



Role of Eosinophil Count and Percentage in Chronic Obstructive Pulmonary Disease Exacerbation: A Retrospective Observational Study

Kronik Obstrüktif Akciğer Hastalığı Alevlenmesinde Eozinofil Sayısı ve Yüzdesinin Rolü: Bir Gözlemsel Retrospektif Çalışma

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ABSTRACT

Aim: To reveal the role of eosinophil count and percentage evaluated at the time of presentation in patients hospitalized with the exacerbation of chronic obstructive pulmonary disease (COPD).

Material and Methods: In this study, the data of patients with a diagnosis of the exacerbation of COPD, who presented to the emergency department, and admitted to the general internal medicine ward, were retrospectively analyzed. The relationship of eosinophil count and ratios with the length of hospital stay and intensive care requirement was investigated. The Spearman correlation analysis was used for investigating correlation between parameters and outcome.

Results: Of the study population, 39.7% were female and 60.3% were male. The ages of the participants ranged from 25 to 94 years, with a median value of 76 years. There was no significant correlation between the length of stay in ward and eosinophil count and percentage ($\rho=-0.148$, $p=0.066$ and $p=0.074$, $\rho=-0.143$, respectively) (Spearman correlation test). The group admitted to the intensive care unit had a significantly higher eosinophil count and percentage of eosinophils than the group that did not require intensive care (0.81 (Inter Quarter Range (IQR):0.41-1.31) versus 1.32 (IQR:0.83-1.43) $p=0.042$ and 1.0 (IQR:0.81-1.21) versus 1.42 (IQR:1.02-1.64), $p=0.018$, respectively) (Mann Whitney U test).

Conclusion: There was no correlation between a high eosinophil count and percentage and the length of hospital stay. However, the number and percentage of eosinophils were significantly higher among the patients requiring intensive care.

Keywords: Chronic obstructive pulmonary disease, Length of hospital stay, Eosinophil, Admission to the intensive care unit

ÖZ

Amaç: Kronik obstrüktif akciğer hastalığı (KOAH) alevlenmesi ile hastaneye yatırılan hastalarda başvuru anında değerlendirilen eozinofil sayısı ve yüzdesinin rolünü ortaya çıkarmak.

Gereç ve Yöntemler: Bu çalışmada, acil servise başvuran ve genel dahiliye servisine yatırılan KOAH alevlenmesi olan 156 hastanın verileri geriye dönük olarak incelendi. Eozinofil sayısı ve oranlarının hastanede kalış süresi ve yoğun bakım gereksinimi ile ilişkisi araştırıldı. Spearman korelasyon testi ile sonlanım ile parametreler arası korelasyon araştırıldı.



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Bulgular: Çalışma popülasyonunun, %39,7'si kadın ve %60,3'ü erkek idi. Olguların yaşları 25 ile 94 arasında değişmekte olup, medyan değeri 76 idi. Serviste kalış süresi ile eozinofil sayısı ve yüzdesi arasında anlamlı bir ilişki yoktu (sırasıyla $\rho=-0,148$, $p=0,066$ ve $p=0,074$, $\rho=-0,143$) (Spearman korelasyon testi). Yoğun bakım ünitesine kabul edilen grup, yoğun bakım gerektirmeyen gruba göre önemli ölçüde daha yüksek eozinofil sayısına ve eozinofil yüzdesine sahipti (0,81(Çeyrekler arası aralık (ÇAA):0,41-1,31)' e karşı 1,32 (ÇAA:0,83-1,43) $p=0,042$ ve 1,0 (ÇAA:0,81-1,21)'e karşı 1,42 (ÇAA:1,02-1,64), $p=0,018$, sırasıyla).

Sonuç: Yüksek eozinofil sayısı ve yüzdesi ile hastanede kalış süresi arasında ilişki yoktu. Ancak yoğun bakıma ihtiyacı olan hastalarda eozinofil sayısı ve yüzdesi anlamlı olarak daha yüksekti.

Anahtar Sözcükler: Kronik obstrüktif akciğer hastalığı, Hastanede kalış süresi, Eozinofil, Yoğun bakım ünitesi yatışı

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease associated with a recurrent chronic inflammatory response triggered by harmful gases and environmental particles and personal risk factors and causes progressive airway obstruction and airflow limitation in the lungs. This chronic inflammation also has systemic features and leads to physiological and pathological changes in the airway, which can be permanent (1). Today, COPD has become the third cause of death across the world and is responsible for 5.6% of all deaths. COPD is responsible for early mortality, high death rates, and a serious financial burden on the health system (2).

In recent years, it has been shown that not only the lung involvement, but also systemic inflammation is present in COPD (3). In COPD, inflammation occurs in all central and peripheral airways (4). The role of eosinophils in the pathogenesis of COPD is not yet fully known. However, most studies have suggested that there is an increase in the number of eosinophils in the airway during an exacerbation (5,6).

In this study, we aimed to reveal the relationship between eosinophil count and percentage COPD exacerbation using patients' intensive care and ward hospitalization and hospital stay.

MATERIAL and METHODS

Study design and population

This research was designed as a single-center retrospective observational study. Adult patients who presented to the emergency department of Okmeydani Training and Research Hospital, a tertiary care center, between January 1, 2015, and December 31, 2015, and were admitted to the internal medicine ward with the diagnosis of COPD exacerbation were included in the study. Patients with a history of COPD and cardinal signs of acute exacerbations of COPD (breathlessness, cough, and wheezing, with increased sputum production and purulence) were considered as acute COPD exacerbation. The criteria for admission to the internal medicine ward were persistent symptoms despite six hours of treatment in the emergency department, severe

increase in dyspnea, severe comorbidities, newly developed arrhythmia, and severe COPD (with increased oxygen support need) in the history.

In addition, increased dyspnea, confusion, lethargy, coma, worsening hypoxia ($\text{PaO}_2 < 50$ mmHg or hypoxia not regressed despite supplement oxygen treatment with nasal cannula and mask), severe hypercapnia ($\text{PaCO}_2 > 70$ mmHg), acidosis (despite treatment) were used as hospitalization criteria in study center. Patients who needed noninvasive or invasive mechanical ventilation were transferred to the intensive care unit.

Patients who were referred to another center during their hospital stay and those with missing data were excluded from the study (Figure 1).

Data Collection

The patients' demographic data, length of hospital stay, comorbid diseases, leukocyte counts, eosinophil percentages, eosinophil counts, C-reactive protein (CRP) levels, and hospital discharge status were obtained from the Hospital Information Management by a researcher (EG) between April 1, 2016, and May 31, 2016. Comorbidities were grouped as hypertension, congestive heart failure, coronary artery disease, chronic renal failure, malignancy, and other diseases. Alzheimer's disease, cerebrovascular disease and chronic liver disease were recorded as other diseases. For the laboratory parameters of the patients, the results of the tests performed at the time of presentation to the emergency department were used.

Blood Tests

Blood samples were obtained on admission from the antebrachial vein. Hemogram was tested with an Automated Blood Cell Analyzer (Pentra120 Retic Hematology Analysis Device, ABX, Montpellier, France). Eosinophil count and percentage results were obtained from the hemogram test.

Ethical Approval

The necessary permission for the study was obtained from the Ethics Committee of the hospital (approval date: 30.03.2016, number: 21761). Since the data evaluated in the study did not include any personal information of the

patients and the study had a retrospective design, informed consent was not obtained from the patients within the knowledge of the ethics committee.

Statistical Analysis

We used IBM SPSS Statistics for Mac, NY, IBM Corp, Version 22.0 was used for data analyses. Mean, standard deviation, median, lowest, highest, frequency, and percentage values were used as descriptive statistics, and the distribution of variables was checked with the Kolmogorov-Smirnov test. The patients were grouped as eosinophilic ($\geq 2\%$) and non-eosinophilic ($< 2\%$) according to the percentage of eosinophils. The Mann-Whitney U test was used in the analysis of quantitative data. The chi-square test was used in the analysis of qualitative data. The Spearman correlation analysis was used in the correlation analysis. A p value of < 0.05 was considered statistically significant. The study population was determined as 122 with Jamovi (Version 1.6.21.0; The Jamovi Project, 2020; R Core Team, 2019) by taking impact size 0.6, $\alpha = 0.05$, power $(1 - \beta) = 0.95$ at a confidence level of 95%.

RESULTS

This study was conducted with a total of 156 cases, 39.7% female and 60.3% male. The ages of the participants ranged from 25 to 94 years, with a median value of 76 years. Of the cases, 89.7% (n=140) were followed up in the internal medicine ward and 10.3% (n=16) in the intensive care unit. The length of ward stay ranged from 1 to 22 days, with a median of 7 days, and the length of intensive care stay ranged from 1 to 14 days, with a median of 4 days. Table 1 presents demographics and laboratory parameters of the study population.

There was a history of comorbid diseases in 78.2% of the cases, and the distribution of comorbidities was as follows: hypertension, 55.1%; congestive heart failure, 32.7%; coronary artery disease, 30.8%; chronic renal failure, 12.2%; malignancy, 10.9%; and other diseases, 10.9%. Table 2 shows the comparisons of the patients' demographic data and comorbidities according to the presence of eosinophilia.

Table 1: Demographics and laboratory parameters of the study population.

Variables	Findings
Age (years)*	76 (42-79)
Gender	Male n (%)
	Female n (%)
C-reactive protein (mg/dL) *	77.3 (26.8-304.1)
Lymphocyte count (μL) *	12.55(6.65-43.7)
Eosinophil count (μL) *	0.04 (0.02-0.9)
Eosinophil percentage (%) *	0.4 (0.2-0.8)

*Median (Inter Quarter Range)

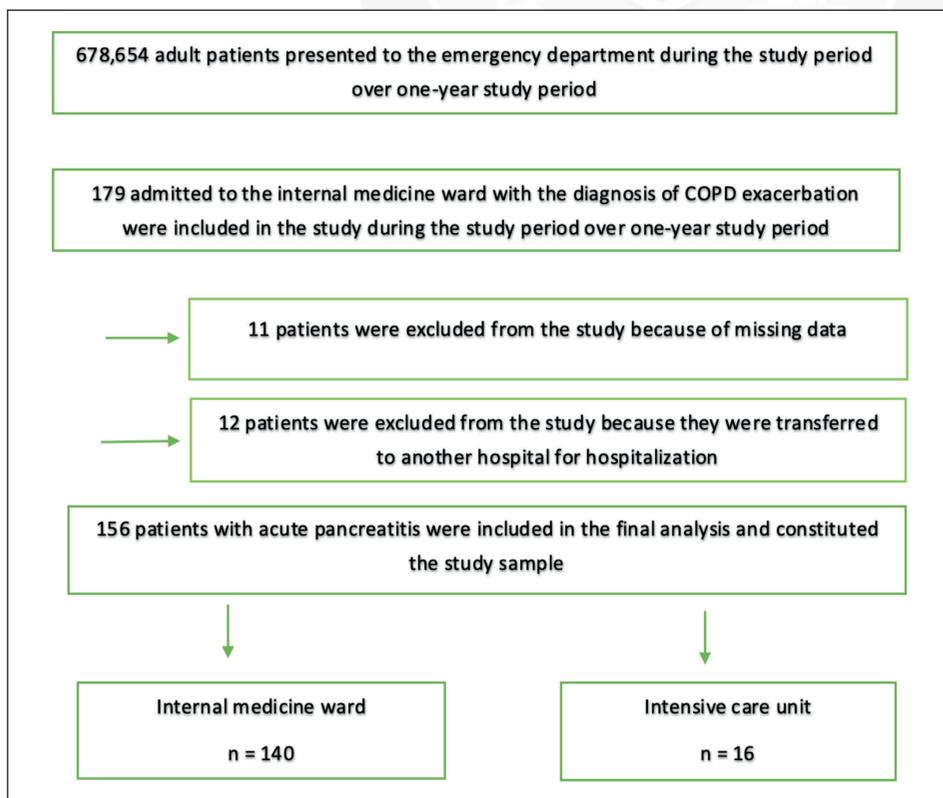


Figure 1: Flowchart of the study.

Table 2: Distribution of comorbidities in non-eosinophilic and eosinophilic groups.

Comorbidities *	Eosinophil percentage <2%	Eosinophil percentage ≥2%	P
Presence of comorbid disease	99 (63.4)	23 (14.7)	0.577
Diabetes mellitus	37 (23.7)	7 (4.4)	0.677
Hypertension	68 (43.5)	18 (11.5)	0.282
Congestive heart failure	41 (26.2)	10 (6.4)	0.707
Chronic renal failure	14 (8.9)	5 (3.2)	0.311
Coronary artery disease	38 (24.3)	10 (6.4)	0.531
Malignancy	15 (9.6)	2 (1.2)	0.482

*Data are presented as n (%)

The peripheral blood CRP values of the cases ranged from 2.7 to 501.4 mg/dL, with a median of 77.3 mg/dL. The number of leukocyte count varied between 0.75 / μ L and 53.62/ μ L, the median value was 12.55/ μ L. The percentage of eosinophils ranged from 0.1 and 10%, with a median of 0.4, and eosinophil count from 0.01 / μ L to 1.11/ μ L, with a median of 0.04 / μ L.

There was a significant positive correlation between the length of ward stay and CRP ($\rho=0.213$ $p=0.008$). No significant correlation was observed between the length of ward stay and leukocyte count, percentage of eosinophils, and eosinophil count ($\rho=0.025$, $p=0.756$; $r=-0.148$, $p=0.066$; and $p=0.074$, $\rho=-0.143$, respectively) (Spearman's correlation test).

The group admitted to the intensive care unit had a significantly higher eosinophil count and percentage of eosinophils than the group that did not require intensive care (0.81(IQR: 0.41-1.31 versus 1.32(IQR:0.83-1.43) $p=0.042$ and 1.0 (IQR: 0.81-1.21 versus 1.42(IQR:1.02-1.64), $p=0.018$, respectively) (Mann-Whitney U test).

DISCUSSION

This study investigated the relationship between eosinophil response and COPD exacerbation. Although a high eosinophil level did not have a significant correlation with the length of hospital stay, eosinophils were significantly higher in the group that required intensive care.

Although COPD exacerbations are often neutrophilic, approximately 10-25% are eosinophilic. Eosinophilia in blood is correlated with eosinophilic airway inflammation (7). In some studies, an increased blood eosinophil level has been found to be associated with response to inhaled steroids (8). In the treatment of COPD exacerbations, clinical improvement has been observed in patients with blood eosinophilia following oral corticosteroid therapy (9). High sputum and blood eosinophil counts in patients with COPD are associated with increased corticosteroid response (10). In a retrospective observational cohort study conducted with 1,704 patients hospitalized due to COPD exacerbation at a

tertiary hospital, Duman et al. divided the patients according to their peripheral blood eosinophilia levels into two groups as eosinophilic (>2%) and non-eosinophilic $\leq 2\%$. The authors found that six-month mortality was similar between the eosinophilic and non-eosinophilic groups (14.2% and 15.2%, respectively), but the length of hospital stay was longer and readmission rate was higher in the non-eosinophilic group (11). Couillard et al.'s study, published in 2017 in the journal *Chest*, was also prepared with similar methodology and prepared the groups in a similar way. Couillard et al. showed that eosinophilia was associated with an increased risk of 12-month COPD-related readmission, an increased risk of 12-month all-cause readmission, and a shorter time to first COPD-related readmission. On the other hand, they reported that the length of stay was not statistically different between eosinophilic and non-eosinophilic patients (12). The results of the present study were also in line with the literature.

In a study conducted by Saltürk et al., COPD cases with a peripheral eosinophil percentage of 2% and above were discharged from the intensive care unit with a better outcome, and the authors attributed this to a better steroid and antibiotic response (13). In the ECLIPSE cohort study, eosinophilia was found in 37% of patients with COPD, and 10% of these patients required intensive care (14). It has been shown that all mortality cases among patients with peripheral eosinophilia are related to airway diseases when compared to healthy individuals (15). In our study, the eosinophil level was compared according to the requirement of intensive care, and it was found to be significantly higher in those requiring intensive care. Although the rates of pneumonia, sepsis, and mortality have been reported to be more common in non-eosinophilic patients (16), we consider that our finding was related to our non-eosinophilic patients developing fewer complications and our sample also including patients who were admitted to the ward without intensive care requirement.

In the study that Vogelmeier et al. analyzed the data of more than 150,000 exacerbation patients, they showed that small

proportion of COPD patients had frequent exacerbations and eosinophil count ≥ 300 cells/ μ L. They recommended that eosinophil count should be considered while making treatment decisions (17). According to current literature, eosinophils have gained a considerable interest as one of the important factors involved in COPD pathogenesis and as a possible marker (17-19). A plausible explanation for this may be that eosinophilic inflammation is effective in COPD exacerbation in some patients (18,19). It is still mainly unknown why only a certain proportion of patients with COPD have eosinophilic airway inflammation and also, we do not know how eosinophils impact the course of the disease (17).

Our study had several limitations, with the major being the retrospective design. Due to the retrospective design, factors such as etiology of COPD, previous treatments and drugs used that may affect the eosinophil count were not evaluated. The second limitation was the observational design of our study. During the study, it was observed that clinicians used blood gas analysis, peripheral oxygen saturation and clinical status in the management of patients. It was observed that pulmonary function tests were used in clinical decision making in very few (6 patients) patients. Due to the small number of recorded pulmonary function test results and insufficient number for statistical analysis, they were not presented. A third limitation was that we did not have a control group that included COPD patients without exacerbation or that the number and percentage of eosinophils before exacerbation of existing patients were not included in our study. Furthermore, the limited sample size and single-center nature of the study are important factors affecting the generalizability of our results. We suggest that our study results be validated in future multicenter studies to be conducted with larger populations.

In conclusion, according to the results of our study, there was no correlation between a high eosinophil count and percentage and the length of hospital stay. However, the number and percentage of eosinophils were significantly higher among the patients that required intensive care. Our study supports measurement of eosinophils in patients with frequent COPD exacerbations.

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Author Contributions

All authors contributed equally to study concept and design, data acquisition, data analysis and interpretation, manuscript preparation, and critical revision. All authors have seen and approved the manuscript.

Conflicts of Interest

None

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Ethical Approval

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Review Process

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