Original Article

Eosinophilia Is a Favorable Marker for Pneumonia in Chronic Obstructive Pulmonary Disease

https://doi.org/10.4046/trd.2023.0174
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2024;87:465-472

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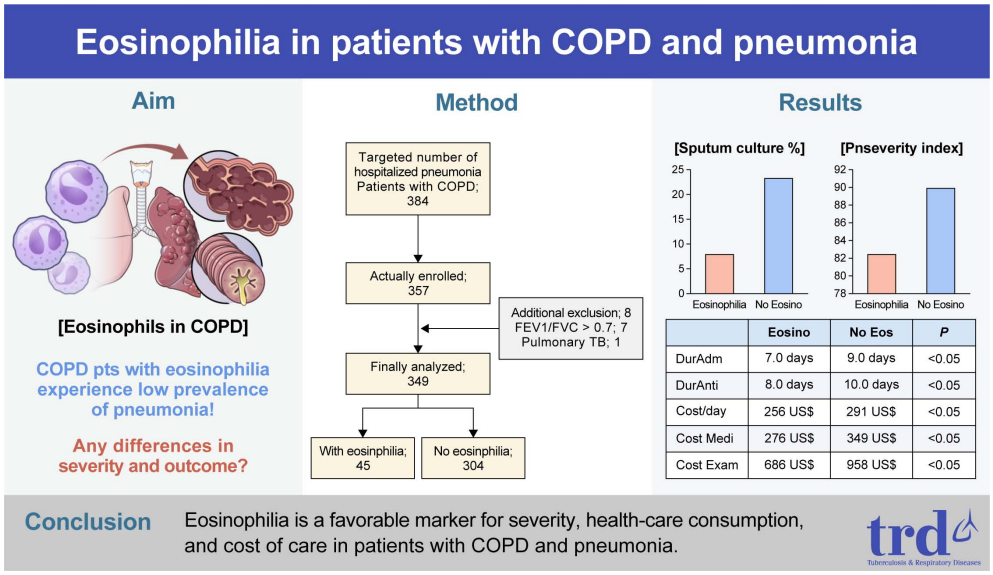
Received Oct. 27, 2023
Revised Jan. 10, 2024
Accepted Apr. 29, 2024
Published online May. 3, 2024



Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) expressing eosinophilia experience slightly fewer episodes of community-acquired pneumonia (CAP), than those without eosinophilia. However, the severity and burden of hospitalized pneumonia patients with COPD involving eosinophilia have not been assessed.

Methods: We evaluated the differences in clinical characteristics between patients with CAP and COPD with or without eosinophilia by a *post hoc* analysis of a prospective, multi-center, cohort study data.

Results: Of 349 CAP patients with COPD, 45 (12.9%) had eosinophilia (blood eosinophil ≥300 cells/μL). Patients with eosinophilia had a lower sputum culture percentile (8.1%

vs. 23.4%, p<0.05), a lower percentile of neutrophils (70.3% vs. 80.2%, p<0.05), reduced C-reactive protein levels (30.6 mg/L vs. 86.6 mg/L, p<0.05), and a lower pneumonia severity index score (82.5 vs. 90.0, p<0.05), than those without eosinophilia. The duration of antibiotic treatment (8.0 days vs. 10.0 days, p<0.05) and hospitalization (7.0 days vs. 9.0 days, p<0.05) were shorter in eosinophilic patients. The cost of medical care per day (256.4 US$ vs. 291.0 US$, p<0.05), cost for the medication (276.4 US$ vs. 349.9 US$, p<0.05), and cost for examination (685.5 US$ vs. 958.1 US$, p<0.05) were lower in patients with eosinophilia than those without eosinophilia.

Conclusion: Eosinophilia serves as a favorable marker for the severity of pneumonia, health-care consumption, and cost of medical care in patients with CAP and COPD.

Keywords: Chronic Obstructive Pulmonary Disease; Pneumonia; Eosinophilia; Severity; Cost

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide[1]. The abnormalities of the airway and/or alveoli in COPD are caused by chronic inflammation which is usually mediated by neutrophils, cytotoxic CD8+ T-lymphocytes, and CD68+ monocytes/macrophages[2]. Eosinophils are important mediators of inflammation in asthma, and the eosinophil count has been used to differentiate between asthma and COPD[3]. On the other hand, in some patients with COPD, eosinophils seem to play a significant role in airway and parenchymal inflammation[4,5]. Studies have indicated that approximately a third of stable COPD patients have evidence of eosinophilic inflammation[6,7]. Patients with COPD who demonstrate peripheral blood eosinophilia respond favorably to systemic corticosteroids for the treatment of exacerbation. Additionally, inhaled corticosteroids (ICSs) are more effective in the prevention of acute exacerbation of COPD (AECOPD) in the aforementioned patients[8]. However, ICSs are also associated with side effects, such as dysphonia, candidiasis, and a small increase in the frequency of pneumonia[9]. In particular, the increase in the risk of pneumonia is a burden to patients with COPD, because their risk of pneumonia is higher than that of the general population[10]. On the other hand, a large retrospective study demonstrated that COPD patients with a blood eosinophil count of ≥2% had slightly fewer episodes of pneumonia than those with less than 2% of eosinophilia, regardless of ICS treatment[11]. The authors speculated that the antimicrobial defense role of eosinophils might have helped clear the lungs of infections, before progressing to pneumonia. In contrast, another study showed that in individuals with COPD and forced expiratory volume in 1 second (FEV_1) <50%, eosinophil count ≥0.34×10^9 cells/L was associated with high risk of hospitalization due to pneumonia[12]. The role of eosinophils in the development and progression of pneumonia in patients with COPD requires further elucidation.

We performed a *post hoc* analysis of a prospective, multi-center, cohort study conducted at seven university-affiliated hospitals to define the serotype-specific prevalence of pneumococcal pneumonia. We evaluated the differences in clinical characteristics of COPD patients with and without eosinophilia, all of whom were hospitalized for the treatment of community-acquired pneumonia (CAP).

Materials and Methods

1. Objectives of the study

The aim of the present study was to elucidate the role of eosinophils in patients with COPD who were hospitalized due to CAP. The primary objective of this study was to identify differences in the severity and outcomes of patients with CAP and COPD depending on the presence of eosinophilia.

2. Definition of eosinophilia

We used the data of complete blood cell count for the calculation of eosinophil count on the day of hospitalization. Eosinophilia was defined as the eosinophil count in blood ≥300 cells/μL, which was calculated by multiplying the total leukocyte count by the percentage of eosinophils[13].

3. A prospective, cohort data for COPD patients hospitalized due to CAP

We had conducted a prospective, multi-center, cohort study of patients with COPD admitted for CAP. The primary objective was to identify the serotype-specific prevalence of *Streptococcus pneumonia*[14]. Seven university-affiliated hospitals participated in the study, which was conducted between May 2, 2017, and February 2, 2020.

4. Institutional Review Board approval and informed consent

This study was approved by the Institutional Review Board (IRB) of each participating hospital. The IRB number of the representative hospital, Chung-Ang University Hospital, is CAUH 1601-001-254. Informed consent was obtained from all participants. Data were collected from the seven participating institutions using a web-based registration program (http://project.swu.ac.kr/copdcap).

5. Inclusion criteria for COPD and CAP

The inclusion criteria for COPD were (1) male or female >40 years; (2) either current or ex-smokers with smoking history ≥10 pack-years; (3) FEV_1/forced vital capacity (FVC) ratio (post-bronchodilator) less than 0.7; (4) no other chest radiologic abnormalities that could have caused the obstructive pattern abnormality in spirometry; and (5) no history of bronchial asthma. The classification of the COPD group was determined by the 2016 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, which was updated in 2023[2]. The inclusion criteria for CAP were adopted from a published article with some modifications, which were new infiltrations on chest radiography with at least one of the following three criteria: (1) body temperature <36°C or ≥38.0°C; (2) white blood cell count <5,000/mm^3 or >10,000/mm^3; or (3) cough with/or without sputum[15].

6. Identification of pathogens

Methods of pathogen identification of pneumonia included sputum gram staining/culture, with or without two sets of blood cultures. The serotype-specific urine antigen detection (SS-UAD) assay for pneumococci was performed at the Pfizer Central Lab (Manhattan, NY, USA) by a standardized protocol[16].

7. Calculation of the required number of COPD patients hospitalized for CAP

Our previous study described in detail the calculation of the required number of patients with COPD hospitalized for CAP[14]. In brief, we anticipated the difference in the confusion, uremia, respiratory rate, blood pressure, and age ≥65 (CURB-65) score between pneumococcal conjugate vaccine 13 recipients and non-recipients to be one point, and assumed the prevalence of pneumococcal pneumonia to be 30%. The total number required was 384, with an allowance of 10% possible data loss.

8. Other clinical characteristics evaluated

We compared the pneumonia severity index (PSI), CURB-65 score, acute-phase reactants, cost of care, duration of admission, intensive care unit (ICU) admission rate, and mortality rate between the two groups. The outcome was determined at the time of hospital discharge. We considered the patients to be "improved" when they were still alive, and had not been transferred to other institutions for further treatment.

9. Statistical analysis

Continuous variables were evaluated using non-normally distributed analysis. Continuous variables were presented as medians (interquartile range), and categorical data as frequencies and percentiles. Intergroup comparisons of continuous variables and categorical data between patients with and without eosinophilia were performed using the Mann-Whitney test, Chi-square test, and Fisher's exact test, respectively. The results were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). p-values less than 0.05 were considered significant.

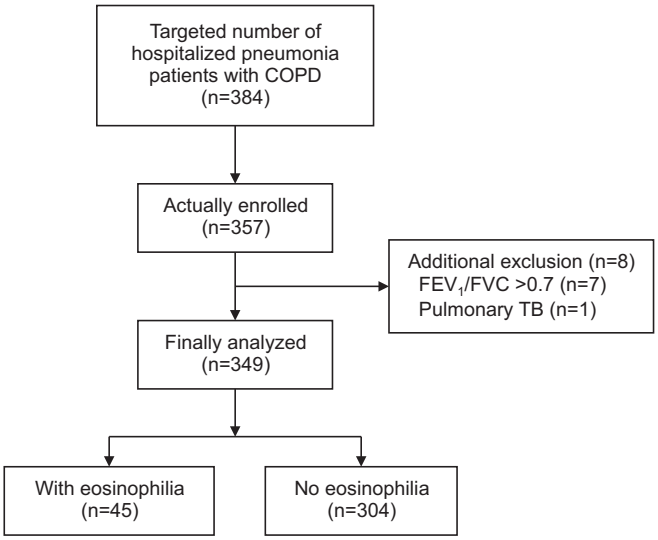


Figure 1. Flow sheet for the enrollment of participants. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TB: tuberculosis.

Results

1. Number of enrolled patients

The target number of recruitments was 384, and the minimum required number of enrollments was 346. Due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, enrollment was closed earlier than scheduled. The total number of recruits was 357 (92.9% of the target). Eight participants were additionally excluded (seven due to $FEV_1/FVC \geq 0.7$, and one was diagnosed with tuberculosis), and 349 patients were finally selected for the analysis, surpassing the minimum number of requirements (Figure 1).

2. Differences in the clinical characteristics of COPD between patients with and without eosinophilia

Of the 349 patients, 45 (12.9%) had eosinophilia. Patients with eosinophilia exhibited a trend toward a lower life-long smoking history (30 pack-year vs. 40 pack-year, p=0.07), than those without eosinophilia. However, no significant differences in other parameters, such as age, sex, pulmonary function test results, COPD assessment test (CAT), modified Medical Research Council (mMRC), or the number of acute exacerbations within 1 year, were observed. The use of ICSs did not differ between the two groups (46.7% with eosinophilia vs. 47.4% without eosinophilia) (Table 1).

3. Differences in the clinical characteristics of pneumonia between patients with or without eosinophilia

Patients with eosinophilia showed lower PSI scores, lower neutrophil percentiles, and lower C-reactive protein (CRP), than those without eosinophilia. Furthermore, patients with eosinophilia also shoed lower sputum culture rate, compared to those without eosinophilia. The duration of antibiotic treatment and hospitalization was shorter for patients with eosinophilia,

Table 1. Differences in clinical characteristics of COPD between patients with or without eosinophilia

Characteristic	COPD without eosinophilia	COPD with eosinophilia	p-value
Number	304	45	
Male sex	289 (95.1)	43 (95.6)	1.000
Age, yr	77.0 (71.0–82.0)	75.0 (70.0–81.0)	0.351
Smoking			
Status (current/ex-smokers)	63 (20.7)/241 (79.3)	9 (20.0)/36 (80.0)	1.000
Amount, life-long, pack-yr	40.0 (20.0–55.0)	30.0 (20.0–40.0)	0.070
Pulmonary function			
FEV_1, % predicted	55.0 (39.0–69.0)	59.0 (42.0–70.0)	0.404
FVC, % predicted	73.0 (62.0–85.0)	79.0 (61.0–89.0)	0.246
FEV_1/FVC, postbronchodilation, %	52.0 (37.7–62.9)	52.4 (41.8–60.0)	0.839
Dyspnea index			
mMRC	3.0 (2.0–3.0)	2.0 (2.0–3.0)	0.300
COPD assessment test	25.0 (17.0–30.0)	23.0 (18.0–29.0)	0.480
Acute exacerbation within 1 year (no/one/two or more)	176 (57.9)/80 (26.3)/48 (15.8)	30 (66.7)/8 (17.8)/7 (15.6)	0.439
COPD group (A/B/C/D)	15 (4.9)/163 (53.6)/ 7 (2.3)/119 (39.1)	5 (11.1)/25 (55.6)/ 2 (4.4)/13 (28.9)	0.219
Maintenance therapy			
Inhaled corticosteroids	144 (47.4)	21 (46.7)	1.000
Long acting beta 2 agonists	223 (73.4)	33 (73.3)	1.000
Long acting muscarinic antagonists	193 (63.5)	32 (71.1)	0.404
Home oxygen therapy	24 (7.9)	4 (8.9)	0.770

Values are presented as number (%) or median (interquartile range).
COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council.

Table 2. Differences in clinical characteristics of pneumonia between patients with or without eosinophilia

Characteristic	COPD without eosinophilia	COPD with eosinophilia	p-value
Number	304	45	
Severity of pneumonia			
PSI classes (I/II/III/IV/V), %	0.7/10.6/39.3/40.6/8.9	2.3/22.7/38.6/31.8/4.5	0.112
PSI score	90.0 (78.0–107.5)	82.5 (70.5–97.0)	0.020*
CURB-65	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.998
Radiologic findings			
Bilateral pneumonia	118 (39.5)	17 (37.8)	0.871
Pleural effusion, accompanied	49 (18.6)	9 (24.3)	0.412
Acute-phase reactants			
Total white cell counts, /μL	10,310.0 (7,825.0–13,545.0)	11,100.0 (8,600.0–12,920.0)	0.372
Neutrophils, %	80.2 (74.5–86.0)	70.3 (60.8–77.4)	<0.001*
C-reactive protein, mg/L	86.6 (27.7–160.3)	30.6 (6.2–65.9)	0.001*
Microbiologic results			
Sputum culture	59 (23.4)	3 (8.1)	0.033*
Pseudomonas aeruginosa	15 (5.7)	0	0.230
Haemophilus influenzae	12 (4.6)	0	0.373
Klebsiella pneumonia	7 (2.7)	0	0.603
Streptococcus pneumoniae	3 (1.1)	2 (5.4)	0.118
Others	5 (1.9)	0	1.000
Serotype-specific urine antigen detection test	29 (9.5)	3 (6.8)	0.781
22F/6A/6B/10A/11A/3/19A/others	4/4/4/2/3/3/3/7	0/0/0/1/0/0/0/2	0.441
Treatment			
Combination of antibiotics	197 (64.8)	30 (66.7)	0.474
Duration of antibiotics treatment, day	10.0 (7.0–14.0)	8.0 (6.0–11.0)	0.019*
Administration of systemic corticosteroid	156 (51.3)	22 (48.9)	0.442
Duration of steroid therapy in users, day	7.0 (5.0–13.0)	5.5 (4.0–11.0)	0.187
Hospital course			
Duration of hospitalization, day	9.0 (6.5–14.0)	7.0 (6.0–10.0)	0.023
Died	13 (4.3)	0	0.161
Admission to ICU	14 (4.6)	1 (2.2)	0.462
Duration of ICU admission, day	4.5 (3.0–15.0)	3.0 (3.0–3.0)	
Medical costs for hospitalization, US$			
Total cost	2,636.3 (1,466.6–4,164.9)	1,960.7 (1,333.5–2,954.3)	0.103
Cost per day of hospitalization	291.0 (214.9–368.9)	256.4 (191.9–344.6)	0.015*
Cost for medication	343.9 (221.9–702.9)	276.4 (171.5–437.7)	0.020*
Cost for examination	958.1 (565.5–1,704.3)	685.5 (487.1–885.0)	0.002*
Cost for others	1,165.2 (647.2–2,060.5)	852.0 (646.2–1,712.0)	0.096
Outcome (improved/died/others)	276 (91.7)/13 (4.3)/12 (4.0)	43 (97.7)/0/1 (2.3)	0.309

Values are presented as median (interquartile range) or number (%).
*p<0.05.
COPD: chronic obstructive pulmonary disease; PSI: pneumonia severity index; CURB-65: confusion, uremia, respiratory rate, blood pressure, and age ≥65; ICU: intensive care unit.

than for those without it. The cost of medical care per day of hospitalization, medication, and examination was lower for patients with eosinophilia (Table 2).

4. The risk of mortality and ICU admission

One patient with eosinophilia was transferred to the ICU. However, no significant difference in ICU admission rates between patients with or without eosinophilia was observed. As none of the patients with eosinophilia died, performing a logistic regression analysis for mortality associated with eosinophilia proved impossible. Mortality risk was high in patients with hypertension and malignancy.

Discussion

COPD is the comorbid condition that is associated with the highest incidence of hospitalization due to CAP (8.9 times higher than the control)[17]. In the present study, we evaluated the differences in the clinical characteristics of patients with COPD who were hospitalized because of CAP depending on the presence of eosinophilia. We performed a *post hoc* analysis of a prospective, multi-center, cohort study that we had previously conducted at seven university-affiliated hospitals to define the serotype-specific prevalence of pneumococcal pneumonia[14].

We observed a significant difference in some clinical features of pneumonia, depending on the presence of eosinophilia. The percentile of sputum culture was lower in eosinophilic patients, than in those without eosinophilia (Table 2). The sputum gram stain and culture is one of the most important diagnostic tools for the identification of pathogens in CAP. Among other factors, the burden of pathogens influences positive results for sputum culture[18]. The difference in the sputum culture rate between patients with and without eosinophilia, at least in part, could have derived from the clearing effect of infecting pathogens by eosinophils. The decreased burden of infectious pathogens in eosinophilic patients was reflected in the lowering of pneumonia severity and acute-phase reactants. Patients with eosinophilia showed lower PSI scores, lower neutrophil percentiles, and lower CRP levels, than those without eosinophilia (Table 2). The duration of antibiotic treatment and hospitalization were shorter in eosinophilic patients than for those without eosinophilia. Additionally, the cost of care was lower for patients with eosinophilia. The cost of medical care per day, cost of medication, and cost of examination were lower in eosinophilic patients (Table 2). As a major cause of morbidity and mortality worldwide, CAP is associated with excessive health-care consumption and cost. To the best of our knowledge, the present study is the first to provide information regarding the benefits of eosinophilia in terms of healthcare utilization and the cost of medical care in patients with COPD hospitalized for CAP.

No significant difference was identified in the clinical characteristics of COPD between patients with and without eosinophilia, including CAT, mMRC scores, and the number of acute exacerbations within 1 year. We expected patients with COPD and eosinophilia to use ICS more frequently than those without eosinophilia because COPD patients with eosinophilia (blood eosinophils ≥300/μL) experience frequent exacerbation, which requires ICS inhalation[19,20]. The percentile of patients with frequent exacerbation (≥2 within a year) did not differ between patients with and without eosinophilia, which might explain the lack of difference in ICS usage between the two groups (Table 1).

In large clinical trials for the treatment of COPD, GOLD groups B and D comprised the majority of patients[19,21]. In accordance, GOLD COPD group B was the most common, followed by group D in the present study (Table 1). Patients with CAP with PSI class III or higher are usually recommended for hospitalization[22]. In our study, most of the participants were classified as PSI class III or higher (Table 2). Thus, the COPD with CAP population in the present study can be considered representative of a real-world, standard population.

Eosinophils are white blood cells of the granulocytic lineage, and are involved in a wide array of host immune responses to infection, tissue remodeling, and the maintenance of other immune cells[23,24]. Although a high level of eosinophils (≥1,500/μL) can damage tissues, an adequate level of eosinophils is important for protection against infection[25]. For example, eosinophils behaved as a protective cell in patients with ventilator-associated pneumonia caused by *Staphylococcus aureus*[26]. Bacterial pneumonia is usually accompanied by an eosinopenic response, partly due to the activation of endogenous glucocorticoid production. For this reason, eosinopenia was suggested to be a good diagnostic marker for distinguishing between non-infection and infection[27]. In addition, eosinopenia was a reliable marker of severe disease and unfavorable outcome in pneumonia associated with SARS-CoV-2 and in hospitalized AECOPD patients with CAP[28,29]. The authors suggested the eosinophil count at admission as a prognostic marker of mortality in pneumonia. This is consistent with our finding that eosinophilia was associated with the decrease in the severity of pneumonia and acute-phase reactants. No deaths were reported in patients with eosinophilia, compared to the 13 deaths in

patients without eosinophilia, although a small number of patients with eosinophilia did not show statistical significance (Table 2).

The present study has some limitations. The percentage of eosinophils was used to define eosinophilia (≥300/μL). However, peripheral blood eosinophilia is better defined by the absolute eosinophil count, than by the percentage of eosinophils. In addition, although the minimum requirement number for analysis was achieved, the target number of 384 was not reached, due to the SARS-CoV-2 pandemic. About 51% of all patients received systemic corticosteroid during hospitalization for pneumonia, for 5 to 7 days, maybe for the treatment of accompanying AECOPD. Although the statistics of percentage and duration did not differ in statistics, the favorable outcome of pneumonia in eosinophilic patients may be, in part, related to the effect of systemic corticosteroid on the accompanying AECOPD. Lastly, we were unable to prove the beneficial effects of eosinophilia on the mortality rate, because this study was not able to compare mortality between eosinophilia and non-eosinophilia groups.

Despite these limitations, we were able to find that eosinophilia serves as a favorable marker in assessing the severity of pneumonia, health-utility consumption, and cost of care in hospitalized CAP patients with COPD.

Authors' Contributions

Conceptualization: Kang MJ. Methodology: Kim JY. Formal analysis: Jung JW, Park JS. Data curation: Kim DK, Choi H, Cho YJ, Jang SH, Lee CH, Oh YM, Park JS. Funding acquisition: Kim JY. Investigation: Kim DK, Choi H, Cho YJ, Jang SH, Lee CH, Oh YM, Park JS. Writing - original draft preparation: Gu KM, Jung JW. Writing - review and editing: Kim DK, Choi H, Cho YJ, Jang SH, Lee CH, Oh YM. Approval of final manuscript: all authors.

Conflicts of Interest

Deog Kyeom Kim, Young-Jae Cho, and Chang-Hoon Lee are editors of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

This study was supported by Pfizer Grant WI221325.

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