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## Prevalence of blood eosinophilia in hospitalized patients with acute exacerbation of COPD

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### Abstract

In this cohort of 3,084 patients hospitalized for acute exacerbation of COPD (AECOPD), we found that 17% had blood eosinophilia ( $> 300$  cells/ $\mu$ l); the use of an alternative cut-off level ( $> 2\%$ ) demonstrated that 40% had elevated eosinophil count. Patients with eosinophilia had higher frequency of readmission for AECOPD during 1-year follow-up period. This is the first study to investigate the prevalence of eosinophilia among inpatients with AECOPD – the population with the highest morbidity and healthcare utilization.

### Keywords

chronic obstructive pulmonary disease; hospitalization; eosinophilia; readmission; mortality

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide (1). In the U.S., acute exacerbation of COPD (AECOPD) was responsible for approximately 700,000 hospitalizations (2) and 50%–70% of the cost associated with COPD (3). There has been little differentiation in AECOPD management in the inpatient setting. However, the clinical syndrome of COPD is increasingly recognized as comprised of various phenotypes (4), including a subset of patients with eosinophilic airway inflammation (5). To date, however, no studies have reported the prevalence of blood eosinophilia – a marker for this eosinophilic airway inflammation – and its clinical relevance in patients hospitalized for AECOPD – the population with the highest morbidity and healthcare utilization (1). To address this knowledge gap, we determined the prevalence of blood eosinophilia in inpatients with AECOPD and investigated associations between eosinophilia and two post-hospitalization outcomes: readmission and mortality within a 1-year from the index hospitalization.

We conducted a retrospective cohort study of patients hospitalized for AECOPD at two teaching hospitals in Boston: Brigham and Women’s Hospital and Massachusetts General Hospital. Details of the study design, setting, data collection, and analysis may be found in the Online Repository. Briefly, using data from the Research Patient Data Registry, a data

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warehouse for all patient records at these hospitals (6), we used the following *ICD-9-CM* codes to identify all hospitalizations for AECOPD made by patients aged 40 years or older, from January 1, 2003 through December 31, 2012: 1) chronic bronchitis (491.xx), emphysema (492.xx), or chronic airway obstruction (496.xx) as the primary diagnosis; or 2) acute respiratory failure (518.81, 518.82, or 518.84) as the primary diagnosis and COPD listed as the secondary diagnosis (491.xx, 492.xx, or 496.xx)(7). Our institutional review board approved the study.

The primary outcome was prevalence of blood eosinophilia. Based on the literature (8–10), eosinophilia was defined as an absolute eosinophil count  $\geq 300$  cells/ $\mu$ l in peripheral blood on the first-measured cell counts with differentials during the in-hospital course (including pre-hospitalization emergency department/clinic visit). Additionally, based on the other COPD studies (11–14), we also used an alternative cut-off of  $\geq 2\%$  of total white cell count in peripheral blood. Secondary outcomes were frequency of readmission for AECOPD and all-cause mortality within 1 year from the index hospitalization.

To investigate the adjusted association of eosinophilia with frequency of readmission for AECOPD, we constructed negative binomial models adjusting for 12 patient-level confounders (age, sex, race/ethnicity, primary care physician status, body mass index, comorbidities [asthma, congestive heart failure, coronary artery disease, diabetes], use of oral corticosteroids prior to the hospitalization, and use of non-invasive and invasive mechanical ventilation during the index hospitalization). We also used generalized estimating equations to account for patient clustering within hospitals. Next, the time-to-death was analyzed using multivariable Cox proportional hazards models. In the sensitivity analysis, we repeated the models excluding patients with concomitant diagnosis of asthma.

We identified 3,084 patients hospitalized for AECOPD during the study period. The median age was 70 years (IQR, 61–79 years), and 50% were female. Additionally, 8% of patients had been treated with oral corticosteroids within 7 days before the hospitalization. Overall, 17% (95%CI, 15%–18%) of patients had blood eosinophilia ( $\geq 300$  cells/ $\mu$ l) based on the first-measured cell counts during in-hospital course. The use of an alternative cut-off level ( $\geq 2\%$  of total white cell count) demonstrated that 40% (95%CI, 38%–41%) of patients had an elevated eosinophil count.

Patient characteristics differed across the two groups (Table 1). For example, compared to patients without eosinophilia, those with eosinophilia ( $\geq 300$  cells/ $\mu$ l) were less likely to be female and non-Hispanic white but more likely to have concomitant diagnosis of asthma (all,  $P < 0.05$ ). However, in-hospital course (e.g., length-of-stay, in-hospital mortality) did not differ across the groups (all  $P > 0.05$ ).

Compared to patients without eosinophilia, those with eosinophilia had a higher frequency of readmission for AECOPD during the 1-year follow-up period (median, 0 vs. 1;  $P = 0.005$ ; Table 1). In the multivariable analysis adjusting for 12 variables, patients with eosinophilia continued to exhibit a higher frequency (incidence rate ratio, 1.11; 95%CI, 1.02–1.21;  $P = 0.02$ ; Table E1). However, 1-year mortality did not significantly differ neither in unadjusted (24% vs. 21%;  $P = 0.12$ ) nor adjusted analyses (hazard ratio, 0.88, 95%CI, 0.73–

1.06; P=0.18). In the sensitivity analysis excluding patients with concomitant diagnosis of asthma, these results did not change materially (Table E2).

Our finding is consistent with recent report demonstrating a high prevalence (37%) of elevated eosinophil count (eosinophils  $\geq 2\%$ ) in patients with stable COPD (14), although no prior observational studies had examined that of eosinophilia (defined as  $\geq 300$  cells/ $\mu\text{l}$ ). Likewise, the observed association between eosinophilia and higher frequency of readmission for AECOPD is in agreement with the post-hoc analysis of two randomized trials reporting that the rate of AECOPD increased progressively with increasing blood eosinophil counts among stable patients with COPD (11). The underlying mechanisms linking eosinophilia to increased risk of AECOPD are unclear and undoubtedly complex. Similar to our COPD population, patients with eosinophilic (Th2-high) asthma have been shown to be at higher risk of exacerbations (15). Prior studies suggest that, in a subset of COPD patients, Th2 cytokines could drive eosinophilic airway inflammation and bronchial hyperresponsiveness (4). Our cohort study corroborates these findings and extends them by demonstrating the robustness of findings in patients hospitalized for AECOPD.

Blood eosinophilia is a marker for eosinophilic airway inflammation (14). Studies have reported that this biomarker can guide use of oral and inhaled corticosteroid therapy in patients with AECOPD (11–13). Additionally, a prespecified subgroup analysis from a randomized trial of anti-interleukin-5 receptor  $\alpha$  monoclonal antibody (benralizumab) suggested improved outcomes in patients with eosinophilia (8). Identification of COPD patients who might benefit from a more targeted therapy based on this eosinophilic inflammation pathway is of great interest.

This study has several potential limitations. First, as with any studies using administrative data, there might be some misclassification of hospitalizations for AECOPD. However, assuming that the frequency of misclassification does not vary significantly between patients with eosinophilia and those without, this non-differential misclassification would not have biased our inferences. Second, the observed association might be confounded by unmeasured factors (e.g., baseline pulmonary function, cigarette smoking, triggers of exacerbation, pre- and post-hospitalization management). Third, the lack of significant difference in 1-year mortality between the groups might be attributable to a limited statistical power to detect the observed small difference. Fourth, the study was performed in two teaching hospitals, and thus the results may not be applicable to the other settings (e.g., rural hospitals). Finally, we did not examine patients who were treated and released at the ambulatory settings were not studied. Nonetheless, we focused on the population with the highest morbidity and healthcare utilization; it is precisely this population for which targeted therapies are most urgently warranted.

In sum, based on the data from a cohort of 3,084 patients hospitalized for AECOPD, we found that 17% had blood eosinophilia (defined as  $\geq 300$  cells/ $\mu\text{l}$ ). We also found that these patients had a higher frequency of readmission for AECOPD during the 1-year follow-up period. Our findings should facilitate research into better identification of acutely ill patients at increased risk of future AECOPD. In addition, because of potential role of eosinophil-

mediated inflammation in patients with COPD (8), our data also encourage researchers to develop targeted treatment strategies in this high-risk and costly patient population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS

<b>AECOPD</b>	acute exacerbation of chronic obstructive pulmonary disease
<b>CI</b>	confidence interval
<b>COPD</b>	chronic obstructive pulmonary disease

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**Table 1.**

Characteristics and Outcomes of Patients Hospitalized for Acute Exacerbation of Chronic Obstructive Pulmonary Disease, According to Blood Eosinophilia Status

Variables	No Eosinophilia (<300 cells/ $\mu$ l) n=2,571 (83%)	Eosinophilia (≥ 300 cells/ $\mu$ l) n=513 (17%)	P value
<b>Patient characteristics</b>			
Age (year), median (IQR)	70 (61–79)	71 (62–79)	0.32
40–49 years	158 (6)	24 (5)	
50–59 years	414 (16)	81 (16)	
60–69 years	699 (27)	130 (25)	
70–79 years	753 (29)	165 (32)	
80 years	547 (21)	113 (22)	
Female sex	1,329 (52)	223 (43)	<0.001
Race/ethnicity			<0.001
Non-Hispanic white	2,151 (84)	414 (81)	
Non-Hispanic black	162 (6)	28 (5)	
Hispanic ethnicity	60 (2)	30 (6)	
Others	71 (3)	18 (4)	
Missing	127 (5)	23 (4)	
Having primary care physician	2,055 (80)	437 (85)	0.006
Body mass index (kg/m <sup>2</sup> ), median (IQR) Comorbidities *	27 (22–32)	28 (23–32)	0.19
Asthma	341 (13)	85 (17)	0.048
Congestive heart failure	468 (18)	93 (18)	0.63
Coronary artery disease	424 (16)	89 (17)	0.97
Diabetes	273 (11)	56 (11)	0.84
Gastroesophageal reflux	257 (10)	63 (12)	0.12
Systemic/oral corticosteroids within 7 days prior to index hospitalization	206 (8)	37 (7)	0.54
Laboratory data, median (IQR)			
Blood eosinophil count (cells/ $\mu$ l)	80 (30–160)	430 (350–590)	-
Blood neutrophil count (cells/ $\mu$ l)	7,240 (5,190–10,460)	6,480 (5,030–8,690)	<0.001
In-hospital management †			
Non-invasive positive pressure ventilation	28 (1)	7 (1)	0.65
Intubation and mechanical ventilation	19 (1)	4 (1)	0.79
Hospital length-of-stay (d), median (IQR)	2 (0–4)	2 (1–4)	0.95
Died in the hospital	6 (<1)	0 (0)	0.60
Hospital ‡			
Brigham and Women's Hospital	890 (35)	172 (34)	
Massachusetts General Hospital	1,681 (65)	341 (66)	
<b>Post-hospitalization outcomes within 1 year from index hospitalization</b>			
Frequency of readmission for AECOPD, median (IQR)	0 (0–2)	1 (0–2)	0.005 <sup>§</sup>
Mortality	605 (24)	105 (21)	0.12 <sup>  </sup>

IQR, interquartile range; AECOPD, acute exacerbation of chronic obstructive pulmonary disease

Data were presented as % unless otherwise indicated.

\* Identified by using *ICD-9-CM* codes: asthma (493.xx), congestive heart failure (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 429.0), coronary artery disease (410.xx-414.xx), diabetes (250.xx), and gastroesophageal reflux (530.11 and 530.81) prior to the index hospitalization.

† Non-invasive positive pressure ventilation was identified by using Current Procedural Terminology code, 94660. Intubation and mechanical ventilation was identified by using Current Procedural Terminology code, 31500.

‡ Prevalence of eosinophilia (  $> 300$  cells/ $\mu$ l) was 16.2% at Brigham and Women's Hospital and 16.9% at Massachusetts General Hospital.

§ Unadjusted negative binomial model accounting for clustering of patients within hospitals by using generalized estimating equations.

// Unadjusted Cox proportional hazards models accounting for clustering of patients within hospitals by using the robust sandwich estimate.