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The Association Of Peripheral Eosinophilia and Other Factors With Six -Month Mortality in Patients Admitted with Severe Chronic Obstructive Pulmonary Disease Exacerbation

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Abstract

Background: In this study, we investigated whether peripheral eosinophilia, demographic and other laboratory parameters were effective on six-month mortality in chronic obstructive pulmonary disease (COPD) exacerbations requiring hospitalization.

Methods: The study is a retrospective, observational study. Between January 2015 and November 2016, a total of 410 patients admitted to the emergency or outpatient services with COPD exacerbation were enrolled. Demographic characteristics, baseline complete blood count (CBC) parameters, serum albumin, C-reactive protein levels and arterial blood gas measurements and hospitalization durations were recorded. All hospital admission records up to 1 year before hospitalization and for 6 months after discharge were reviewed. At the end of 6th month of follow-up, survivals were investigated. Patients with ≥2% eosinophil ratio in CBC of peripheral blood were classified as eosinophilic COPD exacerbations, and those with less than 2% eosinophil ratio were classified as neutrophilic exacerbation COPD exacerbations. The characteristics of the patients with mortality and survived groups were compared.

Results: Of the 410 patients included in the study, 69% were male and mean age was 69 years (min-max: 37- 92 years). Eighty-seven percent of hospitalizations were made via the emergency service. The mean duration of hospitalization was 6 days (min-max:1-26 days). The 6-month mortality rate after exacerbation was 19% (n=79). The survival rate of those with peripheral eosinophilia was significantly better (p = 0.004).

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Advanced age and male gender were the factors that increased mortality (p = 0.01, and p = 0.04, respectively). Hemoglobin and serum albumin values were significantly lower (p = 0.001, for both) in the mortality group, while charlson comorbidity index was significantly higher compared to those who survived (p =0.02). In addition, the number of severe exacerbations 1 year before admission was higher in the mortality group (p =0.040). Independent variables associated with mortality were advanced age (HR=1.030, 95% CI=1.008-1.054, p=0.009), peripheral eosinophilia (HR=0.415, 95% CI=0.199-0.863, p=0.018) and male gender (HR=1.765, 95% CI=1.023-3.045, p=0.041)..

Conclusion: Our results suggest that peripheral eosinophilia is independently associated with survival, while does not influence the frequency of recurrent COPD exacerbations in patients admitted with COPD exacerbations required hospitalization. Advanced age, neutrophilic exacerbation and male gender were identified as independent risk factors s affecting mortality at the end of six- months in COPD patients with exacerbation. These patients may require closer monitoring.

Keywords: Chronic Obstructive Pulmonary Disease (COPD); exacerbation; Eosinophilia; Mortality

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; RICU: Respiratory İntensive Care Unit; NLR: Neutrophil to Lymphocyte Ratio; CCI: Charlson Comorbidity Index; LTOT: Long Term Oxygen Use; NIMV: Non-Invasive Mechanical Ventilation At Home; CRP: C-Reactive Protein; ABG: Arterial Blood Gas.

Introduction

Exacerbations are an important cause of morbidity and mortality in chronic obstructive pulmonary disease (COPD) patients. Nine per thousand to 2.4 percent of all COPD patıents experience severe exacerbations requiring hospitalization per year. These exacerbations negatively affect the course of the disease and quality of life and pose an important burden on health expenditures in the global country economy [1,2].

Some patients with COPD are reported to have eosinophilic inflammation during the stabilized period and exacerbations [3,4]. In acute exacerbations of COPD, the patients with eosinophilic inflammation are reported to have different prognosis than those with neutrophilic exacerbation. Today, eosinophilia ≥2% of white blood cell count in complete blood count (CBC) is considered to be a reliable marker of eosinophilic airway inflammation [4].

In current literature, there are publications reporting contradictory results in the treatment response and prognosis of eosinophilic and neutrophilic patients during COPD exacerbations. There are studies suggesting that COPD patients with eosinophilic phenotype have shorter hospitalization duration [4] and less frequent annual exacerbations and re-admissions to the hospital. In addition, shorter hospital stay and less in-hospital mortality have been reported in these subgroup patients with acute respiratory failure. Eosinopenia has also been reported to be an independent risk factor for inhospital mortality. On the other hand, a number of studies report that acute exacerbations are more frequent in patients with eosinophilic inflammation and that there is no association between eosinophilia and mortality. In a limited number of studies investigating long-term survival in these patients, different results have been reported, suggesting that eosinophilia both prolongs and does not affect survival [5-11].

Independent risk factors for long-term mortality have been reported as advanced age, low hemoglobin and albumin, high comorbidity index, number of episodes before hospitalization [12,13] Better patient management can be achieved by knowledge on prognostic factors.

The aim of this study was to investigate whether peripheral eosinophilia, a practical and inexpensive method, is associated with long-term mortality in COPD patients hospitalized with severe exacerbations. We also aimed to determine the relation between the demographics, laboratory outcomes and mortality.

Materials and Methods

This retrospective observational cohort study was conducted between 1 January 2015 and 1 November 2016 in the pulmonary diseases clinic of a tertiary education and research hospital. The study was approved by the local Ethics Committee. A total of 410 patients admitted with COPD exacerbation and hospitalized from the pulmonary diseases outpatient clinic or emergency service were enrolled (Figure 1). Patient information was obtained from the hospital's electronic database.

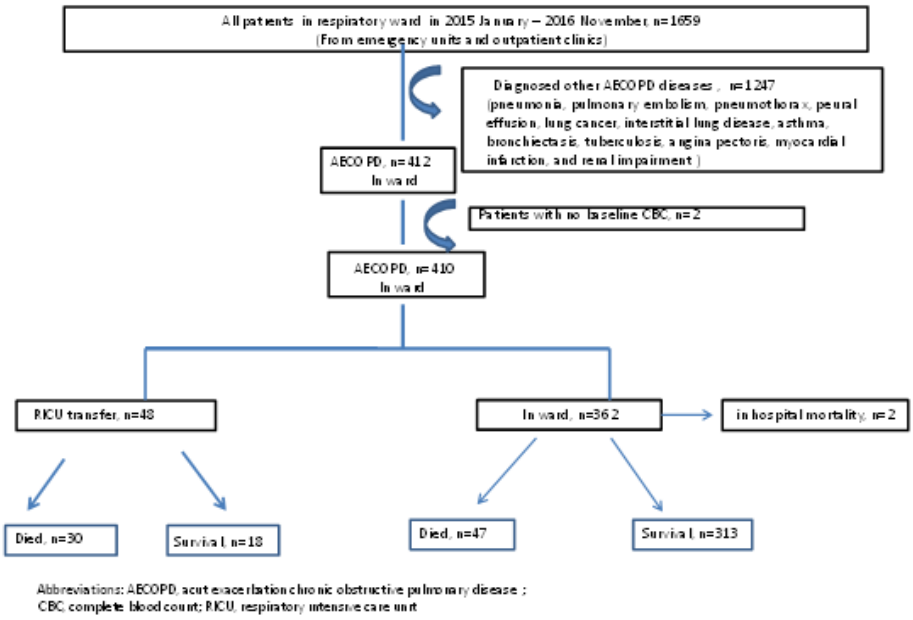

Figure 1: Flow chart of patient enrollment.

Patients

Patients who had previously been diagnosed with COPD by a pulmonologist for at least 2 years, receiving active treatment and followed up, and who admitted to the hospital due to COPD exacerbation, constituted the study population.

Inclusion criteria: The hospitalized acute exacerbation of chronic obstructive pulmonary disease patients who admitted to the emergency units and outpatient clinics were enrolled.

Excusion criteria: Patients who were previously diagnosed with non-COPD diagnosis (pneumonia, pulmonary embolism, pneumothorax, peural effusion lung cancer, interstitial lung disease, asthma, bronchiectasis, tuberculosis, angina pectoris, myocardial infarction, and renal impairment) were excluded from the study.

The hospitalization of the patients due to COPD exacerbation who were included in the study was accepted as baseline hospitalization. When the patient had multiple hospitalizations, the first admission was taken into consideration. Survival rates were evaluated at the end of the six-month after COPD exacerbation. Data for the duration of mortality were obtained from the web site of National Death Notification System belonging to the Ministry of Health [14]. Hospital admissions (to the emergency service, pulmonary diseases clinics, respiratory intensive care unit [RICU]) and number of applications were recorded from 1 year before the date of admission to 6 months after acute exacerbation.

Definitions

- **COPD** diagnosis was established in the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD in patients with appropriate symptoms and significant exposures to noxious stimuli [1].
- **COPD exacerbation** is an acute change in a patient's baseline dyspnea, cough, or sputum that is beyond normal variability, and that is sufficient to warrant a change in therapy[1].
- **Severe COPD exacerbation** is deteriorations requiring urgent admission and hospitalization [1].
- **Ex-smoker** is defined as individuals who have not smoked for at least 1 year [15].
- **Biomass fuel exposure** is the source of energy used for domestic and non-domestic heating, cooking and other domestic needs [1].
- **Eosinophilic exacerbation** is the number of eosinophil count that is greater than ≥ 2% of the total number of white blood cells (WBC) in CBC measured at the time of hospital admission of COPD patients with acute exacerbation [4].
- **Neutrophilic exacerbation** is defined as that without eosinophil count of more than 2% WBC count [4].

- **Neutrophil to lymphocyte ratio (NLR)** is the ratio of the absolute neutrophil count to lymphocyte count in CBC.
- **Co-morbid diseases** The Charlson index, which predicts mortality due to various chronic diseases, is calculated according to age. A total of 19 chronic diseases which take place in Charlson comorbidity index (CCI) were investigated [16]. In addition, systemic hypertension not included in the CCI index was also investigated.

Measurements

Patient demographic information, admitted medical service, smoking history, charlson index, long term oxygen use (LTOT), non-invasive mechanical ventilation at home (NIMV), nebulized and/or oral corticosteroid treatment and hospitalization duration were recorded. Nebulized form fluticasone or budesonide was administered every 12 hours and the oral systemic corticosteroid at a dose of 40 mg to 60 mg/day. Although the duration of corticosteroid treatment depends on the clinical status, patients were received 5 days from the baseline of hospitalization. In addition, nasal oxygen, antibiotics and bronchodilator treatments were adjusted according to the clinical findings. In case of respiratory failure, NIMV was performed in our clinic, while the patients were transferred to the RICU when invasive mechanical ventilation is necessary. Complete blood count, NLR, serum albumin and C-reactive protein (CRP) levels, and arterial blood gas (ABG) analysis were implemented at the admission to the hospital (within the first 2 hours of hospitalization to the clinic, and immediately just after admission to the emergency department). NLR values were calculated. CRP value was not available in 28 patients, serum albumin in 8 patients and ABG analysis in 66 patients. Complete blood count parameters were determined using a Coulter LH 780 Hematology Analyzer (Beckman Coulter, Inc., Brea, CA, USA). CRP was checked by the nephelometry method using a BN II System with a Siemens (Germany). The normal range of CRP is 0-5 mg/L. Respiratory function test results could not be recorded because they were not available electronically.

Study design

Patients were divided into 2 groups according to the presence of peripheral eosinophilia in CBC performed at hospital admission: eosinophilic and neutrophilic patients. Two study groups were compared in terms of demographic characteristics, treatment administered in hospital, duration of hospitalization, number of hospital admission before and after hospitalization due to COPD exacerbation.

In the assessment of mortality, the patients who died and survived following for six months acute exacerbation of COPD exacerbation were compared in terms of demographic characteristics, CCI, LTOT, home NIMV use, medication, hospital admissions, baseline laboratory parameters, ABG analyses, and peripheral eosinophilia.

Statistical analysis

Descriptive analysis was used to investigate patient demographics and clinical data. The SPSS portable 20.0 package program (IBM Corporation, Armonk, NY, USA) was used for analysis. Groups were compared using student's t-tests for parametric continuous variables. Chi-square tests were employed for dichotomous variables. The mean ± SD was used for parametric continuous variables. Count and percentage were used when applicable. Significant independent risk factors in univariate analysis were assessed by multivariate cox regression analysis. The Kaplan–Meier survival analysis was carried out to predict the long-term mortality in the patient groups after hospital discharge If the P-value was <0.05, it was accepted as statistically significant. Logistic regression analysis was performed to define mortality risk factors in the study population. Age, sex, CCI, hemoglobin, eosinophilia, LTOT, home NIV use were included in the model.

Results

Of the 410 patients included, 69% were male and mean age was 69 ± 11 years (min-max: 37-92 years). Most (87%) of the hospitalized patients were admitted to emergency department. Only 18% of the patients had no smoking history (Table 1).

	All patients (n=410)	Died (n=79)	Alive (n=331)	P
Age, years (mean±SD)	69 ±11	71±10	68±11	**0,018**
Sex, n(%)				
Male	283(69)	62(78)	221(67)	**0,043**
Female	127(31)	17(22)	110(33)	
Admission service, n (%)				
Emergency department	355(87)	75(94.9)	280(84.6)	**0,016**
Outpatient clinic	55(13)	4 (5.1)	51(15.4)	

Smoking history*, n (%)				
Non smoker	69(18)	11(15)	58(18)	0,66
Ex-smoker	211(56)	44(61)	167(55)	
Smoker	53(14)	8(11)	45(15)	
Bıomass fuel exposure	45(12)	9 (13)	36 (12)	0.51
LTOT, n (%)	183(44.6)	36(45,6)	147(44,4)	0.47
Home NIMV, n (%)	86(21)	16(20.2)	70(21.1)	0.86
Length of hospital stay, days (mean± SD)	6.3±3.6	6.1±3.3	7.2±4.7	0.06
Corticosteroid treatment, n(%)				
Nebulized form **+ oral corticosteroid	96(23.4)	17(21.5)	79(23.9)	0.94
Oral corticosteroid	190(46.3)	36(45.6)	154(46.5)	
Nebulized form	34(8.3)	7(8.9)	27(8.2)	
No corticosteroid	90(22.0)	19(24.1)	71(21.5)	
NIV performed, n (%)	126(31)	25(32)	101(31)	0.8
NIV not performed, n (%)	284(69)	54(68)	230(69)	
Number of AECOPD within 1 year of prior hospitalization (mean± SD)	3,48±4.5	4.42±5.9	3.26±4.1	**0.040**
Number of AECOPD within 6 month of discharge, (mean± SD)	1.64±3.1	1.25±2.1	1.74±3.3	0.22

Notes: SD, standard deviation; *Smoking status was not available in 32 patients.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; LTOT, long-term oxygen therapy; NIMV, noninvasive ventilation; **fluticasone or budesonide

Table 1: Demographic characteristics of the patients who died and survived after acute COPD exacerbation.

Table 1 shows treatment with LTOT, home NIMV usage, mean duration of hospitalization, corticosteroid treatments during hospitalization, and the number of exacerbations before and after hospitalization of all patients. Corticosteroid (oral and /or nebul) therapy was used in 78% (n = 320) of all patients. Most of this treatment (46%) was oral corticosteroid; while 22% (n = 90) did not receive any corticosteroid treatment. Most of the patients (88.8%) had at least one admission to the hospital during the previous one year. In 92% of these patients the number of hospital admission was <10 times while 8% (n = 33) had admitted more than 10 times (not shown in the table). Of the patients hospitalized in the clinic, 2 patients died and 48 (12%) patients were transferred to the RICU (Figure 1).

The most common comorbid diseases were hypertension, congestive heart failure and diabetes mellitus (36%, 23%, and 20%, respectively) The mean Charlson comorbidity index of whole study population was 5.20 ± 1.68 (Table 2).

	All patients (n=410)	**Died (n=79)**	**Alive (n=331)**	**P**
Co-orbid Diseases, n (%)				
Hypertension	148 (36.1)	25(31,6)	123(37,2)	0,36
Congestive heart failure	95(23.2)	21(26,6)	74(22,4)	0.42
Diabetes mellitus	81(19.8)	11(13,9)	70(21,1)	0.14
İschemic heart disease	55(13.4)	14(17,7)	41(12,4)	0.21
Malignancy	37(9.0)	15(19,0)	22(6,6)	**0.001**
Chronic renal diseases	8(2.0)	4(5,1)	4(1,2)	**0.026**
Charlson comorbidity ındex	5,20 ±1,68	5.72±1.8	5.08±1.6	**0.002**

Table 2: Comorbid diseases and charlson comorbidity ındex in acute exacerbation of chronic obstructive pulmonary disease.

Table 3 shows the mean of CBC parameters, NLR, CRP, serum albumin and ABG analysis of all patients. There were 86 (21%) patients with peripheral eosinophilia. The mean eosinophil ratio of all patients was 1.33 ± 2.67%.

	All patıents (n=410)	Died (n=79)	Alive (n=331)	P
Leukocyte count, mean ± SD (×109 /L)	11.9± 5.4	12.66 ± 5.52	11,75± 5,31	0.17
Eosinophil %, mean ± SD	1.33± 2.67	0.81±1.03	1.46± 2.92	**0.02**
Hemoglobin, mean ± SD (g/dL)	12.8±2.2	11.71± 2.4	13.06± 2.09	**0.001**
Platelet, mean ± SD (×109 /L)	281.2 ± 117.2	292.05 ± 119.4	278.60± 116.4	0.36
NLR, mean ± SD	9.27 ± 10.66	10.06± 14.02	9.08± 9.70	0.38
CRP, mean ± SD(mg/dL)	64.6±74.4	66.8 ± 67.0	64.1± 76.2	0.77
Albumin, mean ± SD (g/dl)	3.6± 0.5	3.3 ± 0,6	3.7± 0,5	**0,001**
Arterial blood gas, mean±SD				
pH	7.39± 0.7	7.39± 0,08	7.40± 0,06	0.36
PaO2 (mmHg)	63.7± 27.2	65.92± 34,72	63.14± 24.99	0.52
PaCO2 (mmHg)	49.2± 13.5	47.72± 14.90	49.59± 13.11	0.3

Notes: SD, standard deviation.
Abbreviations: CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio
Table 3: Laboratory results of the patients who died and survived after acute COPD exacerbation.

Table 4 shows age, gender, use of corticosteroids, and duration of hospitalization and there was no significant difference between eosinophilic and non eosinophilic groups (p >0.05 for all). There was no significant difference between the two groups in terms of the number of admittance to the hospital with severe exacerbation 1 year before hospitalization and 6 months after discharge (p = 0.96, p=0.71, respectively).

	Eosinophilic (n=86)	Neutrophilic (n=322)	p
Age, years (mean ± SD)	67±11	69±10	0.2
Sex, n(%)			
Female	31(36)	96(30)	0.26
Male	55 (64)	226(70)	
Hemoglobine(gr/dl)(mean ± SD)	12.85±2.20	12.64±2.29	0.17
Albumin(gr/dl(mean ± SD)	3.6±0.5	3.8±0.5	0.69
Cortıcosteroid treatment, n(%)			
Nebulized form	7(8)	26(8)	0,84
Nebulized form* +oral corticosteroids	16(19)	79(25)	
Oral corticosteroid	39(45)	151(47)	
No corticosteroid	24 (28)	66 (21)	
Hospital length of stay (days) (mean ± SD)	6.26±3.6	6.34±3.6	0.28
Number of AECOPD within 1 year of prior hospitalization (mean ± SD)	3.48±4.7	3.50±4.5	0.96
Number of AECOPD within 6 month of discharge (mean ± SD)	1.76±3.7	1.62±2.2	0.71

Note: SD, standard deviation
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; *fluticasone or budesonide.
Table 4: General characteristics of the patients with and without peripheral eosinophilia for acute exacerbation chronic obstructive pulmonary disease.

Six-month mortality after chronic obstructive pulmonary disease acute exacerbation

Of 410 patients, 79 (19%) died following for 6 months after acute exacerbation of chronic obstructive pulmonary disease (Table 1). The significant mortality was associated with elderly and male sex predominant (p = 0.018, 0.043, respectively). The mortality rate was higher in the patients who admitted to the emergency department

compared to those admitted outpatient clinic (p = 0.016) (Table 1).

There was no significant difference between the patients died and alived in terms of the use of LTOT and home NIMV, the mean hospital stay, the use of corticosteroids in the hospital, the use of NIMV during hospital stay, and the number of post-discharge COPD episodes. Survival was shorter in patients who admitted to hospital more in the previous 1 year (p = 0.040) (Table 1).

In the mortality group, CCI value was significantly higher (5.72 vs. 5.08, p = 0.002), and comorbid diseases of malignancy and chronic renal failure were more frequent compared to those survived (p = 0.001, p = 0.026, respectively) (Table 2).

There was no significant difference between mortality and survival groups in terms of leukocyte count, NLR, CRP and ABG analysis values. Hemoglobin and serum albumin values of the mortality group were significantly lower than those alived (p =0.001 for both). Mortality occurred in 9% (n = 8) of the patients with eosinophilia and 22% (n = 71) of those without eosinophilia (p = 0.004). The mean eosinophil percentage was significantly higher in the alived groups than those of the mortality group (1.46 ± 2.92% vs. 0.81 ± 1.03%, p = 0.02) (Table 3).

The most powerful independent risk factor on mortality in the Cox regression was advanced age (p = 0.009, hazard ratio HR 1.030, 95% CI 1.008-1.054), followed by presence of eosinophilia and male gender. While mortality was significantly reduced in eosinophilia (HR=0.415, 95% CI: 0.199-0.863, p = 0.018), male sex increased mortality by 1.76 times (HR=1.76 95% CI 1.02-3.04, p = 0.041) (Table 5). In the Kaplan Meier survival analysis, gender and eosinophilia were associated with a 6-month mortality (Figures 2 and 3). Survival was significantly shorter in male patients (p = 0.051) compared to women; while it was significantly longer in the eosinophilic group than that of neutrophilic group (p = 0.008).

Characteristics	HR	95% CI	P value
Age, years	1.030	1.008-1.054	0.009
Sex, male	1.765	1.0233- 3.045	0.041
Eosinophilia	0.415	0.199-0.863	0.018
Abbreviations: CI, confidence interval; HR, hazard ratio			

Table 5: Predictors of 6 months measured at hospital admission for acute exacerbation chronic obstructive pulmonary disease (Cox proportional hazards)

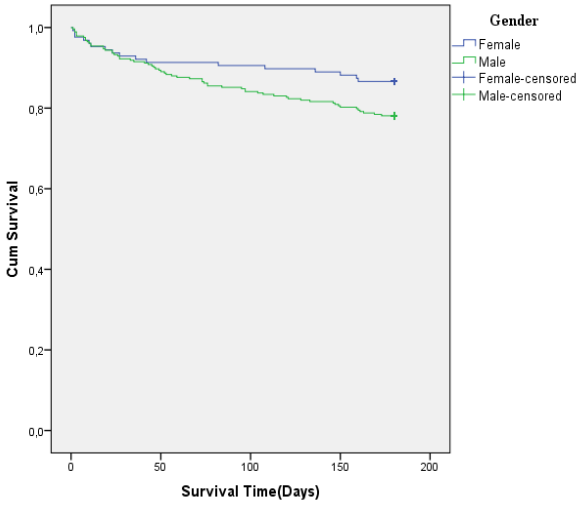

Figure 2: Kaplan-Meier curve for the probability of COPD patients after exacerbation according to gender followed for 6 months.

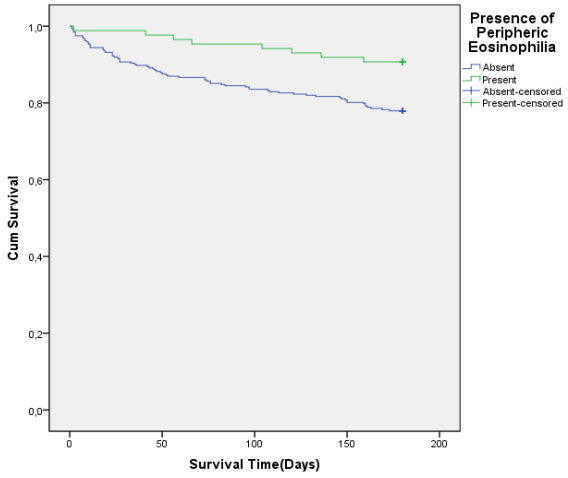

Figure 3: Kaplan-Meier curve for the probability of COPD patients after exacerbation according to presence of peripheric eosinophilia followed for 6 months.

Discussion

In COPD patients with severe exacerbations, mortality increases up to one in five patients within the first 6 months after the acute exacerbation. The presence of eosinophilia ≥ 2% in the CBC was found as an independent risk factor affecting the survival positively. Age and sex, duration of hospitalization, and frequency of exacerbations were observed at similar rates among eosinophilic and neutrophilic patients. Other factors that increased mortality were older age, male gender, high Charlson comorbidity Index, and low hemoglobin and albumin values. The strongest predictive factor for mortality was advanced age, peripheral eosinophil, and gender.

COPD is a chronic inflammatory heterogeneous disease with different phenotypes and endotypes [17]. In the case of exacerbations, mainly neutrophilic airway inflammation develops according to the etiological cause; while eosinophilic inflammation is observed in 20-40% [18]. It has been reported that a value of ≥2% of the eosinophil percentage in WBCs is a reliable and simple indicator of eosinophilia in sputum and tissues [4, 19, 20]. Eosinophilia is reported in 19-40% of patients with severe COPD exacerbations in clinical trials [8, 20]. In this study, consistantly, eosinophilia was detected in one of 5 patients.

Patients with eosinophilic inflammation have different clinical features, prognosis and treatment responses than those with neutrophilic inflammation. One of the largest known series on this subject conducted with 1483 COPD patients followed for three years, ECLIPS (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study reported that, patients with eosinophilia had fewer symptomatic patients and had better quality of life [21].

Different results have been reported in studies investigating the relationship between eosinophilia and survival in exacerbations of COPD patients [10,18,20]. It has been reported that there is no association between peripheral eosinophilia and one-year mortality in a series containing 3084 COPD patients with exacerbation [8]. In this study, however, only 7% of the patients in both groups had oral corticosteroids 1 week prior to admission, but not in the hospital. In another similar study conducted with 207 COPD patients showed similar mortality between two groups [20]. In a recent study, 3-year mortality was assessed in 458 COPD patients and the mortality was not detected to be affected by eosinophilia at different cut-off values [10]. Patients in the last two studies consisted of COPD patients with fewer serious COPD (moderate weight at the GOLD stage) and an average annual exacerbation rate of 0-1. In our series, patients had severe COPD patients with frequent exacerbations and significant respiratory failure. In our study, we found a positive correlation between eosinophilia and long-term survival rate and demonstrated that eosinophilia is a good prognostic factor. The first study showing increased mortality with reduction in eosinophil count in COPD exacerbations was conducted by Holland M et al. among 65 COPD patients, eosinopenic ones had a significantly higher mortality [7]. In 605 COPD patients admitted with severe exacerbation, the 28-day mortality after exacerbation was found to be significantly lower in those with eosinophilia than neutrophilic group [22]. In a study by Casanova et al., in patients without eosinophilia, life time was shorter and mortality was 7.3 times higher compared to those with eosinophilia. The authors could not fully explain the cause of this result and interpreted eosinophilia as a poor prognostic factor [19]. In a recently published prospective study, mortality was increased with a decrease in the number of eosinotephils in a survival analysis of 431 stable COPD patients; even mortality was additionally increased when low eosinophil value was accompanied by normal CRP value [11].

Salturk et al. concluded that the mortality rate in COPD exacerbations with acute respiratory failure was higher in non-eosinophilic group when compared with eosinophilic group [6]. Several hypotheses have been suggested about why better surveillance in patients with peripheral eosinophilia. One of them is that low eosinophil value is associated with acute infection and inflammation and is a marker for bacterial infection [23]. It has been discussed that eosinophils increase immunological responses to infections due to antimicrobial functions and it has been advocated that the lung clearance capacity from infections is better in patients with eosinophil value≥ 2 [24,25]. In another hypothesis, it has been suggested that COPD patients with eosinophilia are more likely to respond better to treatment with corticosteroids [3,4]. Clinical studies have reported that patients with eosinophilia have more improved respiratory function with steroid treatment, better quality of life and fewer attacks [18]. There was no significant difference in the leukocyte, NLO, or CRP values, which were known as infection parameters, compared with the patients with or without eosinophilia in our study. Therefore, the first hypothesis did not support the result of our study. The corticosteroid treatment of patients was similar in the group with and without eosinophilia. Better survival in COPD patients with eosinophilia supports the hypothesis that corticosteroid treatment is more effective in these patients [7,8].

The 6-month mortality after exacerbation of COPD was reported to be 7 to 33% [20, 26, 27]. It has been reported mortality of the patients that the number of annual exacerbations ≥ 3 and above is about 4 times higher than that of those with fewer exacerbations [28,29]. Similar results were obtained in many later studies [13,26]. The 6-month mortality rates in our study were consistent with the literature. There was a positive correlation between mortality and the number of exacerbations. This result supports the conclusion that every severe exacerbation causes more and more functional loss in the lungs of the patients [30].

In our study, advanced age was found to be an independent risk factor that increased mortality as in previous studies [26,27]. In our country, as in the whole world, COPD is diagnosed later in life than it actually is. As the respiratory function decreases with age, late diagnosis of the patients with COPD will increase the negative effect on mortality [31, 32].

In our study, the mortality rate was 1.7 times higher in males than that of females. There are a few studies showing that mortality is higher in men than in women. In a study it was reported that the low number of female patients is the reason for this difference. In a study including equal number of male and female patients by Slenter et al, it has been reported that the male gender was found to be an independent risk factor for mortality. Due to the sociocultural characteristics of some regions in our country, women have the use of biomass fuel that is an important cause of COPD [33-35]. Our hospital is a training and research hospital and a reference center that serves a large number of patients from these regions in our country. In our series, female patients are exposed to more frequent biomas, and are less likely to smoke. In our study, presence of smoking in the majority of male patients might be a more exaggerated inflammatory response compared to the female biomass exposure, and this was thought to be a worse prognostic factor affecting long-term mortality.

The most important limitation of the study is the single center cohort, and retrospective design of the study. The other is that the respiratory function test cannot be performed because it is not registered in the hospital automation system. Another limitation is that the percentage of eosinophils in the patients' total blood count is once done. Studies have shown that eosinophilic inflammation changes over time. Therefore, we do not know that the value of eosinophil in our series is temporary or permanent. The first of its strengths is the large number of patients. Second, reliable data is obtained with patient information being available in the patient's medical records. In addition, our mortality rate was close to one in five patients, allowing for the analysis of demographic and other laboratory data other than eosinophilia. In our opinion, the evaluation of all patients in the study by a pulmonologist important in terms of minimizing deficiencies and mistakes in the diagnosis and follow-up.

Conclusion

Peripheral eosinophilia is a good long-term prognostic factor in patients with severe COPD exacerbations. Advanced age, male gender, chronic renal failure and malignancy increase long term mortality in COPD patients. The survival shortens with lower hemoglobin and serum albumin values. The strongest independent risk factor that increased mortality was older age, while the second and third most important factors were non-eosinophilic attack and male gender, respectively. Determination of poor prognostic factors is important for the clinician to identify high risk patients who require close follow up and treatment changes.

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