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Eosinophil Levels and Prognosis in Patients Hospitalized with COPD Exacerbation

Hasan Furkan AVCI[1], Seyma Baslilar[2], Bengu Saylan[3], Gokce Kulah[4]*, Tayfun Caliskan[5], Zafer Kartaloglu[6], Fatih Özçelik[7]and Oğuzhan Okutan[8]

[1]Department of Allergy and Immunology Diseases, University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Pulmonology, University of Health Sciences, Sultan 2. Abdulhamit Han Training and Research Hospital, Istanbul, Turkey
[3]Department of Pulmonology, University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[4]Department of Pulmonology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey
[5]Department of Pulmonology, Anadolu Medical Center Hospital, Kocaeli, Turkey
[6]Department of Pulmonology, University of Health Sciences, Istanbul, Turkey
[7]Department of Medical Biochemistry, University of Health Sciences, Istanbul, Turkey
[8]Department of Pulmonology, Maltepe University Hospital, Istanbul, Turkey

Abstract

Objective: The eosinophil count ≥ 300 cells/μL is known to be related to the increased risk for exacerbations in stable COPD. But the precise 'eosinophil threshold value' that can predict the disease course during exacerbations is still unclear. We aimed to determine a cut- off value for the peripheral blood eosinophils during COPD exacerbations that will predict the outcome and recurrence.

Methods: 711 patients hospitalised due to COPD exacerbation between Oct 1st, 2016 and Jan1st, 2020 were analyzed retrospectively. The cut-off values for Peripheral Blood Eosinophil Count (PBEC) and Ratio (PBER) predicting the risk for severe and recurrent exacerbations and, mortality were determined.

Results: The cut-off values for PBEC and PBER were found as 170/μL and 1.15% (90.7% sensitivity, 28.3% specificity and 80.0% sensitivity, 37.3% specificity, respectively, p<0.001). The patients with low PBEC and low PBER were transferred to intensive care unit more frequently (11.3% vs. 3.2%, p<0.001 and 11.4% vs. 5.1%, p=0.008). Low PBER group had higher in hospital mortality (3.1% vs. 0.04%, p=0.036) while the long term mortality rate was higher in low PBEC group (57.7% vs. 43.9%, p<0.001). The rate of the patients with recurrent exacerbations and number of exacerbations per year were increased in both high PBEC and high PBER groups (p<0.001).

Conclusions: It was determined that COPD patients hospitalized due to exacerbations with low eosinophil levels had a worse prognosis while patients with high eosinophil levels had more frequent exacerbations.

Keywords: Chronic obstructive pulmonary disease • Cut-off value • Eosinophil • Exacerbation • Mortality

Introduction

Acute Exacerbations of COPD (AECOPD) are closely related to the progression and prognosis of the disease [1]. The increased number of exacerbations and need for hospitalisation are related to increased disease severity and severe exacerbations are related to the short and long term mortality [2].

It is well known that the eosinophilia during stable phase is related to the increased risk for exacerbations of COPD and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guide 2023 proposed that COPD patients with an eosinophil count over 300 cells/μlshould be treated with Inhaled Corticosteroids (ICS) [3]. But the threshold value for the eosinophils and whether the Peripheral Blood Eosinophil Count (PBEC) or Ratio (PBER) should be used as a biomarker to predict the outcome during exacerbations are still unclear. Previous studies used different cut-off points varying from 200-300 cells/μL and 2-2.5% [4-11]. In this study we aimed to assess the cut-off values which predict the outcome of AECOPD predicting the progression, clinical outcomeand readmission for both the Peripheral Blood Eosinophil Count (PBEC) and Ratio (PBER).

***Address for Correspondence:** Gokce Kulah, Department of Pulmonology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey, E-mail: gokcekulah@gmail.com*

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Materials and Methods

Adult patients over 40 years of age hospitalised with a diagnosis of AECOPD in our clinic between 1 October 2016 and 1 January 2020, were included in the study. Between October 1, 2016 and January 1, 2020, the records of 3280 patients examined by a pulmonologist in hospital emergency departments and outpatient clinics and admitted to our pulmonology service with a chronic obstructive pulmonary disease diagnosis were evaluated. After excluding recurrent admissions, data from 2394 patients were obtained. After applying the inclusion and exclusion criteria among 2394 patients, the final number of 711 patients was reached (Figure 1).

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This study was approved by the local ethics committee (B.10.1.TKH.4.34.H.GP.0.01/58, date 18 March 2020). The exclusion criteria were as follows: Smoking history of fewer than 10 packages, Years, a diagnosis of asthma-COPD overlap syndrome, suspect infiltrations and/or

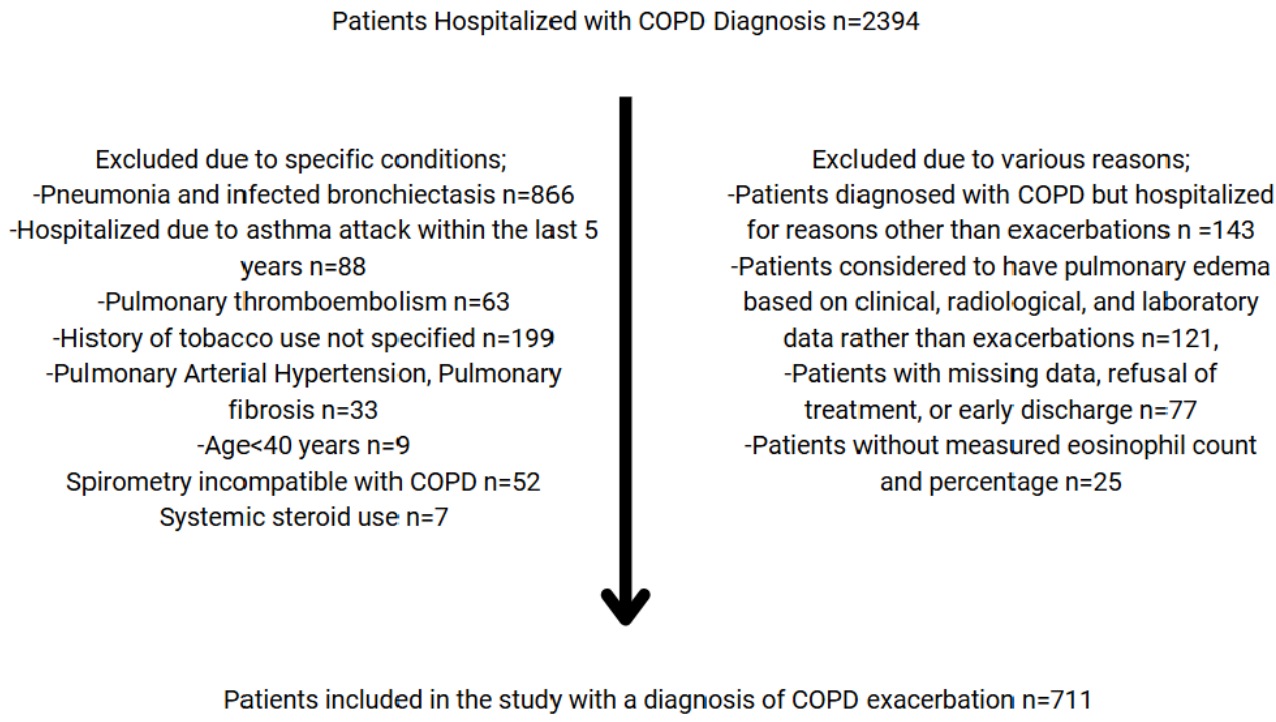

Figure 1. Applying the inclusion and exclusion criteria among patients with COPD diagnosis.

fibrosis in chest X-ray concerning pneumonia or pulmonary fibrosis, systemic fungal infections, long-term regular use of Systemic Corticosteroids (SCS) or short-term SCS use within one month before the study.

Data were obtained from the hospital database. The data collected from the patients were analyzed with IBM SPSS for Windows and Med Calc version 15.8. Descriptive statistics were presented as mean and standard deviation, or frequency and percentage, for continuous and categorical data, respectively. The t-test and Mann-Whitney Test were used to compare the data of two independent groups. The Pearson correlation analysis and correlation analysis were used for the correlational analysis of the parametric and non-parametric data respectively. The chi-square test was used to evaluate categorical data. Threshold values were determined by ROC analysis to determine the effect of eosinophil count and percentage on follow-up. The results were considered statistically significant when the P value was <0.05.

Results

A total of 711 patients (511 males, 71.9%) with a mean age of 74.02 ± 10.33 years were included in the study. The 71.4% (508 cases) had at least one of the comorbidities, the most frequent of which were HT (38.1%) followed by CAD (19.7%), DM (17.7%), CHF (12.4%) and arrhythmia (9.1%).196/711(27.6%) were current smokers and mean smoking amount was 56.52 ± 36.82 package years.

The mean PBEC and PBER were 146 ± 258/μL and 1.39 ± 2.15%, respectively. The mean duration for hospitalization was 6.94 ± 5.75 days. Of the 711 patients; 272(38.3%) were followed up with NIMV, 65(9.1%) were transferred to the ICU, 40(5.6%) were intubated, 15(2.1%) died during hospitalization and 300 (42.2%) applied with a new exacerbation in the first year after discharge. The mean number of exacerbations in the first year was 1.83 ± 1.33. The mean total follow-up duration for the whole study group was 3.58 ± 0.84 years and the long-term mean number of exacerbations/year was 1.59 ± 2.72. The long-term any-cause mortality rate was 53.9% (383/711 patients) (Table 1).

The correlation analysis was performed to assess the correlation of PBEC and PBER with the duration of hospitalization, need for NIMV, ICU follow-up and, intubation and, hospital mortality (Table 2). The PBEC and PBER were found to be correlated with ICU follow up while there was no significant correlation between PBEC and PBER with the duration of hospitalization, need for NIMV and intubation or death during hospitalization.

The patients were divided into groups according to the threshold values and compared.

The ICU follow-up was more frequent and the long-term mortality rate was higher in the low PBEC group (11.3% *vs*.3.2%, p<0.001 and 57.7% *vs*. 43.9%, p<0.001 respectively). While, the patient ratio was exacerbated in the first year and the number of exacerbations/year was significantly higher in the high PBEC group (60.1% *vs*. 35.8%, p<0.001 and 0.71 ± 0.83 *vs*. 0.35 ± 0.66, p<0.001) (Table 3).

The ICU follow-up, intubation and hospital mortality rate were increased in the low PBER group (11.4% *vs*. 5.1%, p=0.008, 7% *vs*. 3.1%, p= 0.049 and, 3.1% *vs*. 0.04%, p=0.036, respectively). The first-year exacerbation rate and number of exacerbations/year (58.3% *vs*. 33.3%, p<0.001 and 0.66 ± 0.79 *vs*. 0.33 ± 0.66, p<0.001) (Table 4).

Statistical significance was evaluated between the detected threshold values and the compared parameters. When the groups with low and high eosinophils were compared among themselves, it was observed that intubation and death were more common in the group with an eosinophil ratio of 1.15% or less. In the exacerbation/year ratio, the group with high eosinophils had more exacerbations than the group with low eosinophils (p=0.01) (Table 5).

The threshold values for PBEC and PBER assessed by the ROC analysis were 170/μL (with a 90.7% sensitivity and 28.3% specificity) and 1.15% (with an 80% sensitivity and, 37.3% specificity, respectively) (Figure 2).

Discussion

The PBEC and PBER may alter in stable COPD and during exacerbations and, due to the systemic corticosteroid use. Previous studies investigating the effect of eosinophils on the outcome of exacerbations used different cut-off points varying from 200-300 cells/μL and 2-2.5% [4-13]. In this study, we calculated the cut-off value which predicts the outcome of AECOPD as 170/μL for PBEC and 1.15% for PBER; which were lower than the cut-off values mentioned above.

The first end-point of the study was hospitalisation duration which was

similar between the low and high PBER and PBEC groups. Most of the previous studies revealed that patients with higher eosinophils need shorter hospital stays [5,6,11,12,14-16], but a few studies supported our findings [8,17]. The lower cut-off value in our study may also account for this result.

There is limited information concerning the relationship between blood eosinophils and ICU follow-up. Two previous studies revealed that the need for ICU follow-up was similar in eosinophilic and non eosinophilic patients [14,18]. While in our study the patients with high eosinophils were transferred to ICU less frequently. The discrepancy between our results and former studies may be due to the difference in decision-making for transferring the patient to the ICU.

Wu, et al. reported that the low PBEC was an independent factor predicting the need for NIMV use reflecting the hyperinflammatory status and inadequate immune response [14]. In our study, there was no difference in eosinophilic and non eosinophilic patients concerning NIMV use. This contradiction may be explained by the limited data for NIMV use in our study. The data for NIMV use was only for the patients followed at the ward but, ignored the NIMV use in ICU.

Table 1. The follow-up and mortality data of the patients during hospitalization and after discharge.

	Mean /n(%)	± Standart deviation	Minimum-maximum
Hospital stay (days)	6.94	5.75	0 – 63
NIMV use	272 (38.3%)	-	-
ICU follow up	65 (9.1%)	-	-
Intubation	40 (5.6%)	-	-
Death during hospitalisation	15 (2.1%)	-	-
Number of patients with exacerbations in the first year	300 (42.2%)	-	-
Number of exacerbations in the first year	1.83	1,33	1 – 10
Total follow-up duration (years)	3.58	0.84	0.5 -5.2
Total number of exacerbations	1.59	2.72	
Any cause of mortality during follow-up	383 (53.9%)	-	-

NIMV: Noninvasive Mechanical Ventilation, ICU: Intensive Care Unit.

Table 2. Correlation analysis of the data.

	1	2	3	4	5	6	7	8	9	10
PBEC	1	0.966**	-0.068	-0.004	-0.093*	-0.048	-0.035	0.26**	0.295**	-0.136**
PBER	0.966**	1	-0.062	0.005	-0.093*	-0.054	-0.05	0.25**	0.271**	-0.121**
Hospital stay duration	-0.068	-0.062	1	0.283**	0.178**	0.146**	0.164**	-0.016	-0.052	0.154**
NIMV use	-0.004	0.005	0.283**	1	0.222**	0.122**	0.046	0.007	-0.021	0.148**
ICU follow up	-0.093*	-0.093*	0.178**	0.222**	1	0.706**	0.293**	-0.143**	-0.171**	0.127**
Intubation	-0.048	-0.054	0.146**	0.122**	0.706**	1	0.516**	-0.122**	-0.147**	0.128**
Hospital mortality	-0.035	-0.05	0.164**	0.046	0.293**	0.516**	1,000	-0.125**	-0.142**	0.136**
Exacerbation in the first year	0.26**	0.25**	-0.016	0.007	-0.143**	-0.122**	-0.125**	1	0.81**	-0.215**
Number of exacerbations/year	0.295**	0.271**	-0.052	-0.021	-0.171**	-0.147**	-0.142**	0.81**	1	-0.361**
Any cause mortality	-.0136**	-0.121**	0.154**	0.148**	0.127**	0.128**	0.136**	-0.215**	-0.361**	1

Spearman analysis. **Correlation significance is 0,01. *Correlation significance is 0,05. PBEC: Peripheral Blood Eosinophil Count. PBER: Peripheral Blood Eosinophil Ratio, ICU: Intensive Care Unit, NIMV: Noninvasive Mechanical Ventilation.

Table 3. Comparison of the patients according to the PBEC.

		LowPBEC (n=523)	High PBEC (n=188)	Statistical test
Median hospital stay Days, (min-max)		6.92(0-63)	7.01(1-62)	[a]0.792
ICU follow up	No (%90.9)	464 (88.7)	182 (96.8)	p:<0.001
	Yes (%9.1)	59 (11.3)	6 (3.2)	
NIMV Use	No (%61.7)	322 (61,7)	117 (62.2)	p:0.941
	Yes (%38.3)	201 (38.4)	71 (37.8)	
Intubation	No (%94.4)	488 (93.3)	183 (97.3)	p:0.061
	Yes (%5.6)	35 (6.7)	5 (2.7)	
Hospital Mortality	No (%97.9)	509 (97.3)	187 (99.5)	p:0.144
	Yes (%2.1)	14 (2.7)	1 (0.5)	
First-year exacerbation	No (%57.8)	336 (64.2)	75 (39.9)	p:<0.001
	Yes (%42.2)	187 (35.8)	113 (60.1)	
Number of exacerbations/ yearmean ± SD		0.35 ± 0.66	0.71 ± 0.83	[a]<0.001
Long term mortality	No (%46.1)	221 (42.3)	107 (56.1)	p:<0.001

a: Mann-Whitney U test

Table 4. Comparison of the patients according to PBER.

		Low PBER (n=457)	High PBER (n=254)	Statistical test
Median hospital stay duration days, (min-max)		6.71(0-63)	7.07(0-62)	[a]0,172
ICU follow-up	No	405 (88.6)	241 (94.9)	p:0.008
	Yes	52 (11.4)	13 (5.1)	
NIMV Use	No	285 (62.4)	154 (60.6)	p:0.70
	Yes	172 (37.6)	100 (39.4)	
Intubation	No	425 (93)	246 (96.9)	p:0.049
	Yes	32 (7)	8 (3.1)	
Hospital mortality	No	443 (96.9)	253 (99.6)	p:0.036
	Yes	14 (3.1)	1 (0.04)	
First-year exacerbation	No	305 (66.7)	106 (41.7)	p:<0.001
	Yes	152 (33.3)	148 (58.3)	
Number of exacerbations/year(mean ± SD)		0.33 ± 0.66	0.66 ± 0.79	a<0.001
Long term mortality	No	198 (43.3)	130 (51.2)	p:0.053
	Yes	259 (56.7)	124 (48.8)	

a: Mann-Whitney U test, SD: Standard deviation.

Table 5. Comparison of hospitalization duration and total exacerbations in the follow-up year according to eosinophil ratio.

	Eos ≤1.15%	Eos >1.15%	Z	P
	Median (Q1-Q3)	Median (Q1-Q3)		
Length of Hospitalization	6.0 (4.0-9.0)	6.0 (4.0-8.0)	-0.66	0.51
Exacerbation/Year Rate	0.0 (0.0-0.5)	0.4 (0.0-1.1)	-6.60	0.01

z: Mann Whitney-U test.

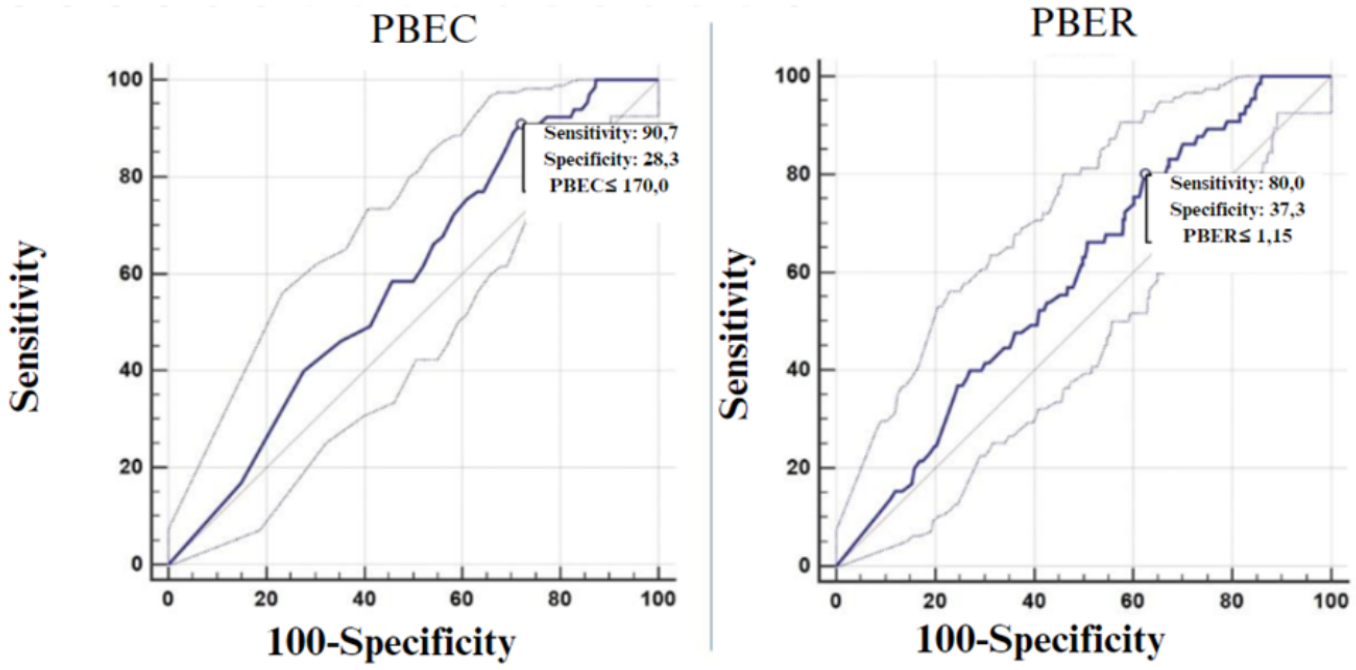

Figure 2. The threshold values for PBEC and PBER assessed by the ROC analysis.

The rate of patients transferred to the ICU unit was higher in the low PBEC group and the rate of patients intubated or died was higher in the low PBER group which was similar among PBEC groups. Two former studies reported that intubation and mortality rates did not differ between low and high PBEC groups [18,19]. On the other hand, Wu, et al, declared that the IMV use and mortality were similar between low and high PBEC groups while the mortality rate was higher in patients with low PBER. This was explained by poor response to systemic corticosteroids in non eosinophilic patients [14].

In the study, the recurrence of exacerbations both in the first year after discharge and long-term follow-up was more frequent in patients with high PBEC and PBER. Results of previous studies regarding the association between eosinophilic exacerbations and readmission are conflicting. Some studies revealed that patients with eosinophilic exacerbations had higher readmission rates while some concluded that the recurrence was not related to eosinophils [8,15,20]. These contradictory results may be due to different cut-off values and follow-up periods.

In our study, the eosinophilic patients had more frequent recurrent exacerbations in the first year after discharge while the long-term mortality rate was lower in this group. High PBEC was reported to be related to frequent exacerbations in many studies formerly [7-10].

There were a few limitations of our study. First, it was a single-center, retrospective study. The detailed data about the clinical features of patients were lacking such as pulmonary function test results before admission, GOLD stage and the outcome of patients referred to the different hospitals. Also, the detailed information about SCS use before admission may be erroneous. Although we included the patients admitted before the start of the COVID-19 pandemic in our country, some patients might be exacerbated due to viral infections which may in turn affect the peripheral blood cell counts. On the other hand, the eosinophil counts may differ from day to day. Patients with low eosinophil counts had an increased incidence of death on intubation and hospitalization but no difference in all-cause mortality. However, all-cause mortality was more frequent in patients with low eosinophil counts.

Conclusion

We concluded that the COPD patients with PBEC≤170/μL and PBER≤1,15% were more frequently transferred to ICU and, intubated and died at the hospital while suffering less from recurring exacerbations in the short (12 months) and long-term follow-up. Low eosinophils during admission with acute exacerbation were related to poor short-term prognosis in COPD patients.

Acknowledgement

In this study, the ethical standards of the Ethics Committee of Ümraniye Training and Research Hospital and the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards were followed.

Conflict of Interest

There is no conflict of interest in this study.

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