Blood Eosinophil Count Predicts Treatment Failure and Hospital Readmission for COPD

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Readmission for COPD Exacerbation (Cohort 2)

	Cohort 1	Cohort 2
Variable	(N=6,416)	(N=10,245)
Charlson comorbidity index		
≤1	4,023 (62.7)	6,199 (60.5)
2-4	1,344 (20.9)	1,730 (16.9)
5+	1,049 (16.3)	2,316 (22.6)
Maintenance therapy		
None	755 (11.8)	1,253 (12.2)
Short-acting BD only	592 (9.2)	687 (6.7)
Long-acting BD only	680 (10.6)	1,232 (12.0)
ICS+LABA	1,500 (23.4)	2,674 (26.1)
Triple therapy	2,889 (45.0)	4,399 (42.9)
Daily ICS dosage, median (IQR) ^a	361.7 (82.0–721.3)	393.5 (92.9–739.8)
\geq 1 SABA inhaler prescribed	4,687 (73.1)	7,594 (74.1)
\geq 1 SAMA inhaler prescribed	1,066 (16.6)	3,563 (34.8)
Cumulative average daily OCS	15(09.20)	04(0014)
dosage, median (IQR) ^b	1.5 (0.8–2.9)	0.4 (0.0–1.4)
Number of COPD exacerbations ^c		
0	0 (0)	0 (0)
1	520 (8.1)	2,348 (22.9)
2	2,331 (36.3)	2,325 (22.7)
3	1,155 (18.0)	1,831 (17.9)
≥4	2,410 (37.6)	3,741 (36.5)
Number of short-term OCS courses ^c		
0	0 (0)	4,796 (46.8)
1	1,946 (30.3)	2,332 (22.8)
2	1,225 (19.1)	1,215 (11.9)
3	945 (14.7)	753 (7.3)
≥4	2,300 (35.8)	1,149 (11.2)
mMRC dyspnoea score		
n	5,460	8,789
0	409 (7.5)	314 (3.6)
1	2,256 (41.3)	3,883 (44.2)
2	1,527 (28.0)	1,976 (22.5)
3	1,030 (18.9)	1,823 (20.7)
4	238 (4.4)	793 (9.0)

BD, bronchodilator; COPD, chronic obstructive pulmonary disease; ICS, inhaled

corticosteroids; IQR, interquartile range; LABA, long-acting β_2 -agonists; mMRC, modified Medical Research Council; OCS, oral corticosteroids; SABA, short-acting β_2 -agonists;

SAMA, short-acting muscarinic antagonists.

Data expressed as n (%) unless otherwise noted.

^aICS dosage expressed as fluticasone propionate or equivalent (µg).

^bOCS dosage expressed as prednisolone or equivalent (mg).

^cIncluding exacerbation on index date.

		Blood eosinophil category (cells/µL)							
		<50	50-<150	150-<250	250-<350	350-<450	450-<550	550-<650	≥650
Cohort 1		(n=275)	(n=2048)	(n=1768)	(n=1033)	(n=502)	(n=287)	(n=169)	(n=334)
	None	37 (13.5)	262 (12.8)	209 (11.8)	107 (10.4)	54 (10.8)	33 (11.5)	15 (8.9)	38 (11.4)
Maintenance	Short-acting BD only	30 (10.9)	193 (9.4)	145 (8.2)	106 (10.3)	45 (9.0)	30 (10.5)	16 (9.5)	27 (8.1)
	Long-acting BD only	35 (12.7)	220 (10.7)	180 (10.2)	97 (9.4)	46 (9.2)	33 (11.5)	27 (16.0)	42 (12.6)
therapy	ICS+LABA	58 (21.1)	451 (22.0)	440 (24.9)	240 (23.2)	118 (23.5)	69 (24.0)	37 (21.9)	87 (26.0)
	Triple therapy	115 (41.8)	922 (45.0)	794 (44.9)	483 (46.8)	239 (47.6)	122 (42.5)	74 (43.8)	140 (41.9)
ICS mean	Median (IQR)	731.5 (114.8–	786.9 (164.4—	794.0 (246.6–	746.9 (197.0–	788.0 (163.9–	731.5 (164.4—	657.5 (164.4—	739.7 (164.4—
daily dosage		1530.1)	1528.8)	1506.8)	1479.5)	1479.5)	1315.1)	1315.1)	1475.4)
Cohort 2		(n=734)	(n=3035)	(n=2794)	(n=1608)	(n=834)	(n=480)	(n=234)	(n=526)
	None	108 (14.7)	399 (13.1)	314 (11.2)	196 (12.2)	93 (11.2)	53 (11.0)	24 (10.3)	66 (12.5)
Maintenance	Short-acting BD only	53 (7.2)	200 (6.6)	166 (5.9)	103 (6.4)	79 (9.5)	30 (6.3)	21 (9.0)	35 (6.7)
therapy	Long-acting BD only	83 (11.3)	368 (12.1)	363 (13.0)	179 (11.1)	85 (10.2)	53 (11.0)	27 (11.5)	74 (14.1)
	ICS+LABA	200 (27.2)	778 (25.6)	696 (24.9)	447 (27.8)	209 (25.1)	126 (26.3)	61 (26.1)	157 (29.8)
	Triple therapy	290 (39.5)	1,290 (42.5)	1,255 (44.9)	683 (42.5)	368 (44.1)	218 (45.4)	101 (43.2)	194 (36.9)
ICS mean	Median (IQR)	657.5 (54.8–	723.3 (109.6–	737.7 (164.4—	710.4 (163.9–	690.4 (164.4—	657.5 (109.6–	684.9 (137.0–	657.5 (164.4—
daily dosage		1315.1)	1479.5)	1444.6)	1315.1)	1479.5)	1315.1)	1315.1)	1479.5)

Table S2. Baseline Patient Maintenance Therapy by Blood Eosinophil Count Category

BD, bronchodilator; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β_2 -agonists.

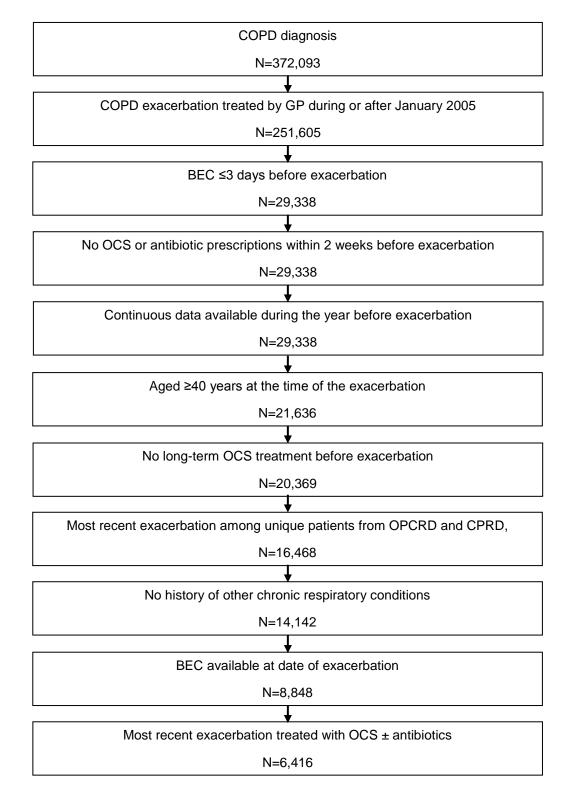
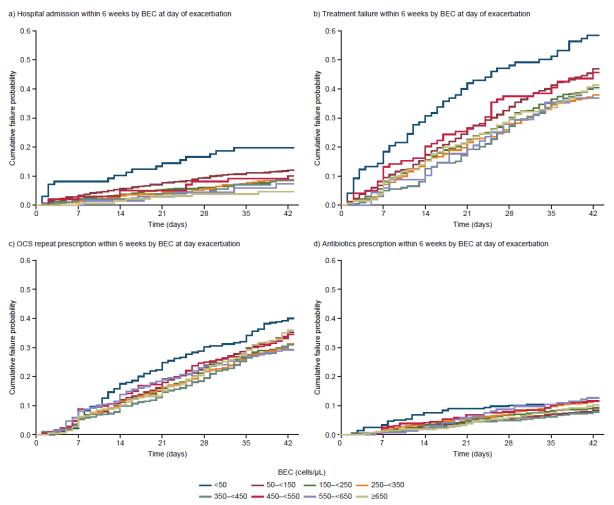


Figure S1. Cohort 1 Patient Flow Diagram

BEC, blood eosinophil counts; CPRD, Clinical Practice Research Datalink; COPD, chronic obstructive pulmonary disease; GP, general practitioner; OCS, oral corticosteroids; OPCRD, Optimum Patient Care Research Database. Figure S2. Kaplan-Meier Curves for the Unadjusted Association Between Blood Eosinophil Counts Recorded on the Day of an OCS-Treated Exacerbation and Time to First Outcome Event Within 6 Weeks (Cohort 1)



Panel a: Hospital admission. Panel b: Treatment failure. Panel c: OCS prescription.

Panel d: Antibiotic prescription.

BEC, blood eosinophil counts; OCS, oral corticosteroids.

BEC are classified in incremental categories with 50-<150 cells/µL as the reference category.

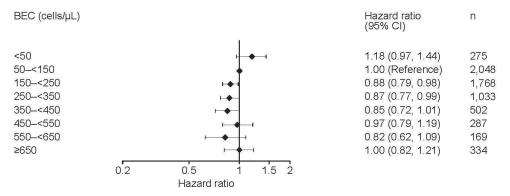
Figure S3. Association Between Blood Eosinophil Counts Recorded on the Day of an OCS-

Treated Exacerbation and Treatment Failure Within 6 Weeks (Cohort 1)

BEC (cells/µL) Hazard ratio n (95% CI) <50 1.46 (1.11, 1.93) 95 50-<150 1.00 (Reference) 860 150-<250 0.84 (0.72, 0.97) 666 250-<350 0.77 (0.64, 0.93) 379 350-<450 0.80 (0.63, 1.02) 193 450-<550 0.97 (0.71, 1.31) 96 550-<650 0.69 (0.46, 1.04) 66 ≥650 0.83 (0.63, 1.11) 127 0.2 0.5 2 1.5 1 Hazard ratio

a) Treatment failure within 6 weeks by BEC at day of exacerbation

b) OCS repeat prescription within 6 weeks by BEC at day of exacerbation



c) Antibiotics prescription within 6 weeks by BEC at day of exacerbation

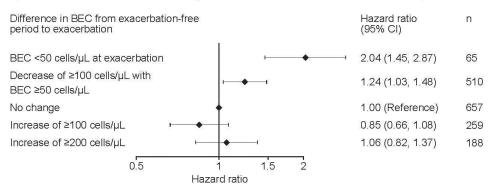
BEC (cells/µL)			Hazard ratio (95% CI)	n
<50 50-<150 150-<250 250-<350 350-<450 450-<550 550-<650 ≥650	0.2	0.5 1 1.5 2 Hazard ratio	1.49 (1.02, 2.18) 1.00 (Reference) 1.12 (0.91, 1.39) 1.43 (1.13, 1.80) 0.93 (0.66, 1.31) 1.43 (0.99, 2.07) 1.51 (0.97, 2.36) 1.23 (0.85, 1.76)	275 2,048 1,768 1,033 502 287 169 334

Panel a: Overall treatment failure (N=2,482). Panel b: Treatment failure defined as a repeat OCS prescription (N=6,416). Panel c: Treatment failure defined as an antibiotic prescription (N=6,416).

BEC, blood eosinophil counts; CI, confidence interval; OCS, oral corticosteroids.

Figure S4. Association Between Change in Blood Eosinophil Counts from an Exacerbation-Free Period to Index Exacerbation Date and Treatment Failure Within 6 Weeks (Cohort 1)

a) Treatment failure within 6 weeks by BEC at exacerbation vs. exacerbation-free period



b) OCS repeat prescription within 6 weeks by BEC at exacerbation vs. exacerbation-free period

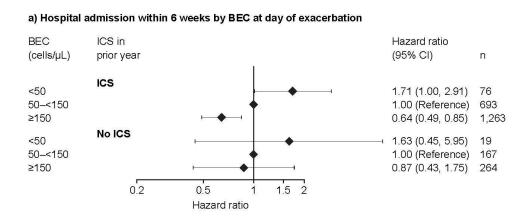
Difference in BEC from exacerbation-free period to exacerbation	Hazard ratio (95% CI)	n
BEC <50 cells/µL at exacerbation	1.20 (0.93, 1.54)	197
Decrease of ≥100 cells/µL with BEC ≥50 cells/µL	1.14 (1.00, 1.29)	1,381
No change	1.00 (Reference)	1,721
Increase of ≥100 cells/µL	0.83 (0.70, 0.97)	775
Increase of ≥200 cells/µL	1.06 (0.89, 1.27)	507
0.5 1 1.5 2		
Hazard ratio		

c) Antibiotics prescription within 6 weeks by BEC at exacerbation vs. exacerbation-free period

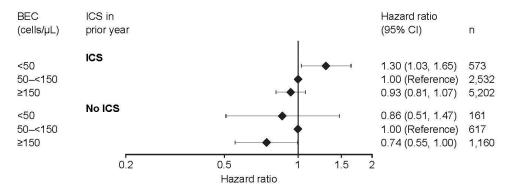
Difference in BEC from exacerbation period to exacerbation	n-free	Hazard ratio (95% CI)	n
BEC <50 cells/µL at exacerbation	· · · · · · · · · · · · · · · · · · ·	1.27 (0.79, 2.05)	197
Decrease of ≥100 cells/µL with BEC ≥50 cells/µL	i	1.00 (0.78, 1.29)	1,381
No change	•	1.00 (Reference)	1,721
Increase of ≥100 cells/µL	⊢ i	1.01 (0.75, 1.36)	775
Increase of ≥200 cells/µL	⊢ ↓	1.24 (0.90, 1.71)	507
0.5	1 1.5 2		
	Hazard ratio		

Panel a: Overall treatment failure. Panel b: Treatment failure defined as a repeat OCSprescription. Panel c: Treatment failure defined as an antibiotic prescription.BEC, blood eosinophil counts; CI, confidence interval; OCS, oral corticosteroids.An exacerbation-free period is defined as at least 4 weeks before any COPD exacerbations.

Figure S5. Association Between Blood Eosinophil Counts and Hospital Admission Within 6 Weeks (Cohort 1) or Readmission Within 4 Weeks (Cohort 2) Stratified by ICS Treatment in the Prior Year



b) Hospital readmission within 4 weeks by BEC during exacerbation-free period in prior year



Panel a: Association between BEC recorded on the day of an exacerbation and hospital admission within 6 weeks for Cohort 1. Panel b: Association between BEC recorded during stable disease (no exacerbations within 4 weeks) and hospital readmission within 6 weeks for Cohort 2.

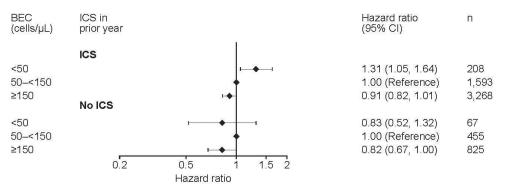
BEC, blood eosinophil counts; CI, confidence interval; ICS, inhaled corticosteroids.

Figure S6. Association Between Blood Eosinophil Counts and Treatment Failure Outcomes Within 6 Weeks, Stratified by ICS Treatment (Cohort 1)

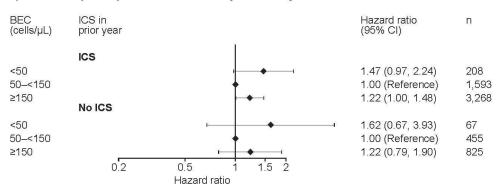
BEC ICS in Hazard ratio n (cells/µL) (95% CI) prior year ICS <50 1.45 (1.06, 1.98) 76 50-<150 1.00 (Reference) 693 ≥150 0.82 (0.71, 0.94) 1,263 No ICS <50 1.47 (0.78, 2.77) 19 50-<150 1.00 (Reference) 167 ≥150 0.80 (0.59, 1.08) 264 0.2 0.5 1.5 2 1 Hazard ratio

a) Treatment failure within 6 weeks by BEC at day of exacerbation

b) OCS repeat prescription within 6 weeks by BEC at day of exacerbation



c) Antibiotics prescription within 6 weeks by BEC at day of exacerbation



Panel a: Overall treatment failure. Panel b: Treatment failure defined as a repeat OCS prescription. Panel c: Treatment failure defined as an antibiotic prescription.

BEC, blood eosinophil counts; CI, confidence interval; ICS, inhaled corticosteroids;

OCS, oral corticosteroids.

Reference range for BEC was 50–<150 cells/ μ L.

Figure S7. Cohort 2 Patient Flow Diagram

COPD diagnosis linked with HES data

N=128,290

≥1 hospital admission for COPD exacerbation within 1 year of BEC measurement

N=25,462

No COPD exacerbation within 4 weeks before BEC measurement

N=20,099

Registered at GP practice at hospital discharge date

N=19,086

Continuous data available during the year before hospital discharge date

N=18,887

Code of COPD/COPD monitoring review before hospital admission

N=13,340

Aged ≥40 years at hospital discharge date

N=13,333

No long-term OCS treatment before index date

N=12,080

No history of other chronic respiratory conditions

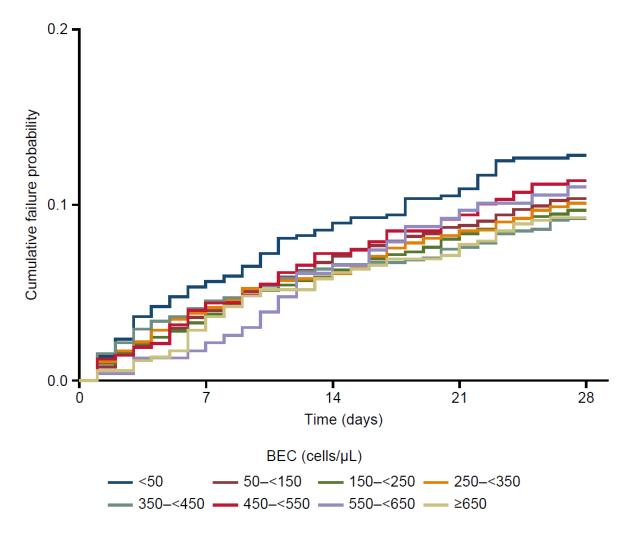
N=11,405

Patient discharged from hospital alive

N=10,245

BEC, blood eosinophil counts; COPD, chronic obstructive pulmonary disease; GP, general practitioner; HES, Hospital Episode Statistics; OCS, oral corticosteroids.

Figure S8. Kaplan-Meier Curves for the Unadjusted Association Between Blood Eosinophil Counts Recorded During an Exacerbation-Free Period and Time to First Hospital Readmission for COPD Exacerbation (Cohort 2)



BEC, blood eosinophil counts; COPD, chronic obstructive pulmonary disease.

An exacerbation-free period was defined as at least 4 weeks before any COPD exacerbations.