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Demographic and Clinical Characteristics of COPD Patients at Different Blood Eosinophil Levels in the UK Clinical Practice Research Datalink

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ABSTRACT

Blood eosinophil count may be a useful biomarker for predicting response to inhaled corticosteroids and exacerbation risk in chronic obstructive pulmonary disease (COPD) patients. The optimal cut point for categorizing blood eosinophil counts in these contexts remains unclear. We aimed to determine the distribution of blood eosinophil count in COPD patients and matched non-COPD controls, and to describe demographic and clinical characteristics at different cut points. We identified COPD patients within the UK Clinical Practice Research Database aged ≥ 40 years with a $FEV_1/FVC < 0.7$, and ≥ 1 blood eosinophil count recorded during stable disease between January 1, 2010 and December 31, 2012. COPD patients were matched on age, sex, and smoking status to non-COPD controls. Using all blood eosinophil counts recorded during a 12-month period, COPD patients were categorized as “always above,” “fluctuating above and below,” and “never above” cut points of 100, 150, and 300 cells/ μL . The geometric mean blood eosinophil count was statistically significantly higher in COPD patients versus matched controls (196.6 cells/ μL vs. 182.1 cells/ μL ; mean difference 8%, 95% CI: 6.8, 9.2), and in COPD patients with versus without a history of asthma (205.0 cells/ μL vs. 192.2 cells/ μL ; mean difference 6.7%, 95% CI: 4.9, 8.5). About half of COPD patients had all blood eosinophil counts above 150 cells/ μL ; this persistent higher eosinophil phenotype was associated with being male, higher body mass index, and history of asthma. In conclusion, COPD patients demonstrated higher blood eosinophil count than non-COPD controls, although there was substantial overlap in the distributions. COPD patients with a history of asthma had significantly higher blood eosinophil count versus those without.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease responsible for persistent limitations in lung airflow (1). It is a major cause of morbidity and mortality, and affects approximately 8% of people in the United Kingdom (2). Although several treatment options are available for COPD, there is variability in both disease presentation and response to treatment (1,3–5), thus warranting an individualized approach to disease management. Traditionally, COPD was considered to be a neutrophilic disease. However, it is becoming increasingly recognized that eosinophil-associated inflammation may play a key role in some patients with COPD. Blood eosinophil count may be a useful biomarker to guide therapeutic decisions in patients with COPD (6–8), and predict those at risk of severe exacerbations (9,10).

A key characteristic of a useful biomarker is that it can be objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biologic responses to a therapeutic intervention (11). Whether a single cut point for blood eosinophils is appropriate in order to categorize patients and inform either treatment choice and/or risk of exacerbation is still under evaluation. A level of ≥ 150 cells/ μL has been investigated to identify patients responding to inhaled corticosteroid treatment, but higher cut points may be more useful for predicting exacerbation risk (6–10). Given the potential for

blood eosinophil count as a biomarker in COPD, it is important to understand the distribution of blood eosinophils in COPD patients and to examine whether there is a particular patient phenotype associated with higher or lower blood eosinophil level.

In the clinical trial setting, 57–75% of COPD patients have blood eosinophil counts $\geq 2\%$ (6,7,12,13). In these trials, patients were mostly highly selected by post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio, age, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I–IV, and prior exacerbations, and may not always be representative of the general COPD population. An analysis of the United States (US) general population, the National Health and Nutrition Examination Survey (NHANES), showed that 70.7% of COPD patients had blood eosinophil levels $> 2\%$ (14). Analysis of data from another US COPD cohort, the Sub-Populations and Intermediate Outcome Measures in COPD study (SPIROMICS), reported that 8% of COPD patients had blood eosinophil levels $< 1\%$, 50% were between 1–3%, and 42% were $> 3\%$ (15). In the Evaluation Of COPD Longitudinally To Identify Predictive Surrogate End-points (ECLIPSE) cohort, almost half of patients had blood eosinophil levels that oscillated above and below 2%, 14% were persistently $< 2\%$, and 37% were always $\geq 2\%$ (16). Data from a

cohort of 456 COPD patients recruited from tertiary care hospitals in France reported that 51% of patients had blood eosinophil levels $<2\%$, 16% between $\geq 2\%$ and $<3\%$, 13% between $\geq 3\%$ and $<4\%$, and 20% were $\geq 4\%$ (17). In a study by Oshagbemi et al. conducted in the UK Clinical Practice Database (the same databased used for the present analysis), the distribution of blood eosinophils was 36% with blood eosinophil levels $<2\%$, 38% between $\geq 2\%$ and $<4\%$, 16% between $\geq 4\%$ and $<6\%$, and 9% were $\geq 6\%$ (18). This study also showed that COPD patients had a higher mean blood eosinophil cell count than matched non-COPD controls (matched by sex, year of birth and medical practice).

Higher blood eosinophil count (i.e., >2 or 3%) has been associated with certain patient characteristics including older age, being male, white race, higher body mass index (BMI), and not being a current smoker in large population based studies, (14–16) but these findings were not replicated in smaller cohorts in France (17) and Korea (19). In the NHANES study, a current asthma diagnosis was also associated with higher blood eosinophil level (data by asthma status not reported for SPIROMICS and asthma patients were excluded from ECLIPSE) (14). Higher blood eosinophil count was associated with worse disease severity using some measures, such as higher GOLD stage (III/IV) (14–16,20) and longer six minute walk test (15,16), yet also with less breathlessness as measured by the modified Medical Research Council (MRC) scores and lower St George's Respiratory Questionnaire scores (16). Lower SGRQ score was also associated with higher eosinophil levels in the French BPCO clinical cohort (17) but was not associated with blood eosinophil level in the Korean KOCOSS cohort (19). The heterogeneity between populations studied and choice of eosinophil cut points in the existing research make comparisons between studies difficult.

While blood eosinophil distribution has been examined in several US-based COPD populations, data from the United Kingdom (UK) are limited and are primarily from clinical trial populations. In this analysis, we aimed to compare and describe blood eosinophil count by disease state, and to determine the demographic and clinical characteristics of COPD patients with differing levels of blood eosinophils. We also explored the correlation between blood eosinophils expressed as percentages and absolute cell counts, in order to aid inter-study comparison when blood eosinophils are reported in different units. Of note, we previously published an analysis using only the COPD patients from this matched cohort to explore the stability of the measurement over time in COPD, another important characteristic to understand the utility of blood eosinophil count as a biomarker for use in clinical practice (21).

Patients and methods

Study design

We conducted a retrospective cohort study of patients with COPD identified from a primary care setting with the objective to describe the distribution and stability of blood eosinophils over time. Results for the stability analysis were published previously (21), and herein we report on the distribution of blood eosinophils in the COPD cohort as well as a matched cohort of primary care patients with similar age, sex and smoking

status but who do not have a recorded diagnosis of COPD.. All patients were identified using the UK Clinical Practice Research Datalink (CPRD), a governmental, not-for-profit research service providing anonymized primary care medical records from the National Health Service for use in public health research (<https://www.cprd.com/home/>). The protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC protocol 14_197R).

The inclusion criteria for the COPD cohort were described previously (21) and briefly included patients aged 40 and older with spirometry confirmed ($FEV_1/FVC < 0.7$) diagnosis for COPD recorded between January 1, 2010 and December 31, 2012 (first COPD code during this period selected as the index date) and; at least 12 months of history in the CPRD before the index date. Patients were also required to have at least one blood eosinophil count recorded during the stable disease state (i.e., not within ± 14 days of a COPD exacerbation) within 6 months of the index date. For the current analysis, each COPD patient was also matched 1:1 on sex, smoking status, and age, to a control patient with no code for a COPD diagnosis recorded in the CPRD. Eligible controls were required to have ≥ 12 -month history in the CPRD and ≥ 1 blood eosinophil measurement ≤ 6 months of the index date of the matched pair. The CPRD records for both COPD cases and matched controls were searched for up to 12 months to identify all blood eosinophil measurements; for COPD patients, any measurement taken within ± 14 days of a COPD exacerbation was removed in order to achieve a stable state cohort.

Patient demographics (age, sex, BMI, and smoking status) and disease characteristics (dyspnea grade and airflow limitation) at index date were described. Dyspnea was assessed using the MRC scale (22) and airflow limitation was defined as GOLD I–IV. Comorbid conditions, which occurred at any time in the patient's CPRD record prior to the index date, were also captured. A history of asthma was defined as at least two asthma medical codes recorded at any time before the index date. For COPD patients, we also described the history of moderate-to-severe COPD exacerbations in the 12 months before the index date (categorized as none, 1, or ≥ 2 events). COPD exacerbations were categorized as 'severe' episodes if they resulted in hospitalization or emergency room visits, or 'moderate' episodes if managed with COPD-specific antibiotics combined with oral corticosteroids and/or medical diagnosis of COPD exacerbations outside of hospital.

Data analysis

Patient demographics and disease characteristics for the COPD patients and matched non-COPD controls, were assessed using descriptive statistics. Using the first blood eosinophil count recorded after the index date, the distribution of blood eosinophils (untransformed values) was described using a histogram and the population mean blood eosinophil count was calculated after taking a log transformation of the data (values presented represent back transformed means); thus all means reported herein are geometric means. The mean values are presented for COPD patients and matched non-COPD controls overall, and stratified by history of asthma diagnosis; statistical comparison of the means was made using two sample t-tests for binary variables or analysis of variance for categorical variables.

For the cohort of patients with COPD, mean values were calculated and compared for different patient characteristics and disease severity measures.

To explore the stability of blood eosinophil levels over time in COPD patients, we utilized all measurements taken during the 12 months follow-up, all measurements were used to categorize patients as “always above,” “fluctuating above or below,” or “never above” blood eosinophil cut points of 100, 150, and 300 cells/ μ L. To compare patient characteristics and disease severity between these three categories, chi-square tests, t-tests, or Kruskal–Wallis tests for non-parametric data were used.

The correlation between absolute blood eosinophil count and eosinophil counts as a percentage of total white blood cells (WBCs) was examined using a simple linear regression model in a subset of patients ($n = 2,726$) who had a single blood eosinophil measurement recorded in both units.

Results

Patient demographics

The cohort comprised 27,557 matched pairs of COPD patients and non-COPD controls; 52% were male, mean (standard deviation [SD]) age was 71 (11) years, and 34% were current smokers (Table 1). COPD patients were less likely than

non-COPD patients to be overweight (BMI 25.0–29.9 kg/m^2 33% vs. 37%), and were more likely to be underweight (BMI <18.5 kg/m^2 4% vs. 2%). COPD patients were also more likely than non-COPD controls to have a history of asthma (36% vs. 10%). The median number of blood eosinophil counts during follow-up was two (interquartile range [IQR] 1) for COPD patients compared with one for non-COPD patients (IQR 1).

In COPD patients, mean (SD) dyspnea score was 2.6 (1.1); 33% of patients were classified as MRC 2, 25% were MRC 3, and 15% were MRC 4 (Table 1). One-quarter of COPD patients had one exacerbation episode (moderate or severe) and 18% had two or more in the past 12 months.

Distribution of blood eosinophils in patients with COPD and matched controls overall and by history of asthma

The distribution of blood eosinophils among the COPD patients and matched controls is shown in Figure 1. The distribution shows a clustering of values around hundredth whole numbers (i.e., 100, 200, 300 cells/ μ L etc.), suggesting that some laboratories or automated counters report rounded eosinophil counts. In COPD patients, the mean blood eosinophil count was 196.6 cells/ μ L (95% CI: 195.1, 198.3) versus 182.1 cells/ μ L (95% CI: 180.7, 183.5) in non-COPD controls, representing an 8.0% (95% CI: 6.8, 9.2) higher relative mean blood eosinophil count ($p < 0.0001$).

Table 1. Demographic and clinical characteristics for COPD patients and non-COPD matched controls (matched on age, sex and smoking status).

		COPD ($n = 27,557$)*		Non-COPD ($n = 27,557$)	
		N	%	N	%
Sex	Male	14,186	51.5	14,186	51.5
	Female	13,371	48.5	13,371	48.5
Age (years)	40–49	859	3.1	859	3.1
	50–59	3,072	11.1	3,072	11.1
	60–69	7,611	27.6	7,611	27.6
	70+	16,015	58.1	16,015	58.1
	Mean (SD)	71.1 (10.6)		71.1 (10.6)	
	Ex-smoker	16,392	59.5	16,392	59.5
Smoking status	Never	1,926	7.0	1,926	7.0
	Current	9,239	33.5	9,239	33.5
BMI (kg/m^2)	Underweight (<18.5)	1,123	4.1	477	1.7
	Normal (18.5–24.9)	8,509	30.9	7,953	28.9
	Overweight (25.0–29.9)	9,084	33.0	10,315	37.4
	Obese (≥ 30.0)	8,405	30.5	7,925	28.8
	Unknown	436	1.6	887	3.2
	Mean (SD)	27.7 (6.3)		27.8 (5.5)	
Dyspnea score	MRC 1	3,826	13.9	178	0.6
	MRC 2	9,178	33.3	235	0.9
	MRC 3	6,932	25.2	103	0.4
	MRC 4	4,247	15.4	43	0.2
	MRC 5	1,036	3.8	5	0
	Unknown	2,338	8.5	26,993	98.0
	Mean (SD)	2.6 (1.1)		2.1 (0.9)	
GOLD 2006 stage	I (80+)	3,759	13.6	415	1.5
	II (50 to <80)	11,271	40.9	209	0.8
	III (30 to <50)	4,458	16.2	19	0.1
	IV (<30)	766	2.8	-	-
	Unknown	7,303	26.5	26,912	97.7
COPD exacerbations in 12 months prior to index date	0	15,868	57.6	-	-
	1	6,806	24.7	-	-
	2+	4,883	17.7	-	-
Any ICS use during follow up	Yes	18,726	68.0	2751	9.3
History of asthma	Yes	9,833	35.7	2,807	10.2

Index date refers to the COPD diagnosis code date.

* Basic demographics and disease characteristics for the COPD cohort only were reported previously (21).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council; SD, standard deviation.

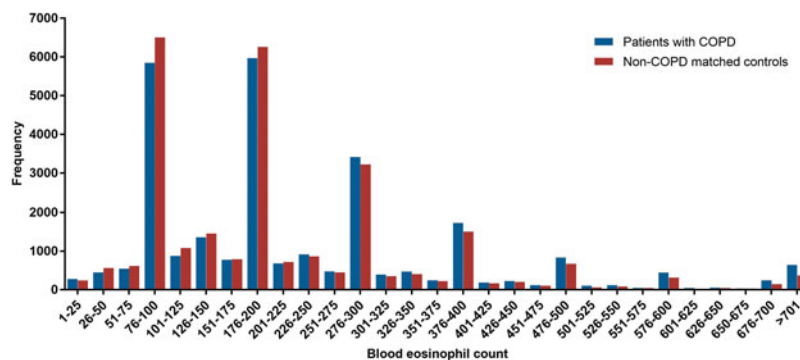


Figure 1. Histogram of blood eosinophil counts (cells/ μ L) for COPD patients and non-COPD controls in the UK Clinical Practice Research Datalink. Histogram based on absolute (untransformed) values. Note: Only the first blood eosinophil count was used in this analysis. COPD, chronic obstructive pulmonary disease.

COPD patients with a history of asthma had a higher mean blood eosinophil value than COPD patients without a history of asthma (205.0 cells/ μ L [95% CI: 202.2, 207.9] vs. 192.2 cells/ μ L [95% CI: 190.2, 194.1]; difference of 6.7%, $p < 0.0001$). The mean value observed for the non-COPD control group with asthma was only slightly lower than the COPD group with asthma (200.9 cells/ μ L [95% CI: 195.9, 206.1]). Control patients with no history of asthma had the lowest mean eosinophil value (180.0 cells/ μ L [95% CI: 178.6, 181.5]).

In COPD patients, the mean blood eosinophil count was statistically significantly higher in patients who were male, overweight or obese, with less breathlessness, a history of exacerbations, and a history of asthma diagnosis (Table 2). These observations mostly held when stratified by history of asthma diagnosis, but with some exceptions. For example, in patients

with a history of asthma, there were no significant differences in mean blood eosinophil by exacerbation history, and a relationship with smoking status was observed (highest mean count in patients who had never smoked) (Supplemental Table 1).

Distribution of COPD patients with blood eosinophil counts “always above,” “fluctuating above and below,” and “never above” cut points of 100, 150, and 300 cells/ μ L

The 13,463 COPD patients with ≥ 2 blood eosinophil counts available were categorized as “always above,” “fluctuating above and below,” and “never above” the cut points of 100, 150, or 300 cells/ μ L. The majority (87%) had blood eosinophil counts that were “always above” 100 cells/ μ L (Figure 2), while at the cut points of 150 and 300 cells/ μ L, the proportion “always above”

Table 2. Mean blood eosinophil counts (cells/ μ L) among COPD patients by demographic and disease characteristics.

		N	Mean (95% CI)	p value
All		27,552	196.6 (195.1, 198.3)	–
Sex	Female	13,367	181.8 (179.8, 183.9)	<0.0001
	Male	14,185	211.7 (209.3, 214.2)	
Age (years)	40–49	859	206.9 (198.3, 215.8)	0.0550
	50–59	3,071	197.4 (192.9, 202.0)	
	60–69	7,608	198.3 (195.2, 201.3)	
	70+	16,014	195.2 (193.1, 197.4)	
Smoking status	Ex-smoker	16,388	198.1 (196.0, 200.2)	0.0627
	Never	1,926	197.7 (191.3, 204.3)	
	Current	9,238	194.0 (191.3, 196.7)	
BMI	Underweight (<18.5)	1,123	172.1 (164.5, 180.0)	<0.0001
	Normal (18.5–24.9)	8,508	191.0 (188.1, 193.9)	
	Overweight (25.0–29.9)	9,083	200.3 (197.5, 203.2)	
	Obese (≥ 30.0)	8,402	202.3 (199.5, 205.2)	
Dyspnea score	MRC 1	3,825	201.8 (197.4, 206.2)	0.0239
	MRC 2	9,177	197.6 (194.9, 200.3)	
	MRC 3	6,930	195.4 (192.3, 198.6)	
	MRC 4	4,246	198.7 (194.5, 203.0)	
	MRC 5	1,036	187.8 (179.3, 196.7)	
GOLD 2006 stage	I (80+)	3,758	197.3 (193.1, 201.6)	0.4633
	II (50 to <80)	11,269	195.7 (193.3, 198.2)	
	III (30 to <50)	4,456	199.3 (195.4, 203.4)	
	IV (<30)	766	194.3 (184.8, 204.3)	
COPD exacerbations in 12 months prior to index date	0	15,863	194.5 (192.5, 196.6)	0.0086
	1	6,806	200.2 (196.9, 203.5)	
	2+	4,883	198.6 (194.6, 202.8)	
History of asthma	Yes	9,831	205.0 (202.2, 207.9)	0.0046
	No	17,721	192.2 (190.2, 194.1)	

Note: *Population mean blood eosinophil count calculated after taking a log transformation of the data (values presented represent back transformed means); N = 5 patients with untransformed value of zero not included in table. Note: Only the first blood eosinophil count was used in this analysis. Index date refers to the COPD diagnosis code date.

BMI, Body Mass Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council.

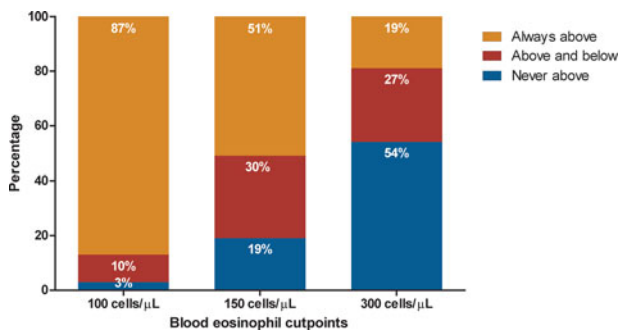


Figure 2. Proportion of blood eosinophil counts “always above,” “fluctuating above and below,” or “never above” cut points of 100, 150, and 300 cells/μL among COPD patients at least two blood eosinophil measurements during follow up ($n = 13,463$). “Always above” defined as all blood eosinophil counts being greater than or equal to the cut point, “fluctuating above and below” defined as at least one blood eosinophil count less than and at least one blood eosinophil count greater than or equal to the cut point, while “never above” defined as being always less than the cut point.

was 51% and 19%, respectively. When stratified by asthma history, this distribution was the same for the 100 cells/μL cut point (Figure 3), while a slightly higher proportion of patients with a history of asthma were “always above” the cut points of 150 (53% vs. 50%) and 300 cells/μL (20% vs. 19%) (Figure 3).

Across all the cut points, COPD patients with blood eosinophil counts “always above” the cut point were significantly more likely to be male and have a higher mean BMI versus other categories (Table 3). Being “always above” the 100 and 150 cells/μL cut points was associated with younger age but this did not hold for the 300 cells/μL cut point. At the 150 and 300 cells/μL cut points, being “always above” the cut point was associated with history of asthma diagnosis, while those who “fluctuated above and below” these cut points had higher dyspnea scores. There were no differences observed for smoking status, GOLD 2006 stage, or exacerbation history across the 100, 150, or 300 cells/μL cut points.

Patients with blood eosinophil levels “always above” 150 cells/μL were significantly more likely than those who “fluctuated above and below” and those who were “never above” to have comorbid hypertension, renal disease (32.1% vs. 25.7%

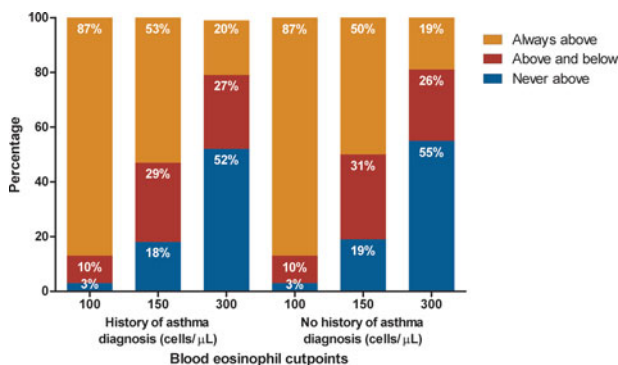


Figure 3. Proportion of blood eosinophil counts “always above,” “fluctuating above and below,” or “never above” cut points of 100, 150, and 300 cells/μL among COPD patients at least two blood eosinophil measurements during follow up ($n = 13,463$), stratified by asthma diagnosis.** Asthma diagnosis defined as at least two asthma medical codes (anytime during the patient’s history prior to the index date). “Always above” defined as all blood eosinophil counts being greater than or equal to the cut point, “fluctuating above and below” defined as at least one blood eosinophil count less than and at least one blood eosinophil count greater than or equal to the cut point, while “never above” defined as being always less than the cut point.

[“above and below”] vs. 30% [“never above”]), diabetes (27.4% vs. 21.7% [“above and below”] vs. 24.3% for [“never above”]), diabetes with complications (7.6% vs. 6.3% [“above and below”] vs. 6.5% [“never above”]), and myocardial infarction (14.1% vs. 10.7% [“above and below”] vs. 12.8% [“never above”]). Similar trends were observed for the 100 and 300 cells/μL cut points (Supplemental Tables 2A–2C).

Correlation between blood eosinophil measurements expressed as percentages of total WBCs and absolute cell counts

In total, 2,726 patients had a single blood eosinophil measurement recorded both as an absolute cell count and as a percentage of total WBCs. A blood eosinophil count of 150 cells/μL was equivalent to approximately 1.9% of total WBC (slope of regression line: 0.0128) (Supplemental Figure 1). Blood eosinophil values of 100 and 300 cells/μL were equivalent to approximately 1.3% and 3.8% of total WBC count, respectively.

Discussion

A number of clinical trials and population-based studies have investigated the distribution of blood eosinophils in COPD patients (6,12–18,20); however, it is difficult to make detailed comparisons between studies as a variety of eosinophil count cut points and a mix of percentage blood eosinophil levels or absolute counts were used. In addition, few studies have compared blood eosinophils in COPD and non-COPD patient populations or explored the potential influence of an asthma diagnosis on blood eosinophil distribution. In this study, we compared the distribution of blood eosinophils in a large (27,557 matched pairs) primary care cohort of COPD patients and non-COPD matched controls. Although we observed a statistically significant difference of 8% in relative mean blood eosinophils count between COPD patients and controls, the 14.5 cells/μL absolute difference in blood eosinophil counts was modest and unlikely to be of clinical importance. Furthermore, there is substantial overlap in the distribution of blood eosinophil counts between COPD patients and matched controls, and the majority of COPD patients have levels well within what is typically considered the normal range. This finding is similar to that reported by Oshagbemi et al who used the same source dataset, however matched the non-COPD patients on a slightly different set of covariates (sex, year of birth and medical practice). (18)

We found 51% of patients with COPD had a blood eosinophil count “always above” 150 cells/μL, and 150 cells/μL was shown to be equivalent to around 1.9% of total white blood cell count. Thus, our observed proportion is lower than that reported in other clinical trials and population-based studies, where between 57% and 75% of patients had blood eosinophil either $>2\%$ or $\geq 2\%$ (6,7,12–17). Stratification by a history of asthma diagnosis did not demonstrably influence the distribution of blood eosinophils, indicating that the biologic/pathologic process underlying the disease rather than the disease label per se may be a more important clinical consideration; for example, 53% of COPD patients with a history of asthma had a blood eosinophil count “always above” 150 cells/μL versus 50%

Table 3. Characteristics of COPD patients with blood eosinophil counts “always above”, “fluctuating above and below”, and “never above” 100, 150, and 300 cells/ μ L among patients at least two blood eosinophil measurements during follow up ($n = 13,463$).

	100 cells/ μ L cut point*				150 cells/ μ L cut point*				300 cells/ μ L cut point*			
	Always above ($n = 11,692$)	Both above and below ($n = 1,332$)	Never above ($n = 439$)	<i>p</i> value	Always above ($n = 6,872$)	Both above and below ($n = 4,059$)	Never above ($n = 2,532$)	<i>p</i> value	Always above ($n = 2,587$)	Both above and below ($n = 3,583$)	Never above ($n = 7,293$)	<i>p</i> value
Male sex, %	51.9	48.7	43.3	0.0003	55.6	48.5	44.0	<0.0001	62.2	53.7	46.3	<0.0001
Mean age (SD) years	72 (10)	73 (10)	74 (10)	<0.0001	72 (10.4)	73 (10.2)	73 (10.4)	0.0075	73 (10)	73 (10)	72 (10)	0.0691
Smoking status, %												
Ex-smoker	63.0	63.4	59.8	0.4159	63.1	63.0	62.4	0.9444	63.5	63.5	62.0	0.2821
Never smoker	6.6	7.4	8.1		6.6	6.8	7.1		7.1	6.8	6.6	
Current smoker	30.4	29.1	32.1		30.3	30.2	30.5		29.4	29.7	31.4	
Mean BMI (SD) kg/m ²	28.0 (6.3)	26.9 (6.3)	27.1 (7.1)	<0.0001	28.4 (6.2)	27.4 (6.5)	27.1 (6.3)	<0.0001	28.2 (6.1)	27.9 (6.7)	27.7 (6.2)	0.0003
Mean dyspnea score (SD)	2.6 (1.1)	2.7 (1.1)	2.6 (1.1)	0.3738	2.6 (1.1)	2.7 (1.1)	2.6 (1.1)	0.0013	2.6 (1.1)	2.7 (1.1)	2.6 (1.1)	0.0072
MRC												
GOLD 2006 stage, %												
I (80+)	20.5	19.8	22.6	0.8202	20.5	20.3	21.1		20.3	20.2	20.6	0.1010
II (50 to <80)	55.9	55.4	55.8		55.4	56.3	55.8		55.1	55.1	56.5	
III (30 to <50)	20.3	21.5	18.1		20.7	19.9	20.1		21.2	20.6	20.0	
IV (<30)	3.3	3.4	3.5		3.4	3.5	3.0		3.3	4.2	2.9	
COPD exacerbations in past 12 months, %												
0	56.3	54.4	58.1	0.3096	56.5	54.3	58.6		58.1	52.2	57.7	0.2205
1	25.5	24.8	22.8		25.6	25.6	23.9		24.7	26.4	24.5	
2+	18.2	20.7	19.1		17.9	20.1	17.5		17.3	21.4	17.7	
History of asthma, %	36.9	36.2	33.7	0.3465	37.9	36.0	34.8	0.0094	39.0	37.6	35.4	0.0022

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic obstructive Lung Disease; MRC, Medical Research Council; SD, standard deviation.

* “Always above” defined as all blood eosinophil counts being greater than or equal to the cut point, “fluctuating above and below” defined as at least one blood eosinophil count less than and at least one blood eosinophil count greater than or equal to the cut point, while “never above” defined as being always less than the cut point.

of those with no history of asthma. These results are again somewhat lower than those reported by the NHANES study, which also reported data by asthma status, where 69.6% of patients without current comorbid asthma had blood eosinophil count $>2\%$ (14).

When exploring blood eosinophil count as a mean value, characteristics associated with a higher blood eosinophil patient sub-type in this primary care population included male sex, having a higher BMI, a history of COPD exacerbations or an asthma diagnosis, and milder breathlessness. These characteristics were largely durable when exploring blood eosinophils as a categorical measure using 100, 150, and 300 cells/ μL cut points; however, in the categorical analysis, there was no relationship between being “always above” a cut point and COPD exacerbations, and both the “always above” and “always below” groups had a lower degree of breathlessness. The associations we observed with sex, BMI, lower breathlessness, and a history of asthma diagnosis corroborate previous population-based surveys (14–16), and both the ECLIPSE cohort and the French BPCO found no relationship with persistently high eosinophil count and a history of exacerbation rate (16,17). We did not, however, replicate the previous observations in NHANES or ECLIPSE between being “always above” a particular cut point and smoking status (14,16), nor the ECLIPSE finding that patients with persistently higher blood eosinophil level were more likely to be older (16). As our analysis examined three different cut points, we saw there was a significant association with a blood eosinophil count “never above” 100 cells/ μL and older age, and with a blood eosinophil count “never above” 300 cells/ μL and younger age. This may suggest that younger patients have higher levels of blood eosinophils than middle-aged patients, with older patients having a mild increase in blood eosinophils (>100 cells/ μL) and younger patients a more pronounced elevation (>300 cells/ μL). This finding highlights the important influence of age if different cut points are used, and further studies will be needed to clarify the association of blood eosinophil count with age.

There were differences in the prevalence of certain comorbidities by cut point categories; for example, patients with blood eosinophils “always above” 150 cells/ μL had a higher prevalence of hypertension, renal disease, diabetes, diabetes with complications, and myocardial infarction. COPD patients who “fluctuated above and below” 150 cells/ μL were more likely to have comorbid anxiety and osteoporosis. Zysman et al also showed a statistically significant relationship between higher blood eosinophil level ($\geq 2\%$) and diabetes, however showed no relationship with cardiovascular disease (17). NHANES and ECLIPSE studies also investigated comorbidities, however the only significant reported findings were that patients in NHANES with blood eosinophil $>2\%$ were less likely to have a heart attack (14,16). This contrasts with the observation for myocardial infarctions in this study. This difference may be due to the larger patient sample used in the current study (27,577 vs 948 [NHANES] and 1,483 [ECLIPSE]), or the older age of patients in this study compared with NHANES (42% vs. 81% aged <70 years), or possibly the exclusion of patients with an asthma history in ECLIPSE. The current findings will inform future studies examining the association between differing cut points of

blood eosinophils with comorbidities (e.g., myocardial infarction), and patient demographics (e.g., age), and help to assess the usefulness of blood eosinophil counts as a biomarker.

There are some limitations in this study that should be considered and are inherent in retrospective database work. Firstly, there is the potential for misclassification of patients as COPD or non-COPD controls. As the UK CPRD only captures diagnosed diseases in the primary care setting, patients who were symptomatic for COPD but had not yet received a COPD diagnosis (potentially milder patients) may not have been included in the COPD group. It is also possible that some matched non-COPD controls are un- (or under-) diagnosed COPD patients, as evidenced by some patients having a record of symptoms like dyspnea and FEV1 measurements, however this number was very small (approximately 2%) and these procedures may also be used in diagnosis and management of asthma and other, non-COPD respiratory conditions. In order to limit this potential misclassification, a published algorithm which combined validated diagnosis codes and spirometry was used to identify the COPD cohort (23). However, this algorithm uses the fixed FEV1/FVC ratio to define airflow limitation which can result in more frequent diagnosis in elderly patients and underdiagnosis in adults <45 years old then using a cutoff based on the lower limit of normal for FEV1/FVC (24), potentially contributing to some misclassification. We also acknowledge that the primary care record does not always record whether pre- or post-bronchodilator spirometry was used, however previous research has shown that the spirometry tracings used to diagnose and manage COPD in the UK is of high quality (25).

Secondly, there may be some recording or observer measurement bias in the blood eosinophil measurements. Laboratory tests conducted in the hospital may not always be reported back to the General Practitioner, and therefore may have been missed. However, it is anticipated that only approximately 10% of COPD patients would have been hospitalized in any given year (24). The distribution of blood eosinophil values reported in the UK CPRD database suggested that blood eosinophil count is often reported by automated cell counters/laboratories to the rounded nearest hundredth whole numbers (i.e., 100, 200, 300 cells/ μL , etc.), which should be considered when taking a decision to categorize this biologic value by discreet cut points. Despite this clustering of values, rounding down from 149 or up from 150 does not invalidate the 150 cut point which is the value most closely associated with the 2% cut point reported in the majority of literature to date. Thirdly, data were missing for some covariates, for example, patients were missing 2%, 9%, and 27% of BMI, dyspnea, and airflow limitation data, respectively. Lastly, the generalizability of the findings may be limited as diagnostic practices may differ in the UK compared with the rest of the world.

In conclusion, these data show that more than half of patients with COPD had blood eosinophil counts “always above” ≥ 150 cells/ μL (equivalent to 1.9% of total WBC count). Patients with blood eosinophil levels persistently at, or over, this cut point were more likely to be male, younger, have a higher BMI, and have a history of asthma diagnosis. Further longitudinal research is needed to understand whether there is an optimal cut point for categorizing blood eosinophil counts to maximize their predictive ability of drug response or exacerbation risk.

Declaration of interest

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Author contributions

SL, RS, JM, and KB contributed to the study design, data acquisition, and data analysis or interpretation. EH and CC contributed to data analysis or interpretation. SL, EH, and CC are employed by GSK. RS and JM were employed by GSK, and KB was a complementary worker on assignment to GSK, at the time of this analysis.

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