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Comparison of Hematological Phenotypes of COPD Exacerbations in Hospitalized Patients after Emergency Department Admission

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ABSTRACT

Introduction: The aging of the communities and higher pollution levels increases chronic obstructive pulmonary disease (COPD) burden and are projected to rise in the number of the patients with COPD and its exacerbations. There is little evidence for short-term outcomes of COPD exacerbations of the biomarkers that are easily available. Biomarker-based hematological phenotype classification is useful and effective for outcome predictions. This study evaluates the relationship between the phenotypes of patients with COPD who presented in the emergency department due to COPD exacerbation and admitted to the hospital have been evaluated.

Methods: All hospitalized patients older than 18 years old who presented to the emergency department due to the COPD exacerbation between July 2018 and July 2020 were included in the study. The patient data evaluated retrospectively for vital parameters, biomarker results, and mortality rates. The primary outcome measure of the study was determined as the thirty-day mortality rates of the groups. Secondary outcome measures were determined by comparing the differences between the trophilic and eosinophilic groups.

Results: One hundred forty-three patients were included in the study. The mean age of the patients was 74.8±10.6. One hundred and two of the patients (71.3%) were male. The neutrophilic and eosinophilic groups had a statistically significant difference in body temperature and heart rate (p=0.018 and p=0.001, respectively). In contrast, no significant difference was observed for systolic blood pressure, diastolic blood pressure, and sPO_2 (p=0.400, p=0.564, p=0.248, respectively). One month mortality of the neutrophilic and eosinophilic groups were 15.9% and 3.2%, respectively. Blood neutrophil count levels have been assigned in 3 different groups for mortality and compared which had no significant difference for 1,3 and 12-month mortality (p=0.142, 0.280, 0.351 respectively).

Conclusion: The patients admitted to the hospital via the emergency department had no mortality difference between different neutrophil levels or hematologic phenotypes. Further studies are required to assess cutoff values of blood neutrophil counts as an independent biomarker.

Keywords: COPD, COPD exacerbation, blood neutrophil count, and blood eosinophil count

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and most of these deaths occur in low and middle-income countries (1). The aging of the communities and higher pollution levels increases the COPD burden and are projected to rise the number of COPD patients and its exacerbations (2). Mostly, COPD exacerbations result in presenting to emergency departments which resulted in 2 million emergency department visits annually in the USA in 2016 (3). Furthermore, in the same year, approximately 35% of these patients were hospitalized and the in-hospital mortality rate of the patients with COPD exacerbations was reported as 17% (4). Since the mortality rate is so high, it is important to be able to predict which patients would have unfavorable progress. Spirometry is an essential method for the prediction of patients with COPD (5). However, spirometry is underused in emergency departments (6). Additionally, in the ECLIPSE study, many biomarkers predicted the one-year mortality of the patients but, none of these biomarkers can be used for anticipating the short-time prognosis. Therefore, a test that is used easily for predicting the mortality of patients with COPD is needed.

Accordingly, many biomarkers have been studied for managing COPD exacerbations. It has been reported that blood eosinophil and neutrophil counts might be the predictor of mortality for COPD exacerbations (7,8). Additionally, according to the GOLD report, blood eosinophil count cut-off values might be used to identify the treatment benefits of inhaled

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corticosteroids (5). In contrast, there have been a few research on cut-off values of blood neutrophil counts. It is uncertain what the precise value of blood neutrophil counts for the increased mortality.

We hypothesized that the different phenotypes of COPD exacerbations might be correlated with different mortality rates, and exploring the hospitalized patients' mortality rates might benefit clinicians. This study measured and compared the mortality rates between hematological COPD groups. In this retrospective study, the relationship between the phenotypes of patients with COPD who presented in the emergency department due to COPD exacerbation and were admitted to the hospital have been evaluated.

Methods

Study Design and Settings

This was a single-center, retrospective study. The participants' demographic and clinical data were extracted from electronic medical records of the hospital. The study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital Local Ethics Committee (approval number: 2020-164, date: 14.01.2021).

Selection of Participants

All hospitalized patients older than 18 years old who presented to the emergency department due to COPD exacerbation between July 2018 and July 2020 were included in the study. Pregnant women were excluded from the study.

Because of the retrospective chart review nature of the study, informed consent was exempted after acquiring appropriate institutional ethics and administrative approval.

Study Protocol

Eosinophilic COPD was defined as ≥200 cells/mL or ≥%2 of white blood cell. Neutrophilic COPD was defined as >7100 cells/mL according to our laboratory cut-off values. Blood neutrophil counts were divided into three categories between 2000-7000 cells/mL, between 7000-15000 cells/mL, and more than 15000 cells/mL. The initial blood eosinophil counts and blood neutrophil counts when the patients presented to the emergency department were recorded in predesigned data sheets. Patients' demographics, 1-month, 3-month, and 1-year mortality rates, and whether non-invasive mechanic ventilation (NIMV) or mechanic ventilation were implemented were attained from the hospital database and recorded. Patients with <7100 cells/mL defined as the neutrophilic group while patients with ≥200 cells/mL defined as the eosinophilic group.

Outcome Measures

The primary outcome measure of the study was determined as the thirty-day mortality rates of the groups. Secondary outcome measures were determined by comparing the differences between the neutrophilic and eosinophilic groups.

Statistical Analysis

SPSS 23.0 (IBM Corporation, Armonk, New York, United States) Statistical Software Package was used for data analysis. Descriptive statistics are presented with numbers and percentages for categorical variables. The Kolmogorov-Smirnov test was used to evaluate the normality of distribution. Differences between the categorical variables in the independent groups were tested with chi-square analysis. Mann-Whitney U test was used to compare variables between two independent groups. The statistical significance was accepted as $p<0.05$.

Results

One hundred forty-three patients were included in the study. The mean age of the patients was 74.8±10.6. One hundred and two of the patients (71.3%) were male. The most common comorbidity was diabetes mellitus (42%). The characteristics and comorbidities of the patient groups have been presented in Table 1.

The mean of the neutrophil count was 8.31±0.35 (10^3 x cells/mm^3), and the mean of the eosinophil count was 0.18±0.02 (10^3 x cells/mm^3). The mean of neutrophils and eosinophils of the NEU group was 11.97±3.77 and 0.19±0.18 (10^3 x cells/mm^3), respectively, while the mean of neutrophils and eosinophils of the EOU group were 5.64±1.22 and 0.35±0.24 (10^3 x cells/mm^3), respectively.

The NEU and the EOU groups had a statistically significant difference in body temperature and heart rate (p=0.018 and p=0.001, respectively). In contrast, no significant difference was observed for systolic blood pressure, diastolic blood pressure, and sPO2 (p=0.400, p=0.564,

Table 1. Characteristics of the patients

	All patients, (n=143)	Neutrophilic patients, (n=63)	Eosinophilic group, (n=31)
Age (mean ± SD)	74.8±10.6	74±10.8	74.78±10.7
Gender (male)	102 (71%)	44 (69.8%)	5 (16.1%)
Coronary artery disease	21 (14.7%)	11 (17.5%)	10 (16.4%)
Congestive heart failure	27(18.9%)	11 (17.5%)	7 (22.6%)
Chronic renal failure	21 (14.7%)	7 (11.1%)	5 (16.1%)
Hypertension	60 (42%)	25 (39.7%)	11 (35.5%)
Diabetes mellitus	52 (36.4%)	26 (41.3%)	8 (25.8%)
Home-dwelling elderly	15 (10.5%)	7 (11.1%)	2 (6.5%)
Malignity	21 (14.7%)	12 (19%)	0 (0%)

SD: Standard deviation

p=0.248, respectively). The comparison of the vital signs of the patients is summarized in Table 2.

Twenty-two (15.4%) of the patients required NIMV in the emergency department. 9 (14.3%) were in the NEU group, and 6 (19.4%) were in the EOU group. Comparison of the NEU and EOU groups, in terms of NIMV application, had no significant difference (p=0.528).

Two patients (1.4%) were intubated in the emergency department (1 patient for each group). There was no statistically significant difference between the groups in terms of intubation need (p=0.553). Patients' 1-month, 3-months, and 1-year mortality results have been summarized in Table 3.

One-month mortality rates for all patients, the NEU group and EOU groups have been determined as 16/143 (11.2%), 10/63 (15.9%), 1/31 (3.2%), respectively. Blood neutrophil count levels have been assigned in 3 different groups for mortality and compared which had no significant difference for 1,3- and 12-month mortality (p=0.142, 0.280, 0.351; respectively). Blood neutrophil count levels and mortality rates have been summarized in Table 4.

Discussion

The current study found that eosinophilic and neutrophilic exacerbations of patients with COPD had no significant difference in terms of mortality. In the study by Kandemir et al. (9), which was conducted in similar settings, the neutrophilic phenotype patients had higher mortality rates than the eosinophilic phenotypes. In their study, neutrophilic patients had 38.9% mortality rates in 3 months, whereas in our study, neutrophilic phenotype patients had 25.4% and 36.5% (3 and 12 months respectively). These mortality rates are higher than expected however both studies examine the patients presenting to the ED. This can be explained by the patient population was much more ill than outpatients, therefore had more unfavorable outcomes. In contrast, our study had higher mortality rates regarding eosinophilic exacerbations 16.1%, 25.8%, (3 and 12 months respectively). This difference might occur due to Kandemir et al. (9) have classified the exacerbations into three groups in their study. These results suggest that classifying hematologic phenotypes further might yield different mortality rates with overall deaths due to COPD remaining the same. Furthermore, their study included patients discharged and admitted to a hospital where we only included hospitalized patients, which might be the reasoning behind the difference in mortality rates for eosinophilic patients (9).

In addition, our study included important features of hematologic phenotypes. Previous studies have presented higher rates of older age, tachycardia, and higher body temperatures for neutrophilic exacerbations. In our study, we also found that tachycardia and increased body temperature and other vital signs were indifferent between the comparison of phenotypes, which was concurrent with the current literature. Furthermore, our study had similar age means in all groups.

Various studies have concluded that the eosinophilic type has lower short- and long-term mortality (10-12). We have found that mortality rates did not significantly change between hematologic phenotypes. This might be the result of our work patients being studied that are admitted to the hospital and excluded discharged patients. Furthermore, our study included patients who have been admitted to the hospital from

Table 2. Comparison of the patient's vital signs

	All patients, (n=143)	Neutrophilic patients, (n=63)	Eosinophilic patients, (n=31)	p-values*
Systolic BP	123.01±24.55	124.44±24.02	121.29±25.92	0.400
Diastolic BP	71.82±12.65	72.06±11.52	71.29±14.08	0.564
Body-tempeture	37.08±0.7	37.05±0.64	36.78±0.55	0.018
Heart rate	103.16±18.1	107.16±18.06	94±13.76	0.001
Oxygen saturation	86.57±8.66	85.41±9,85	87.06±8.93	0.248

*P-values represent comparison between Neutrophilic and Eosinophilic groups, BP: Blood pressure

Table 3. Mortality rates for 1 month, 3 months, and 12 months between patient groups

Mortality	All patients (%), (n=143)	Neutrophilic patients (%), (n=63)	Eosinophilic patients (%), (n=31)	p-values*
1-month	16 (11.2%)	10 (15.9%)	1 (3.2%)	0.066
3-months	30 (%21%)	16 (25.4%)	5 (16.1%)	0.310
1-year	47 (%32.9%)	23 (36.5%)	8 (25.8%)	0.299

*P-values represent comparison between neutrophilic and eosinophilic groups.

Table 4. Neutrophil levels and mortality rates for each group

	1 month mortality, (n=16)	3 month mortality, (n=30)	12 month mortality, (n=47)
2000-7000 cell/mL	4/16	11/30	20/47
7000-15000 cell/mL	10/16	15/30	21/47
>15000 cell/mL	2/16	4/30	6/47
p-value	0.142	0.280	0.351

the emergency department. Therefore, note that patients admitted to the ED with exacerbations were more severely ill than outpatient COPDs. Similar to our findings, Bafadhel et al. (7) study also showed similar 1-year mortality between eosinophilic and non-eosinophilic exacerbations, which would suggest in-patient patients with COPD even with eosinophilic phenotypes might have similar outcomes when discharged and outpatients are excluded. Martínez-Gestoso et al. (13) study discussed blood eosinophil count is not useful in assessing outcomes after patient hospitalizations that was concurrent with our study. In contrast, ICU patient mortality rates were favorable for the eosinophilic phenotype (14).

Finally, neutrophil count levels and cut-offs have not been thoroughly studied in the literature. We have divided neutrophilic phenotypes into three groups (2000-7000, 7000-15000 and >15000 cells/mL) and found no difference between the groups. Further studies must assess blood neutrophil count cut-off values for inpatient and outpatient populations to further examine its use as an independent biomarker for mortality.

Study Limitations

Our study was a single-center study that conducted as a retrospective study; therefore, our results cannot be generalized. Furthermore, even though we included the patients hospitalized in the emergency department, which might be counted as a strength, excluding outpatients and discharged patients also provided a limited view of the population.

Conclusion

There was no mortality difference between different neutrophil levels or hematologic phenotypes for the patients admitted to the hospital via the emergency department. Further studies must assess the cutoff values of blood neutrophil counts as an independent biomarker.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital Local Ethics Committee (approval number: 2020-164, date: 14.01.2021).

Informed Consent: Informed consent was exempted.

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