± 132	213 ± 158	<0.001

The three strata were well matched at baseline. No significant differences were observed in age, sex, smoking intensity, biomass exposure, degree of airflow obstruction, symptom burden or prior exacerbation frequency, indicating that any subsequent divergence in outcome is unlikely to be explained by baseline imbalance. As expected by design, eosinophil counts differed markedly between strata (p<0.001). Notably, prior exacerbation frequency was almost identical across groups (2.06, 2.13 and 2.21), confirming that eosinophil count in this cohort did not itself identify patients at higher baseline risk — only patients more likely to respond.

Table 2. Change in annualised exacerbation rate after 12 months of ICS-containing therapy

Eosinophil stratum	Pre-treatment rate (per patient-year)	Post-treatment rate	Absolute reduction	Relative reduction (%)	p-value (within group)
<100 cells/µL (n=34)	2.06 ± 1.12	1.85 ± 1.09	0.21	10.2	0.284
100–299 cells/µL (n=52)	2.13 ± 1.18	1.54 ± 0.98	0.59	27.7	0.008
≥300 cells/µL (n=34)	2.21 ± 1.24	1.21 ± 0.86	1.00	45.2	<0.001
Total (n=120)	**2.13 ± 1.18**	**1.53 ± 1.00**	**0.60**	**28.2**	**<0.001**
				p for trend	**<0.001**

This table contains the principal finding. A clear dose–response gradient was observed: the relative reduction in exacerbation rate rose from 10.2% in the lowest eosinophil stratum to 27.7% in the intermediate stratum and 45.2% in the highest, with a highly significant test for trend (p<0.001). Critically, the reduction in the <100 cells/µL group did not reach statistical significance (p=0.284), meaning that patients in this stratum derived no demonstrable exacerbation benefit despite 12 months of ICS exposure. The relationship appears graded rather than threshold-driven, with the intermediate group occupying an intermediate position — a pattern consistent with a continuous biological effect rather than a categorical one.

Table 3. Change in lung function and symptom scores at 12 months

Outcome	BEC <100 (n=34)	BEC 100–299 (n=52)	BEC ≥300 (n=34)	p-value (ANOVA)
Δ trough FEV_1, mL (mean ± SD)	+38 ± 96	+82 ± 104	+141 ± 118	0.002
Within-group p-value	0.121	0.001	<0.001	—
Δ FEV_1 ≥100 mL, n (%)	7 (20.6)	19 (36.5)	19 (55.9)	0.012
Δ CAT score (points)	−1.2 ± 2.8	−2.6 ± 3.1	−4.1 ± 3.4	<0.001
CAT improvement ≥2 points, n (%)	11 (32.4)	28 (53.8)	24 (70.6)	0.008
mMRC improvement ≥1 grade, n (%)	9 (26.5)	23 (44.2)	21 (61.8)	0.014

Physiological and symptomatic outcomes reproduced the same gradient. Mean improvement in trough FEV_1 rose almost fourfold across strata, from 38 mL to 141 mL, and only in the two higher strata did the within-group change reach significance. The proportion achieving the widely accepted 100 mL threshold for a clinically meaningful bronchodilator response likewise rose from 20.6% to 55.9%.

Symptom outcomes followed suit. Mean CAT score fell by 4.1 points in the highest stratum — comfortably exceeding the 2-point minimum clinically important difference[25] — compared with 1.2 points in the lowest stratum, which falls below that threshold. The concordance between exacerbation, physiological and patient-reported outcomes strengthens the inference, since these three domains are only loosely correlated with one another in COPD and would not be expected to move together by chance.

Table 4. Responder analysis (≥50% reduction in exacerbation rate)

Eosinophil stratum	Responders n (%)	Non-responders n (%)	p-value
<100 cells/µL (n=34)	8 (23.5)	26 (76.5)	0.006
100–299 cells/µL (n=52)	21 (40.4)	31 (59.6)	
≥300 cells/µL (n=34)	21 (61.8)	13 (38.2)	
Total (n=120)	**50 (41.7)**	**70 (58.3)**	

Using the pre-specified definition, response rates rose from 23.5% to 61.8% across ascending strata (p=0.006). Two observations temper this. First, nearly a quarter of patients with counts below 100 cells/µL nonetheless responded, so a low count does not exclude benefit and should not by itself preclude ICS in a patient with frequent severe exacerbations. Second, over a third of patients with counts ≥300 cells/µL did not respond, so a high count is not a guarantee of benefit. The biomarker shifts probability; it does not determine outcome.

Table 5. Correlation between baseline eosinophil count and treatment response

Variable	Spearman ρ	95% CI	p-value
Proportional reduction in exacerbation rate	0.512	0.362 to 0.638	<0.001
Δ trough FEV_1	0.436	0.276 to 0.573	<0.001
Δ CAT score	−0.398	−0.541 to −0.232	<0.001
Δ mMRC grade	−0.311	−0.467 to −0.138	0.001
Post-treatment exacerbation rate	−0.294	−0.452 to −0.120	0.001

Treating eosinophil count as a continuous variable rather than a categorical one produced moderate but highly significant correlations with every outcome measured. The negative coefficients for CAT and mMRC reflect the fact that lower scores denote improvement, so the direction of effect is concordant throughout. The magnitude of these coefficients ($\rho \approx 0.3–0.5$) indicates that eosinophil count explains perhaps a quarter of the variance in treatment response, which is substantial for a single inexpensive biomarker but far from deterministic.

Table 6. Multivariable logistic regression for predictors of response

Variable	Adjusted OR	95% CI	p-value
BEC ≥300 vs <100 cells/μL	5.25	1.86–14.82	0.002
BEC 100–299 vs <100 cells/μL	2.14	0.82–5.59	0.121
Age (per year)	0.98	0.94–1.03	0.436
Male sex	1.12	0.42–2.98	0.821
FEV_1 % predicted (per 10%)	1.16	0.88–1.53	0.294
Pack-years (per 10)	0.94	0.74–1.19	0.606
Biomass exposure	0.86	0.35–2.14	0.751
Prior exacerbations (per event)	1.38	0.96–1.98	0.081

After adjustment for demographic, physiological and exposure variables, an eosinophil count ≥300 cells/μL remained an independent predictor of response, with more than a fivefold increase in odds (p=0.002). The intermediate stratum showed a non-significant trend in the same direction, consistent with its intermediate position in Tables 2–4 but underpowered at this sample size. No other variable independently predicted response, although prior exacerbation frequency approached significance (p=0.081), a signal that would merit examination in a larger cohort.

Table 7. Adverse events over 12 months

Adverse event	BEC <100 (n=34)	BEC 100–299 (n=52)	BEC ≥300 (n=34)	Total (n=120)	p-value
Physician-diagnosed pneumonia	3 (8.8)	4 (7.7)	2 (5.9)	9 (7.5)	0.895
Oral candidiasis	4 (11.8)	6 (11.5)	4 (11.8)	14 (11.7)	0.999
Dysphonia	5 (14.7)	7 (13.5)	5 (14.7)	17 (14.2)	0.983
Any adverse event	10 (29.4)	15 (28.8)	10 (29.4)	35 (29.2)	0.997

Adverse events were distributed evenly across strata, with no significant differences. This is the clinically decisive observation: the harms of ICS were borne equally by all three groups while the benefits accrued almost entirely to the two higher strata. In the <100 cells/μL group, 8.8% developed pneumonia while the exacerbation reduction was not statistically significant — an unfavourable balance that constitutes the central argument for eosinophil-guided prescribing.

Eosinophil count stability and discriminatory performance

Repeat eosinophil counts at three months remained within the original stratum in 82 of 120 patients (68.3%). Stability was highest in the <100 cells/μL group (29/34, 85.3%) and lowest in the intermediate group (32/52, 61.5%), consistent with published observations that reproducibility is greatest at lower thresholds.

ROC analysis of baseline eosinophil count as a continuous predictor of response yielded an area under the curve of 0.71 (95% CI 0.62–0.80, p<0.001). The optimal cut-off by the Youden index was 220 cells/μL, giving a sensitivity of 68.0% and specificity of 65.7%. This performance is modest and confirms that eosinophil count is best used to inform, rather than dictate, prescribing decisions.

DISCUSSION

In this prospective cohort of 120 patients with exacerbating COPD, baseline blood eosinophil count showed a graded association with clinical response to ICS-containing therapy across exacerbation, physiological and patient-reported domains. The relative reduction in exacerbation rate rose from 10.2% in patients with counts below 100 cells/μL to 45.2% in those with counts of 300 cells/μL or above, and the association persisted after multivariable adjustment.

These findings align closely with the randomised trial literature. Pascoe et al., analysing pooled fluticasone furoate/vilanterol data, reported a 29% exacerbation reduction in patients with eosinophils ≥2% against 10% below that threshold[8] — figures strikingly similar to our intermediate and low strata. Siddiqui et al. documented an equivalent gradient with extrafine beclometasone/formoterol,[9] and Bafadhel et al., pooling three budesonide trials, showed benefit rising continuously with eosinophil count.[10] The prospective IMPACT modelling analysis remains the strongest evidence, demonstrating that ICS benefit increased in proportion to baseline count with no clear inflexion point,[12] and ETHOS reproduced this with budesonide-containing triple therapy.[13] Meta-analyses pooling these trials have confirmed the gradient across drug classes and delivery devices.[26] Our data, generated in routine practice rather than a trial population, support the external validity of these observations.

The withdrawal literature offers convergent evidence from the opposite direction. In WISDOM, patients with higher eosinophil counts experienced the greatest increase in exacerbations when ICS were removed,[14,15] and in SUNSET, de-escalation from triple therapy was safe except in patients with counts ≥300 cells/µL.[16] That benefit on introduction and harm on withdrawal track the same biomarker in the same direction is a strong argument that the association reflects a genuine biological mechanism — the presence of corticosteroid-responsive type 2 airway inflammation[5,6] — rather than confounding.

Three findings warrant emphasis. First, adverse events were evenly distributed across strata (Table 7) while benefit was not, so the risk–benefit ratio deteriorates sharply at low eosinophil counts. In our lowest stratum, pneumonia occurred in 8.8% while exacerbation reduction was not significant, echoing the concerns raised by Suissa et al.[3] and underpinning the current guideline recommendation that counts below 100 cells/µL indicate a low likelihood of benefit.[18] Second, the relationship was continuous rather than categorical: our ROC-derived cut-off of 220 cells/µL lies between the two guideline thresholds, and the AUC of 0.71 indicates modest discrimination. Eosinophil count should therefore modify prescribing probability alongside exacerbation history rather than serve as a binary gate — a point emphasised in the GOLD 2026 report, which stresses that a low count alone should not preclude ICS in a patient with frequent severe exacerbations.[18] Third, 23.5% of patients with counts below 100 cells/µL nonetheless responded, and 38.2% of those above 300 cells/µL did not, reinforcing that this biomarker identifies populations, not individuals.

Several limitations apply. The observational, single-arm design means that regression to the mean and the natural fluctuation of exacerbation frequency cannot be excluded as partial explanations for the improvements observed; a non-ICS comparator arm would be required to isolate the ICS-specific effect, and our findings should therefore be regarded as hypothesis-generating. The sample was modest, particularly within strata, and the intermediate group was underpowered in regression analysis. Eosinophil counts were categorised from a single baseline measurement, and 31.7% of patients changed stratum by three months, consistent with published variability.[19,20] Adherence was assessed by self-report and canister count rather than electronic monitoring. Finally, this was a single-centre study in one population, and generalisability to other settings requires confirmation.

CONCLUSION

In this prospective observational cohort of patients with exacerbating COPD commenced on ICS-containing triple therapy, baseline blood eosinophil count correlated with clinical response in a graded manner across all outcome domains examined. Patients with counts of 300 cells/µL or above achieved a 45.2% reduction in exacerbation rate, a mean FEV_1 improvement of 141 mL and a clinically meaningful fall in CAT score, whereas those with counts below 100 cells/µL showed no statistically significant exacerbation benefit despite an equivalent burden of adverse effects. A count ≥300 cells/µL independently predicted response after multivariable adjustment.

Blood eosinophil count is inexpensive, universally available and derived from a test already performed routinely, making it well suited to guiding ICS prescribing in resource-constrained settings. On the basis of these data, we suggest that eosinophil count be measured during clinical stability before ICS are initiated or withdrawn, and that the result be integrated with exacerbation history rather than applied as an isolated decision rule. Because the biomarker discriminates only modestly at the individual level, and because a substantial minority of patients with low counts still benefit, clinical judgement remains essential. Adequately powered randomised trials with a non-ICS comparator, incorporating repeated eosinophil measurement, are needed to establish optimal thresholds in South Asian populations.

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