Eosinophils in chronic obstructive pulmonary disease exacerbations are associated with increased readmissions

Eosinophils, exacerbated COPD, and readmissions

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9.12 COPD: Outcomes

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At a Glance Commentary: A subset of patients with chronic obstructive pulmonary disease (COPD) demonstrates eosinophilic inflammation either in their sputum or blood. Previous studies regarding the association between increased blood eosinophils and poor readmission outcomes are conflicting. The objective of this study was to investigate outcomes following severe COPD exacerbations in patients with higher blood eosinophil levels.

We rigorously analyzed real-world observational data on the eosinophilic COPD phenotype, finding that eosinophil levels ≥ 200 cells/μL and/or ≥ 2% at admission for a severe exacerbation of COPD, when assessed in a time frame free of systemic corticosteroids, is associated with an almost threefold increase in 12-month readmission for COPD, more than double 12-month all-cause readmission, and a shorter time to first COPD-related readmission.

These findings reaffirm that adequately phenotyping specific COPD inflammatory profiles is worthwhile and of clinical importance.
ABSTRACT

Rationale: A subset of patients with chronic obstructive pulmonary disease (COPD) demonstrates eosinophilic inflammation either in their sputum or blood. Previous studies regarding the association between increased blood eosinophils and poor readmission outcomes are conflicting.

Objective: Investigate outcomes following severe COPD exacerbations in patients with higher blood eosinophils.

Methods: With an observational study design, hospitalizations for severe COPD exacerbations were retrospectively gathered. Patient health data previous to and up to one year following the index hospitalization were included. Patients were stratified into the eosinophilic group if the blood eosinophil level on admission was ≥200 cells/μL and/or ≥2% of the total white blood cell count. Clinical outcomes were 12-month COPD-related readmission, 12-month all-cause readmission, length of stay, and time to COPD-related readmission. These outcomes were analysed using logistic, negative binomial, and Cox regression models.

Results: A total of 167 patients were included: 55 with eosinophilia. Eosinophilia was associated with an increased risk of 12-month COPD-related readmission (OR 3.59 [1.65-7.82], p=0.0013), an increased risk of 12-month all-cause readmission (2.32 [1.10-4.92], p=0.0277), and a shorter time to first COPD-related readmission (HR 2.74 [1.56-4.83], p=0.0005). The length of stay was not statistically different between eosinophilic and non-eosinophilic patients. Sensitivity analyses using different eosinophilia definitions reveal a proportional increase in effect size with increasing eosinophil cell count definitions for predicting 12-month readmissions.

Conclusion: Blood eosinophils can be used as a biomarker in severe COPD exacerbations for predicting higher readmission rates. Word count: 235
KEY-WORDS

Eosinophils, COPD, patient readmission, corticosteroids
ABREVIATIONS

CBC: complete blood count
COPD: chronic obstructive pulmonary disease
CVD: cardiovascular disease
FEV₁: forced expiratory volume in one second
FVC: forced vital capacity
ICS: inhaled corticosteroid
LABA: long acting β2 agonist
LAMA: long acting muscarinic antagonist
OR: odds ratio
PFT: pulmonary function tests
RCT: randomized control trial
SABA: short acting β2 agonist
SAM: short acting muscarinic antagonist
WBC: white blood cell
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and its associated acute exacerbations account for the highest per capita hospitalization rate among all ambulatory care sensitive conditions in Canada. In the United States, where COPD 30-day readmission rates are observed to be as high as 20%, pay-for-performance programs such as the Hospital Readmissions Reductions Program are expected to target COPD outcomes as of October 2016. Despite smoking cessation campaigns, public health efforts, and scientific progress, COPD morbidity and mortality continue to increase.

Though classically neutrophilic and Th1-mediated, different COPD inflammatory profiles have recently gained interest. Eosinophilic inflammation has been observed in stable and exacerbated COPD patients’ blood and sputum. It has been hypothesized that “eosinophilic” COPD patients may represent a different phenotype which responds favorably to inhaled corticosteroids (ICS) and systemic corticosteroids. Compared to other biological clusters, exacerbations with higher sputum eosinophil counts are more often non-infectious. This phenotype can readily be identified with blood eosinophils as a sputum eosinophils surrogate. Of note, equal proportions of general and COPD populations – approximately 40%, depending on the cohort – demonstrate blood eosinophil levels ≥200 cells/μL and/or ≥2%. However, COPD patients’ lungs have been shown to contain an excess number of eosinophils compared to controls.

Post-hoc analyses of prospective studies have shown inconsistent relationships between blood eosinophils and increased exacerbation rates. In their analysis of the ECLIPSE cohort, Singh et al. failed to demonstrate this association. Siddiqui et al. and Pascoe et al., who studied randomized controlled trials’ (RCT) cohorts, found increased exacerbation rates that mirrored increased eosinophils. Vedel-Krogh et al. noted an association between eosinophil levels and an increase
in moderate to severe exacerbation rates amongst eosinophilic COPD patients in the general population\textsuperscript{17}. More recently, Bafadhel \textit{et al.} did not find a significant difference between eosinophilic and non-eosinophilic COPD patients regarding 12-month readmission rate and time to first exacerbation, though eosinophils in presence of corticosteroid therapy did predict a shorter hospital stay\textsuperscript{13}. Conflicting results between these studies raise the possibility of a confounding factor.

Corticosteroids are the mainstay of treatment for severe COPD exacerbations. The eosinopenic effect of cortisone has long been recognized: originally by means of the Thorn test and later by formal pharmacodynamic testing. Eosinophil count is known to fall by more than 50\% within the first four hours following its administration, and then return to baseline within 24 hours\textsuperscript{21}. As the relative timing of corticosteroid administration can potentially mask blood eosinophilia in COPD, it is plausible that a confounding bias arises when studying eosinophilic inflammation, response to corticosteroids, and clinical outcomes.

Thus, the objective of this study was to investigate the association between higher blood eosinophil counts and adverse clinical outcomes following severe COPD exacerbations. Special care was given to control the effect of corticosteroid administration on these variables.

**METHODS**

**Study design**

With an observational study design, all severe exacerbations of COPD in Sherbrooke’s hospital health centers between April 1\textsuperscript{st} 2012 and March 31\textsuperscript{st} 2013 were retrospectively screened through electronic medical records. The main diagnosis of hospitalization had to be registered as “acute
exacerbation of COPD”, with no mention of decompensated asthma in this field and no comorbid bronchiectasis elsewhere. Patients had to have survived the index hospitalization. The institutional Ethics Committee approved the protocol (FWA #00005894).

**Study patients**

All patients were $\geq 40$ years of age and had COPD by symptoms, spirometry, and standard definition of the Global Initiative for Chronic Obstructive Lung Disease\textsuperscript{22}. Upon candidate reassessment, exclusion criteria were: admission for pneumonia, absence of obstructive pattern on pulmonary function tests (PFT), absence of a valid PFT any time between 1998 and one year after index hospitalization, COPD without exacerbation, mislabeled asthmatics (never-smokers with or without obstructive spirometry and no mention of COPD in medical records), and referrals for tertiary care from outside the immediate region (“non-captive” patients). Based on available data, consensus was obtained between authors for questionable cases for selection in the cohort. Patients with an initial complete blood count (CBC) taken in a corticosteroid-free time frame, defined as no systemic corticosteroid between one and 48 hours before venipuncture, were identified.

**Data collection**

Data that was initially collected through electronic records consisted of: anthropometric measures; comorbid conditions; inpatient laboratory blood tests’ dates, times and results; and information pertaining to all previous hospitalizations on file and up to one year following the index hospitalization. Deaths in the year following hospitalization were identified in the hospital database. Additional data collected by manual extraction from medical files consisted of: smoking status; home oxygen use; baseline PFT results up to one year following index hospitalization (PFT used, in order of priority: most recent PFT $< 5$ years prior to admission, PFT $\geq 1$ year after discharge,
PFT between 1998 and <5 years prior); baseline and discharge inhaler therapy; corticosteroid use within 48 hours before index admission, using patients outpatient medication list and medical notes; inpatient definitive treatment components, like corticosteroids and/or antimicrobial(s); and date and time of the first corticosteroid dose.

**Study variables and outcomes**

The main independent variable was a blood eosinophil cell count $\geq 200$ cells/$\mu$L and/or $\geq 2\%$ of total white blood cell (WBC) count on the first inpatient CBC available during the index hospitalization (including emergency department care). This cut-off has previously shown high sensitivity for predicting sputum eosinophilia\(^8\), and was thus considered to indicate an “eosinophilic COPD patient”. The primary outcomes were 12-month COPD-related readmission, 12-month all-cause readmission, and hospital length of stay. The secondary outcome was time to first COPD-related readmission.

**Statistical analyses**

The study variables were compared between eosinophilic and non-eosinophilic patients using the chi-2 test for categorical variables, and the t-test or the Wilcoxon rank test for continuous variables. For binary outcomes, associations between eosinophilia and outcomes were estimated using logistic regression with stepwise selection (forcing age and sex in the models but all other variables were considered only if they reached statistical significance). The association between eosinophilia and the hospital length of stay was estimated using negative binomial regression models\(^23\). For the secondary outcome “time to first COPD-related readmission”, patients were censured at the date of death if deceased or at the end of follow-up (365 days), and the association with eosinophilia was estimated using Cox regression models and Kaplan-Meier survival curves. Sensitivity analyses
were performed using different definitions of eosinophilia: 1- by using a higher eosinophil cut-off (≥300 cells/μL or ≥3% of WBC); 2- by using only eosinophil cell count ≥200 cells/μL; 3- by using eosinophil cell count in three categories with thresholds corresponding to the median and the third quartile (<100, 100-200, ≥200 cells/μL); 4- by using only eosinophil cell percent ≥2% of total WBC count; 5- by using eosinophil cell percent in 3 categories with thresholds corresponding to the median and the third quartile (<0.7%, 0.7%-2.0%, ≥2.0% cells/μL).

RESULTS

Four hundred forty-seven candidate hospitalizations were included and 236 were retained after applying exclusion criteria. From them, only 167 patients had a corticosteroid free CBC available (Figure 1). Patients’ characteristics are presented in Table 1. Fifty-five patients had eosinophilia as defined by the ≥200 cells/μL and/or ≥2% cut-off. Except for eosinophil counts, all differences between eosinophilic and non-eosinophilic patients were not statistically significant.

Primary outcomes

First, 12-month COPD-related readmission (censored for death) differed significantly between groups (adjusted OR [95% CI], eosinophilic vs non-eosinophilic: 3.59 [1.65-7.82], p=0.0013; Table 2) as well as 12-month all-cause readmission (adjusted OR: 2.32 [1.10-4.92], p=0.0277; Table 2). Relative number of deaths was similar between groups (n=14 in the non-eosinophilic, n=6 in the eosinophilic). On the other hand, the hospital length of stay did not differ significantly between groups (median [interquartile range]: 5 [3-7] vs 5 [3-7] days, p=0.75; Table 2), and this remained true even after controlling for the other covariables (exp(β)=1.19 [0.91-1.55], p=0.2096; Table 2).
Primary outcomes were also measured using different definitions of eosinophilia (Table 3). The association between higher eosinophils and 12-month COPD-related and all-cause readmission remained essentially the same across definitions for cell counts or percent exceeding 200 or 2.0% cells/μL. Compared to lower eosinophils levels (100 or 0.7%), intermediate cell counts (100-200) or percent (0.7-2.0%) were not statistically associated with an increased risk of readmission (COPD or all-cause). On the other hand, the hospital length of stay did not differ significantly between groups, regardless of the definition used.

**Secondary outcome**

The Kaplan-Meier curve of the time to the first COPD-related readmission separated significantly (Figure 2). Using the Cox model, the adjusted Hazard Ratio associated with eosinophilia was 2.78 [1.58-4.89], p=0.0004.

As said earlier, the relative timing of corticosteroid administration can potentially mask blood eosinophilia in COPD if we do not consider only patients with an initial CBC taken in a corticosteroid-free time frame. To illustrate the possible bias arising if we do not take this into account, we performed the analysis with the entire sample (n=236), including patients that were not corticosteroid-free at time of CBC measurement. All primary outcomes were non-statistically significant in this case. Specifically, 12-month COPD-related readmission and 12-month all-cause readmission in the entire sample did not differ significantly between eosinophilic and non-
eosinophilic patients (adjusted OR: 1.63 [0.86-3.10], p=0.1370; adjusted OR: 1.53 [0.81-2.90], p=0.1935, respectively).

**DISCUSSION**

The main finding of this study is that increased eosinophils at admission, when defined by a cut-off of \( \geq 200 \) cells/\( \mu L \) and/or \( \geq 2\% \) of WBC count, can predict a more than threefold increase in 12-month readmission for COPD, a more than double increase in 12-month all-cause readmission, and a shorter time to first COPD-related readmission. The influence of eosinophil cell counts on readmissions is consistent throughout the sensitivity analyses conducted on our data.

Previous studies have tentatively associated clinical outcomes with eosinophilia in COPD; careful attention to methodological differences reveals that positive studies were exempt of the confounding effect of systemic corticosteroid use. Singh *et al.*, when studying the ECLIPSE cohort, classified eosinophilia according to yearly stable-state CBCs and did not give thorough consideration to systemic corticosteroid use as possible bias. Their study failed to find a significant association with exacerbation rates\(^{16} \). Siddiqui *et al.* and Pascoe *et al.*, in their *post-hoc* analyses of RCT cohorts, excluded patients having used systemic corticosteroids \( \leq 4 \) weeks before enrollment\(^{19,20,24} \). Accordingly, these studies achieved clinical significance regarding the association between higher eosinophil cell levels and exacerbation rates. Vedel-Krogh *et al.* analyzed the Copenhagen General Population Study cohort, presumably using the participants’ baseline CBC, i.e. at the moment of enrollment between 2003 and present\(^{25} \). They reported inhaled corticosteroid use, and made no mention of systemic corticosteroids. Though they did find an association between eosinophil counts and exacerbation rates, the impact of systemic
corticosteroids was not assessed\textsuperscript{17}. Also, the clinical usefulness of older baseline CBC compared with at-admission CBC to identify the eosinophilic COPD phenotype is debatable\textsuperscript{26}. Bafadhel \textit{et al.} identified corticosteroid use before admission, but determined a ≤4 week cut-off for their subgroup analysis, losing much power and diluting the eosinopenia association with very recent corticosteroids use. Readmission outcomes were not significantly different\textsuperscript{13}. Throughout these studies, one can postulate that lack of consideration of the impact of systemic corticosteroids use might have led to mitigated results.

The antagonism of eosinophils by corticosteroids has long been recognized and studied\textsuperscript{21,27,28}. Here, we considered only patients with no corticosteroid treatment ≤48 hours before the measurement of eosinophil cell counts. This timeframe was justified by previous data which demonstrated eosinopenia between 4-24 hours following cortisone administration\textsuperscript{21}. Of particular interest, the association between increased readmission rates and blood eosinophil levels became non-statistically significant in the whole sample (n=236) if we disregard recent corticosteroid use before identifying the eosinophilic inflammatory profile a COPD patient.

A methodological difference with previous studies is the exclusion of so-called “COPD exacerbations secondary to pneumonia” (n=103 exclusions). Clinically speaking, we differentiate COPD exacerbation – i.e. Anthonisen symptoms\textsuperscript{29} without consolidation on imagery – from pneumonia, as these diagnoses differ in their pathophysiology and treatment components/duration. Moreover, concomitant eosinophilia and pulmonary consolidation evoke a broad range of diagnoses\textsuperscript{30}, most of which would respond favorably to corticosteroids.
The major strengths of this study are its pathophysiological-driven design, consideration of the effect of relative timing of systemic corticosteroid administration on eosinophils, and evaluation of several different eosinophilia definitions. Even if its observational design carries the usual indication bias, no other sample has ever been assembled exclusively to study the association between blood eosinophils and readmission rates, a characteristic which permitted more latitude in choice of selection criteria, and study measurements. Though all potential variables related to the selected outcomes were not included, we are confident the most important ones were taken into account. Nevertheless, the data is retrospective in nature, and as such the signals provided by our study must be interpreted with care. Further studies with larger samples are needed to clarify the issue of which eosinophil count or percent thresholds are associated with an increased risk of readmissions. Lastly, the absolute eosinophil cell count was relatively imprecise in our laboratory, as they were rounded by hundred cells/μL.

In conclusion, we report that higher blood eosinophils at admission for severe exacerbation of COPD, when assessed in a corticosteroid-free time frame, is associated with a more than threefold increase in 12-month readmission for COPD, a more than double 12-month all-cause readmission, and a shorter time to first COPD-related readmission. These findings reaffirm that adequately phenotyping specific COPD inflammatory profiles is worthwhile and of clinical importance.

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REFERENCES


FIGURE LEGENDS

Figure 1.
Flowchart of patient enrollement process.

Figure 2.
Kaplan-Meier curves for time before first COPD-related readmission (Time_COPD; days after discharge) in patients with a corticosteroid-free CBC, eosinophilic (n=55, blue line) vs non-eosinophilic patients (n=112, red line); follow-up 365 days post-discharge, data censored for death; p=0.007.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n=167)</th>
<th>Eosinophilic COPD (n=55)</th>
<th>Non-eosinophilic COPD (n=112)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>86 (51.5)</td>
<td>28 (50.9)</td>
<td>58 (51.8)</td>
<td>0.915</td>
</tr>
<tr>
<td>Age, y</td>
<td>71.4 ± 10.3</td>
<td>69.3 ± 11.0</td>
<td>72.3 ± 9.8</td>
<td>0.076</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>61 (36.5)</td>
<td>16 (29.1)</td>
<td>45 (40.2)</td>
<td>0.162</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40 (24.0)</td>
<td>11 (20.0)</td>
<td>29 (25.9)</td>
<td>0.402</td>
</tr>
<tr>
<td>Asthma</td>
<td>9 (5.4)</td>
<td>5 (9.1)</td>
<td>4 (3.6)</td>
<td>0.138</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1 [0-2]</td>
<td>1 [0-2]</td>
<td>0 [0-2]</td>
<td>0.481</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>78 (46.7)</td>
<td>29 (52.7)</td>
<td>49 (43.8)</td>
<td>0.274</td>
</tr>
<tr>
<td>Current smoker</td>
<td>89 (53.3)</td>
<td>26 (47.3)</td>
<td>63 (56.2)</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ (post-bronchodilator), % predicted</td>
<td>52.2 ± 17.9</td>
<td>53.3 ± 19.2</td>
<td>51.6 ± 17.2</td>
<td>0.585</td>
</tr>
<tr>
<td>FEV$_1$/FVC, %</td>
<td>47.6 ± 12.3</td>
<td>47.7 ± 13.1</td>
<td>47.5 ± 12.0</td>
<td>0.910</td>
</tr>
<tr>
<td>GOLD stage (according to FEV$_1$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13 (7.8)</td>
<td>5 (9.1)</td>
<td>8 (7.1)</td>
<td>0.373</td>
</tr>
<tr>
<td>II</td>
<td>80 (47.9)</td>
<td>28 (50.9)</td>
<td>52 (46.4)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>59 (35.3)</td>
<td>15 (27.3)</td>
<td>44 (39.3)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15 (9.0)</td>
<td>7 (12.7)</td>
<td>8 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Hospitalized for COPD in the previous year</td>
<td>27 (16.2)</td>
<td>9 (16.4)</td>
<td>18 (16.1)</td>
<td>0.962</td>
</tr>
<tr>
<td>Home oxygen use</td>
<td>17 (10.2)</td>
<td>9 (16.4)</td>
<td>8 (7.1)</td>
<td>0.169</td>
</tr>
<tr>
<td>Baseline inhalator use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS</td>
<td>119 (71.3)</td>
<td>38 (69.1)</td>
<td>81 (72.3)</td>
<td>0.665</td>
</tr>
<tr>
<td>LABA</td>
<td>114 (68.3)</td>
<td>36 (65.4)</td>
<td>78 (69.6)</td>
<td>0.585</td>
</tr>
<tr>
<td>LAMA</td>
<td>112 (67.1)</td>
<td>34 (61.8)</td>
<td>78 (69.6)</td>
<td>0.312</td>
</tr>
<tr>
<td>SAMA</td>
<td>7 (4.1)</td>
<td>1 (1.8)</td>
<td>6 (5.4)</td>
<td>0.428</td>
</tr>
<tr>
<td>None or SABA prn only</td>
<td>33 (19.8)</td>
<td>14 (25.4)</td>
<td>19 (17.0)</td>
<td>0.195</td>
</tr>
<tr>
<td>Post-discharge ICS use</td>
<td>137 (82.0)</td>
<td>43 (78.2)</td>
<td>94 (83.9)</td>
<td>0.363</td>
</tr>
<tr>
<td>WBC count at admission, cells x10$^9$/L</td>
<td>10.3 ± 3.9</td>
<td>10.3 ± 3.9</td>
<td>10.3 ± 4.0</td>
<td>0.993</td>
</tr>
<tr>
<td>Eosinophil count, cells x10$^9$/L</td>
<td>0.1 [0.0-0.2]</td>
<td>0.3 [0.2-0.4]</td>
<td>0 [0.0-0.1]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eosinophil count, % of WBC</td>
<td>0.7 [0.2-2.0]</td>
<td>3.1 [2.0-4.2]</td>
<td>0.4 [0.1-0.7]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Definitive inpatient therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>151 (90.4)</td>
<td>51 (92.7)</td>
<td>100 (89.3)</td>
<td>0.478</td>
</tr>
<tr>
<td>Antimicrobial(s)</td>
<td>145 (86.8)</td>
<td>45 (81.8)</td>
<td>100 (89.3)</td>
<td>0.180</td>
</tr>
</tbody>
</table>
n (%) or mean ± SD or median [Interquartile range]; CBC: complete blood count; CVD: cardiovascular Disease; GOLD: Global initiative for chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long acting β-agonist; LAMA: long acting muscarinic antagonist; SABA: short acting β-agonist; SAMA: short acting muscarinic antagonist; WBC: white blood cells
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eosinophilic COPD (n=55)</th>
<th>Non-eosinophilic COPD (n=112)</th>
<th>Crude OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month COPD-related readmission</td>
<td>26 (47.3)</td>
<td>28 (25.0)</td>
<td>2.54 [1.27 - 5.08]**</td>
<td>3.59 [1.65 – 7.82]**</td>
</tr>
<tr>
<td>12-month all-cause readmission</td>
<td>37 (67.3)</td>
<td>60 (53.6)</td>
<td>1.68 [0.85 - 3.31]</td>
<td>2.32 [1.10 – 4.92]*</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>Median [IQR]</td>
<td>Crude exp(β)</td>
<td>Adjusted exp(β)</td>
<td></td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>5 [2-6]</td>
<td>5 [3-7]</td>
<td>1.15 [0.88 – 1.50]</td>
<td>1.19 [0.91 – 1.55]</td>
</tr>
</tbody>
</table>

IQR: Interquartile range; OR (logistic regression) or exp(β) (negative binomial regression) [95% CI]; *p<0.05; **p<0.01; ***p<0.001
**TABLE 3 - Association between eosinophilia and outcomes according to eosinophilia definition**

<table>
<thead>
<tr>
<th>Definition of eosinophilic patients</th>
<th>12-month COPD-related readmission</th>
<th>12-month all-cause readmission</th>
<th>Length of stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &lt; 200 cells/μL and &lt; 2% (n=112)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>≥ 200 cells/μL or ≥ 2% (n=55)</td>
<td>3.59 [1.65 – 7.82]**</td>
<td>2.32 [1.10 – 4.92]*</td>
<td>1.19 [0.91 – 1.55]</td>
</tr>
<tr>
<td>2. &lt; 300 cells/μL and &lt; 3% (n=131)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>≥ 300 cells/μL or ≥ 3% (n=36)</td>
<td>3.21 [1.34 – 7.71]**</td>
<td>1.42 [0.62 – 3.26]</td>
<td>1.00 [0.73 – 1.38]</td>
</tr>
<tr>
<td>3. &lt; 200 cells/μL (n=116)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>≥ 200 cells/μL (n=51)</td>
<td>3.12 [1.42 – 6.88]**</td>
<td>2.17 [1.01 – 4.66]*</td>
<td>1.23 [0.94 – 1.62]</td>
</tr>
<tr>
<td>4. &lt; 100 cells/μL (n=68)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>100-200 cells/μL (n=48)</td>
<td>1.45 [0.59 – 3.58]</td>
<td>1.41 [0.63 – 3.18]</td>
<td>0.83 [0.60 – 1.13]</td>
</tr>
<tr>
<td>≥ 200 cells/μL (n=51)</td>
<td>3.66 [1.51 – 8.91]**</td>
<td>2.51 [1.09 – 5.78]*</td>
<td>1.15 [0.86 – 1.55]</td>
</tr>
<tr>
<td>5. &lt; 2% (n=123)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>≥ 2% (n=44)</td>
<td>3.57 [1.60 – 8.00]**</td>
<td>1.89 [0.86 – 4.13]</td>
<td>1.01 [0.76 – 1.35]</td>
</tr>
<tr>
<td>6. &lt; 0.7% cells/μL (n=78)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>0.7-2.0% cells/μL (n=45)</td>
<td>1.45 [0.58 – 3.61]</td>
<td>1.79 [0.78 – 4.10]</td>
<td>1.05 [0.77 – 1.43]</td>
</tr>
<tr>
<td>≥ 2.0% cells/μL (n=44)</td>
<td>4.12 [1.69 – 10.0]**</td>
<td>2.16 [0.93 – 5.00]</td>
<td>1.02 [0.75 – 1.39]</td>
</tr>
</tbody>
</table>

OR (logistic regression) or exp(β) (negative binomial regression) [95% CI]; Ref: reference group; *p<0.05; **p<0.01; ***p<0.001
447 candidate index hospitalizations

Data collection and reassessment by SC and research assistant

287 remaining candidates

Consensus reached with all authors

236 enrolled subjects

Review of timing of corticosteroid drug

167 subjects included for analysis

160 exclusions
- 103 pneumonias
- 28 non-obstructive lung physiology
- 13 COPD without exacerbation
- 9 asthmatic exacerbations
- 4 non-captive patients
- 2 no valid PFT on file
- 1 transferred to hospice for end-of-life

51 resulting exclusions
- 19 no valid PFT on file
- 12 non-obstructive lung physiology
- 11 asthmatic exacerbations
- 3 COPD without exacerbation
- 3 non-captive patients
- 3 inadequate index hospitalization definition

69 resulting exclusions
- systemic corticosteroid received between 1 to 48 hours before CBC measurement