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Original Article

Impact of Eosinophil Levels on Disease Progression and Clinical Outcomes in Chronic Obstructive Pulmonary Disease (COPD) Patients: A Retrospective Study

Kronik Obstrüktif Akciğer Hastalığı (KOAH) Hastalarında Eozinofil Düzeylerinin Hastalık İlerlemesi ve Klinik Sonuçlar Üzerindeki Etkisi: Retrospektif Bir Çalışma

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ABSTRACT

Objective:: The role of total eosinophil count (EOS) in chronic obstructive pulmonary disease (COPD) remains debated, with studies suggesting both positive and negative impacts on disease progression. This retrospective study aimed to investigate the relationship between stable-state blood EOS levels and clinical outcomes, including hospitalizations, emergency room (ER) visits, and pneumonia, in COPD patients.

Methods: Data from 398 COPD patients were analyzed, focusing on blood EOS counts and percentages acquired during stable periods. Patients were categorized based on EOS thresholds of 150 cells/μL and 2%. The number of hospitalizations, ER visits, and pneumonia diagnoses in the preceding year was retrieved from hospital records and patient reports.

Results: Patients with EOS levels below 150 cells/μL or 2% showed a significantly higher number of hospitalizations. Additionally, patients with EOS percentages below 2% had higher COPD Assessment Test and Modified Medical Research Council scores, indicating greater symptom burden and dyspnea. Logistic regression analysis confirmed that a lower EOS percentage was an independent predictor of increased hospitalizations, similar to its association with lower FEV1% and more than two ER visits.

Conclusions: This study suggests that low blood EOS counts are associated with increased hospitalizations and worse clinical outcomes in COPD patients. This finding highlights the importance of considering EOS levels as a potential biomarker for disease severity and may lead to personalized treatment strategies. Further prospective studies are needed to validate these findings and elucidate the underlying mechanisms.

Keywords: Eosinophils, forced expiratory volume, hospitalization, pulmonary disease, chronic obstructive

ÖZ

Amaç: Kronik Obstrüktif Akciğer Hastalığında (KOAH) eozinofillerin (EOS) rolü hala tartışılmaktadır ve çalışmalar hastalığın ilerlemesi üzerinde hem olumlu hem de olumsuz etkiler olduğunu ileri sürmektedir. Bu retrospektif çalışma, KOAH hastalarında stabil durumdaki kan EOS seviyeleri ile hastane yatışları, acil servis (AS) ziyaretleri ve pnömoni dahil klinik sonuçlar arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Yöntemler: Üç yüz doksan sekiz KOAH hastasından alınan veriler, stabil dönemlerde elde edilen kan EOS sayıları ve yüzdelerine odaklanılarak analiz edildi. Hastalar 150 hücre/μL ve %2'lik EOS eşiklerine göre kategorize edildi. Önceki yıldaki hastane yatışları, AS ziyaretleri ve pnömoni tanıları hastane kayıtlarından ve hasta raporlarından alındı.

Bulgular: EOS seviyeleri 150 hücre/μL veya %2'nin altında olan hastalarda anlamlı sayıda daha fazla hastaneye yatış saptandı. Ek olarak, EOS yüzdeleri %2'nin altında olan hastalarda daha yüksek KOAH değerlendirme testi ve değiştirilmiş tıbbi araştırma konseyi skorları belirlendi ve daha fazla semptom yükü ve şiddetli dispne ile ilişkili olduğu görüldü. Lojistik regresyon analizi, daha düşük EOS yüzdesinin, daha düşük FEV1% ve ikiden fazla AS ziyaretine paralel olarak artan hastane yatışlarının bağımsız bir öngörücüsü olduğu gösterilmiştir.

Sonuçlar: Bu çalışma ile düşük kan EOS sayımlarının KOAH hastalarında artan hastane yatışları ve daha kötü klinik sonuçlarla ilişkili olduğu saptanmıştır. Bu bulgu, EOS düzeylerinin hastalık şiddeti için potansiyel bir biyobelirteç olarak dikkate alınmasının önemini vurgulamakta ve kişiselleştirilmiş tedavi stratejilerinin önünü açacaktır. Elde edilen verilerin ve altta yatan mekanizmaların doğrulanması için daha fazla prospektif çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Eozinofiller, görsel ekspiratuar bölüm, hastane yatışı, kronik obstrüktif akciğer hastalığı

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a preventable condition, presents a significant global health burden. It is the fourth leading cause of death worldwide, causing 3.5 million deaths in 2021. Nearly 90% of the deaths in individuals under 70 years of age occur in low and middle-income countries[1]. It is characterized by airflow limitation, respiratory symptoms, and exacerbations. The development of COPD results from a complex interaction between inherited predispositions, external influences, and inflammatory responses[2]. The focus on total eosinophil count (EOS) and its influence on COPD has grown substantially in the last few years. EOS are white blood cells that play a role in allergic inflammation and certain parasitic infections. EOS activity within COPD patients fluctuates based on specific disease presentations and how the condition progresses[3]. Although the role of EOS in COPD is not yet fully understood, existing evidence suggests that these cells play a significant role in airway inflammation and disease heterogeneity. Traditionally, COPD has been associated with neutrophilic inflammation. However, 37% of patients with COPD have EOS inflammation in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study[4]. This suggests the existence of different COPD phenotypes, each of which may require different treatment approaches[5]. The identification of EOSic COPD phenotypes has significant clinical implications. By monitoring blood EOS counts, clinicians can optimize corticosteroid regimens, potentially decreasing reliance on systemic corticosteroids and mitigating their associated side effects. EOS-guided therapy has been shown to be non-inferior to standard care in terms of days alive and out of hospital, while also reducing corticosteroid exposure in COPD exacerbations[6]. A positive correlation has been observed between increased EOS concentrations and enhanced short-term clinical outcomes in COPD patients, with a particular emphasis on those with a prior history of tobacco use. These patients tend to have shorter hospital stays and a better response to corticosteroid therapy compared to those with lower EOS counts[7].

Eosinopenia has also been associated with an increased risk of treatment failure in COPD exacerbations. Various thresholds for eosinopenia have been used in studies of patients with COPD exacerbations: <50 cells/μL, <150 cells/μL, <0.144 × 109/L, <2%[5,8,9]. Further research is needed on whether eosinopenia can be used as a marker of severity in COPD exacerbations and to determine an appropriate threshold value. The aim of this study was to investigate the relationship between blood EOS levels during the stable period and the number of hospitalizations, pneumonia, and emergency room (ER) admissions detected in the previous year.

MATERIALS and METHODS

The study included participants from two different study cohorts: Yazar et al's[10] and Gürel et al's[11]. In both studies, the relationship was evaluated between demographic characteristics such as age, gender, pulmonary function test values, EOS count and percentages in the blood measured during the stable period, history of hospitalizations due to COPD in the last year, number of ER visits, and history of pneumonia, in patients who have been under treatment and follow-up with a diagnosis of COPD for at least 1 year was evaluated. Both studies from which data were obtained received approval from the local Ethics Committee of Medeniyet University (decision number: 2018/24-05, date: 28.12.2018). First study from Biruni University, second study from Clinical Research Ethics Committee of Medeniyet University, Göztepe Training and Research Hospital. All patients included in the study were informed about the study, and written consent was obtained from them.

The inclusion criteria for patients were the following: 1. age ≥40 years; 2. routine baseline stable state peripheral blood test results before receiving any antibiotic or systemic corticosteroid therapy; 3. patients diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease guideline with previous spirometry detected forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of <0.70.

The exclusion criteria were 1. bronchial asthma, asthma-COPD overlap syndrome, parasites, or other allergic diseases associated with elevated EOS levels in peripheral blood; 3. patients with missing data; 4. Patients who do not consent to participate in the study

The number of hospitalizations due to COPD exacerbations, ER admissions, and pneumonia diagnoses in the previous year was retrieved from the hospital's database and patient's statements.

It has been observed that EOS counts measured during acute exacerbations are not associated with future rehospitalizations or long-term mortality[12]. To assess a patient's overall long-term risk profile and potential for future hospitalizations, EOS levels during the stable state provide a more reliable indicator, as this state is more consistent than the transient inflammatory status observed during an exacerbation. Therefore, blood samples from patients were collected during the stable state, defined as having no recent exacerbation or at least being four weeks after the last exacerbation.

The patients were divided into two groups based on their peripheral blood EOS count and percentage. Cutoff values are selected as 150 cells/mL and 2%.

Statistical Analysis

Continuous variables are expressed as mean values with standard deviation and compared with Student's t-test or Mann-Whitney test as appropriate, whereas categorical variables are expressed as percentages and compared by the chi-square test. Spearman's correlation was used to identify. Multiple logistic regression analyses were performed to assess possible associations between hospitalization and other variables. p-values less than 0.05 were deemed statistically significant.

RESULTS

This retrospective study included 398 patients with COPD. The study population had a mean age of 65.15 years, with a predominance of males (84.4%). A significant proportion of patients (46.3%) were current or former smokers, with a mean smoking history of 47.5 pack-years. The mean FEV1% value was 50.55±18.72, and the mean FVC % was 65.62±19.13 (Table 1). The mean EOS count was 221.67±150.75, and the EOS % was 2.51±1.71. In the year prior to the study, the mean number of hospitalizations was 0.17±0.58, ER admissions was 1.53±3.01, and the diagnosis of pneumonia was 0.79±1.57.

Patients were categorized based on blood EOS count (cutoff: 150 cells/μL) and EOS percentage (cutoff: 2%). Significant differences in the number of hospitalizations were observed between the groups defined by both EOS count and percentage (Table 2). Furthermore, when using the 2% EOS percentage cutoff, significant differences were also found in COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) scores between the groups. Higher number of hospitalizations in the previous year (<2% vs. ≥2%; 0.27±0.74 vs. 0.09±0.43), higher number of patients with CAT score over 10 (<2% vs. ≥2%; %66.3 vs. % 56.0) and higher number of patients with mMRC score over 2 (<2% vs. ≥2%; %57.8 vs. %44.0) were detected in patients with EOS <2%.

The number of hospitalizations was correlated with FEV1% predicted (c: -0.206, p<0.001), ER admissions (c: 0.362, p<0.001), CAT (c: 0.183, p<0.001), and mMRC scores (c: 0.228, p<0.001). Correlations remained significant even when groups were separated (Table 3 and Figure 1).

Logistic regression analysis revealed that previous year's number of hospitalizations was significantly associated with lower predicted FEV1% [odds ratio (OR) 0.970, 95% CI 0.948-0.992, p: 0.008, EOS percentage less than 2% (OR: 2.505, 95% confidence interval (CI) 1.208-5.196, p: 0.014), and more than two ER admissions (OR: 6.361, 95% CI 2.865-14.123, p<0.001) (Table 4).

Table 1. Demographic characteristics of the study population.

Variable	n=398
Age (years)	65.15±8.50
Gender	
Male	336 (84.4)
Female	62 (15.6)
Smoking status	
Smoker	184 (46.30)
Exsmoker	214 (53.70)
Smoking package-year	47.50±27.64
FEV1 (L)	1.38±0.61
FEV1 % predicted	50.55±18.72
FVC (L)	2.25±0.83
FVC % predicted	65.62±19.13
FEV1/FVC	56.78±9.90
EOS count (cell/mL)	221.67±150.75
EOS %	2.51±1.71
Hospitalizations in the previous year	0.00 (0) (min-max 0.00-5.00)
ER admissions in the previous year	0.00 (2) (min-max 0.00-30.00)
Pneumonia diagnosis in the previous year	0.00 (1) (min-max 0.00-10.00)
CAT score	13.42±8.93
mMRC score	1.74±1.26

Data are presented as means±SD, median (Interquartile range and with minimum and maximum values) or number (%). FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, EOS: Total eosinophil count, ER: Emergency room, CAT: Chronic obstructive pulmonary disease assessment test, mMRC: modified medical research council, SD: Standard deviation

Table 2. Patients' characteristics regarding EOS count and %.						
Variables	**EOS <150 n=125**	**EOS ≥150 n=271**	**p-value**	**EOS <2% n=166**	**EOS ≥2% n=230**	**p-value**
FEV1% pred	51.02±19.02	50.33±18.62	0.733	49.87±18.53	51.03±18.89	0.543
FVC% pred	66.14±20.17	65.38±18.66	0.716	65.31±19.49	65.84±18.90	0.786
FEV1/FVC	56.89±9.38	56.73±10.15	0.886	56.39±9.75	57.06±10.02	0.509
Hospitalizations	0.27±0.76	0.12±0.47	0.039	0.27±0.74	0.09±0.43	**0.008**
ER	1.70±3.13	1.46±2.96	0.466	1.81±3.04	1.34±2.99	0.125
Pneumonia	0.82±1.79	0.78±1.47	0.851	0.92±1.77	0.70±1.41	0.189
CAT	12.98±8.69	13.63±9.04	0.506	14.02±8.89	13.00±8.95	0.258
CAT <10 CAT ≥10	48 (38.4) 77 (61.6)	110 (40.3) 163 (59.7)	0.720	56 (33.7) 110 (66.3)	102 (44.0) 130 (56.0)	**0.040**
mMRC	1.86±1.35	1.68±1.21	0.229	2.01±1.31	1.54±1.19	**<0.001**
mMRC <2 mMRC ≥2	59 (47.2) 66 (52.8)	141 (51.6) 132 (48.4)	0.410	70 (42.2) 96 (57.8)	130 (56.0) 102 (44.0)	**0.006**

EOS: Total eosinophil count, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, ER: Emergency room, CAT: chronic obstructive pulmonary disease assessment test, mMRC: modified Medical Research Council

Table 3. Correlation table between hospitalisations, FEV1% predicted, ER admissions, CAT and mMRC score.				
	FEV1 % pred	**ER admission**	**CAT score**	**mMRC score**
Hospitalizations (All)	c: -0.206 p<0.001	c: 0.362 p<0.001	c: 0.183 p<0.001	c: 0.228 p<0.001
EOS < 150 cell/μL	c: -0.242 p: 0.006	c:0.384 p<0.001	c:0.210 p :0.019	c:0.225 p :0.012
EOS ≥ 150 cell/μL	c: -0.195 p: 0.001	c: 0.356 p<0.001	c:0.183 p:0.002	c:0.228 p<0.001
EOS < 2%	c: -0.212 p: 0.006	c: 0.356 p<0.001	c:0.213 p:0.006	c:0.223 p:0.004
EOS ≥ 2%	c: -0.211 p: 0.001	c: 0.381 p<0.001	c:0.148 p:0.025	c:0.199 p:0.002

FEV1 % pred: FEV1: Forced expiratory volume in one second predicted, ER: Emergency room admission, CAT: chronic obstructive pulmonary disease assessment test, mMRC: modified medical research council, EOS: Total eosinophil count,, p<0.05 considered significant, c: Pearson correlation coefficient

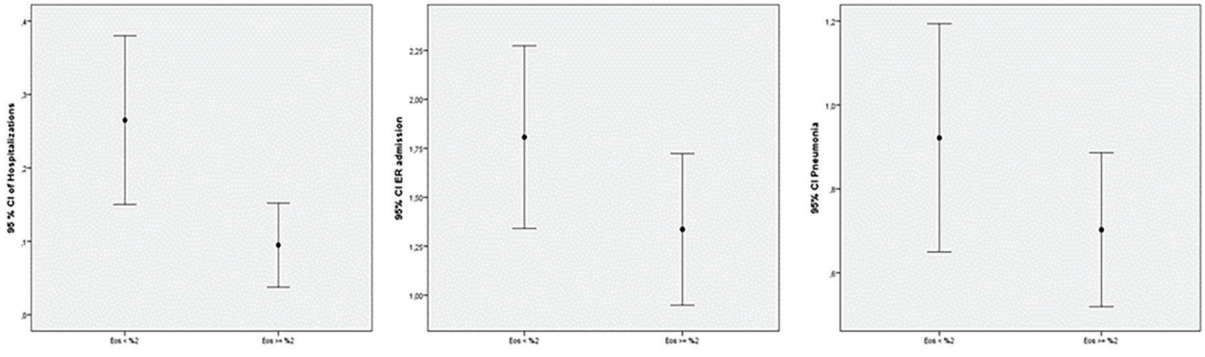

Figure 1. Errorbar graphics between blood EOS % and the number of hospitalizations, ER admissions and pneumonia diagnosis.

EOS: Total eosinophil count, ER: Emergency room, CI: Confidence interval

Table 4. Logistic regression analysis on factors affecting hospitalization.				
Model 1 Dependent variable: Hospitalisation in the previous year				
	B	**OR**	**95% CI**	**p-value**
FEV1% pred	-0.037	0.964	0.942-0.986	0.001
EOS %	-0.295	0.745	0.578-0.959	0.023
ER adm	0.202	1.224	1.107-1.353	<0.001
Model 2 Dependent variable: Hospitalisation in the previous year				
	B	**OR**	**95% CI**	**p-value**
FEV1% pred	-0.030	0.970	0.949-0.992	0.008
EOS ≥150 cell/μL	0.896	2.450	1.183-5.077	0.016
EOS ≥150 cell/μL	0.896	2.450	1.183-5.077	0.016

FEV1 % pred: Forced expiratory volume in one second % predicted, B: Regression coefficient, OR: Odds ratio, CI: Confidence interval, EOS %: Blood eosinophil count %, ER adm: Emergency room admission rate in the previous year, EOS ≥150: Total eosinophil count 150 cells/mL and above, ER adm adm ≥2: Emergency room admission rate 2 and above in the previous year

DISCUSSION

Our study demonstrated significant associations between the number of hospitalizations and predicted FEV1%, ER visits, CAT scores, and mMRC scores. These correlations remained statistically significant after stratifying by EOS count, supporting the hypothesis that low EOS counts may independently affect the clinical course and outcomes of COPD. In addition, this study identified a statistically significant association between low blood EOS counts (≤150 cell/μL or ≤2%) and an increased number of hospitalizations among patients with COPD during a stable phase. Despite ongoing debate regarding the precise mechanisms of EOS in COPD, studies have established a link between elevated EOS counts and exacerbations requiring hospital admission. Conversely, other research suggests that low EOS levels may indicate adverse clinical outcomes. Our findings are consistent with the "non-EOS COPD" phenotype as described in the literature, a distinct phenotype characterized by more severe airflow limitation, a higher frequency of exacerbations, diminished quality of life, and increased mortality risk[13].

The blood EOS level used in COPD phenotyping is related to disease prognosis and management. However, research findings conflict regarding the role of blood EOS levels in COPD exacerbations. Several studies indicate that increased EOS counts (at or above 2% or 300 cells/μL) correlate with improved responses to systemic corticosteroid therapy and reduced length of hospital stays[14,15]. We found that patients with EOS counts less than 150 cells/μL or 2% experienced a significantly higher number of hospital admissions, ER visits, and pneumonia compared to individuals with higher EOS levels.

Several potential mechanisms may explain the link between diminished EOS counts and heightened hospitalization risk. These include the activation of alternative inflammatory pathways, an elevated susceptibility to bacterial infections, a diminished responsiveness to corticosteroid treatment, and exacerbated systemic inflammation[9,14,16]. As EOS are immune cells normally found in the respiratory tract, providing defense against pathogens, their reduction may increase susceptibility to infections. Moreover, investigations have demonstrated that reduced EOS counts often coincide with elevated neutrophil counts, indicating a distinct inflammatory pattern[16]. Although our data did not include neutrophil counts, we observed a higher rate of pneumonia diagnoses in patients with low EOS levels, consistent with these findings.

As patients were categorized based on EOS levels, the distinction among their clinical parameters became particularly evident when a 2% threshold was applied to the EOS percentage in our study. We observed that patients with an EOS percentage below 2 had higher CAT and mMRC scores. This suggests that a low EOS percentage may correlate with the severity of symptoms and dyspnea, affecting patients beyond hospitalization. This finding supports the idea that EOS in COPD may have an impact on the long-term course of the disease and symptom management in addition to acute exacerbations. Similar to our findings, Lv et al.[17] reported significantly increased inflammation, reduced lung function, extended hospital stays, elevated mMRC and CAT scores, higher mortality, and greater utilization of non-invasive mechanical ventilation in patients with EOS counts below 2%. Furthermore, in two studies conducted by Ko et al.[12] and Greulich et al.[14], patients with low EOS

counts (<2% or <100 cells/μL) had consistently longer hospitalizations compared to patients with higher EOS levels.

While discrepancies exist across various studies, a general tendency suggests that elevated blood EOS counts in COPD patients might correlate with better, or at least comparable, lung function, however, the clinical significance of these improvements isn't always substantial. Despite this, high EOS counts have been linked to a rapid decline in lung function as indicated by published data[18-20]. Conversely, it's important to note that lower EOS counts don't consistently correspond to a slower decline. In our study, despite varying EOS thresholds (150 and 2%), no significant differences were observed between groups in baseline respiratory function tests, indicating that these specific EOS cut-offs may not be directly linked to the degree of pulmonary impairment at a stable state. Factors such as a history of smoking and patients' treatment differences are likely to have an influence on this complicated relationship[19,20]. Interestingly, despite the faster decline in FEV1, patients with consistently high EOS levels tend to have better survival rates and improved symptom control compared to those with lower EOS levels[16,21].

Study Limitations

Our investigation is subject to several limitations. A significant limitation is its single-center, retrospective design, which may inherently restrict the generalizability of our findings to broader populations. Furthermore, our analysis was confined to blood EOS counts, and we did not assess sputum EOS, other inflammatory markers such as interleukin-5, or comprehensive systemic inflammation markers. These factors introduce a degree of heterogeneity within our dataset, particularly regarding participants' inhaled corticosteroid use, diverse maintenance therapy regimens, and the presence of various comorbidities. The absence of uniformity in these aspects made the systematic inclusion of these critical variables in our logistic regression analysis infeasible. As a result, we could not precisely ascertain the independent contribution of these factors to the observed outcomes. While our findings offer valuable insights, their interpretation must consider the potential confounding effects of differing medication use and underlying health conditions that were not comprehensively addressed in the statistical models. Further investigations, ideally incorporating controlled, prospective, and multi-center methodologies, are essential to thoroughly decipher these complex interactions.

CONCLUSION

In conclusion, our findings suggest a potential association between low blood EOS counts and an elevated risk of hospitalization in patients with COPD. This finding highlights the heterogeneous nature of COPD and the clinical significance of different inflammatory phenotypes. Closer monitoring of COPD patients with low EOS counts and the development of personalised treatment strategies for this group are necessary. Further research is needed to investigate this area and improve the management of COPD.

Ethics

Ethics Committee Approval: Both studies from which data were obtained received approval from the local ethics committee. First study from Biruni University, second study from Clinical Research Ethics Committee of Istanbul Medeniyet University, Göztepe Training and Research Hospital. (decision number: 2018/24-05, date: 28.12.2018).

Informed Consent: All patients included in the study were informed about the study, and written consents were obtained from them.

Footnotes

Author Contributions

Surgical and Medical Practices: B.A.Y., E.E.Y., Concept: B.A.Y., E.E.Y., Design: B.A.Y., E.E.Y., Data Collection and/or Processing: B.A.Y., E.E.Y., E.H.K., E.Y.O.N., C.D., F.C.G., Analysis or Interpretation: B.A.Y., E.E.Y., E.H.K., E.Y.O.N., C.D., F.C.G., Literature Search: B.A.Y., E.E.Y., E.H.K., E.Y.O.N., C.D., F.C.G., Writing: B.A.Y., E.E.Y., E.H.K., E.Y.O.N., C.D., F.C.G.

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