

COPD and eosinophils: a perspective from the intensive care unit

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by airflow limitation and chronic airway inflammation. Various biomarkers have been investigated to better guide the treatment and predict the prognosis of COPD patients, among which blood eosinophil levels have received particular attention. Unlike many previous studies, our investigation specifically focuses on COPD patients in the intensive care unit (ICU), where disease severity is markedly higher.

Methods: Data from 141 COPD patients admitted to the ICU over a one-year period were retrospectively analyzed. The patients were classified into two groups based on their blood eosinophil counts; a low eosinophil group (0-100 cells/ μ l) and a moderate-high eosinophil group (>100 cells/ μ l). These groups were compared in terms of clinical scoring systems, laboratory parameters, and ICU-related clinical outcomes.

Results: Patients with low eosinophil levels had higher levels of infection-related biomarkers, including procalcitonin, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio. Additionally, a weak positive correlation was observed between increasing eosinophil levels and partial carbon dioxide pressure. However, no statistically significant associations were found between eosinophil levels and outcomes such as mortality, tracheostomy requirement, or the need for inotropic support.

Conclusion: In addition to its established role in predicting response to corticosteroid therapy, the peripheral blood eosinophil count may serve as a potential biomarker for guiding treatment strategies and prognostic evaluation in COPD exacerbations managed in the ICU. It should be noted that in COPD patients with higher eosinophil levels requiring intensive care follow-up, non-infectious exacerbations -such as those triggered by environmental exposures, medication nonadherence, or underlying airway inflammation- may be more prominent.

Keywords: COPD, eosinophil, intensive care, mortality, respiratory disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by chronic airflow limitation, combined with inflammation of the airways. The illness is progressive and highly prevalent in most regions of the world. Acute exacerbation of COPD represents an important clinical issue in that exacerbation not only worsens the course of the disease itself but also increases hospitalization rates and healthcare expenditure associated with COPD.^{1,2} These exacerbations, particularly those severe enough to require intensive care unit (ICU) admission, may have a strong impact on patient outcomes. Thus, the identification of reliable biomarkers predictive of the severity and clinical consequences of COPD exacerbations has become an important research priority.

One biomarker of interest is blood eosinophil count, which has been investigated for its role in the management of COPD. Eosinophils are a specific white blood cell subtype that is intimately related to inflammation and have been reported to correlate with some exacerbation phenotypes in COPD.³

High levels of eosinophils have been reported to be associated with a good response to corticosteroid therapy and may thus impact on clinical outcomes such as length of stay (LOS) in the hospital and overall mortality.^{4,5} However, the value of blood eosinophils for the prediction of clinical outcomes such as LOS in the ICU, mortality, acidotic respiratory failure, or infectious exacerbation in ICU-admitted COPD exacerbation patients is still understudied.⁶

Severe exacerbations of COPD are usually characterized by respiratory acidosis, probably as a consequence of the worsening of gas exchange and increase in respiratory workload. This condition often requires treatment in ICUs and impacts significantly on patients' outcomes. Although of clinical importance, the potential correlation of respiratory acidosis with eosinophils has not been specifically investigated up to now. Moreover, understanding the behavior of eosinophils in infectious versus non-infectious COPD exacerbations may be useful in developing personalized therapeutic approaches.⁷ Such analyses, when done in the ICU setting, may have

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important implications for improving current prognostic models and guiding individualized management.

In this retrospective study, we retrospectively analyzed the data of 141 admitted COPD exacerbation patients to the ICU within one year. Our objective was to elucidate the association between the blood eosinophil counts with major clinical outcomes, which included ICU LOS, mortality, respiratory acidosis, and infectious exacerbations. This study will contribute to the current understanding of the role of eosinophils in the management of COPD, particularly in critically ill patients, and add to the evolving evidence in this field. Unlike many previous studies, our investigation specifically focuses on COPD patients in the ICU, where disease severity is markedly higher.

METHODS

The study was performed in accordance with the Helsinki Declaration. After obtaining ethical approval from the Ankara Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 11.12.2024, Decision No: 2024-BÇEK 185), the study commenced. All patients hospitalized in a tertiary-level ICU, predominantly treating respiratory diseases, were screened over a one-year period from January 2022 to January 2023. Informed consent forms were obtained from patients and/or their legal guardians prior to accessing patient information. A total of 387 patient files were reviewed, of which 149 were identified as being admitted to the ICU with a diagnosis of COPD exacerbation.

Before initiating our study, we ensured that the informed consent forms, which we routinely obtain from patients and/or their legal guardians in our ICUs, were fully completed and approved. These forms grant permission for the use of patients' clinical and radiological data in scientific research.

Among these, 8 patients were excluded as they had died within the first 24 hours of ICU admission. These exclusions were made because it was not possible to rule out causes of mortality unrelated to COPD. Consequently, 141 patients were included in the study (Figure 1). Demographic data, including age and sex, were recorded. The included patients were then divided into two groups based on their peripheral blood eosinophil absolute counts.

- **Group 1:** Comprised patients with blood eosinophil levels between 0-100 cells/ μ L and was defined as the low eosinophil group.
- **Group 2:** Included patients with blood eosinophil levels ≥ 100 cells/ μ L and was defined as the moderate-high eosinophil group (Figure 1).

For both groups, initial ICU admission measurements of C-reactive protein (CRP), procalcitonin, D-dimer, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were recorded as markers of infection and inflammation. Additionally, partial carbon dioxide pressure (pCO₂) levels at ICU admission were documented, and patients were classified according to respiratory failure subtypes.

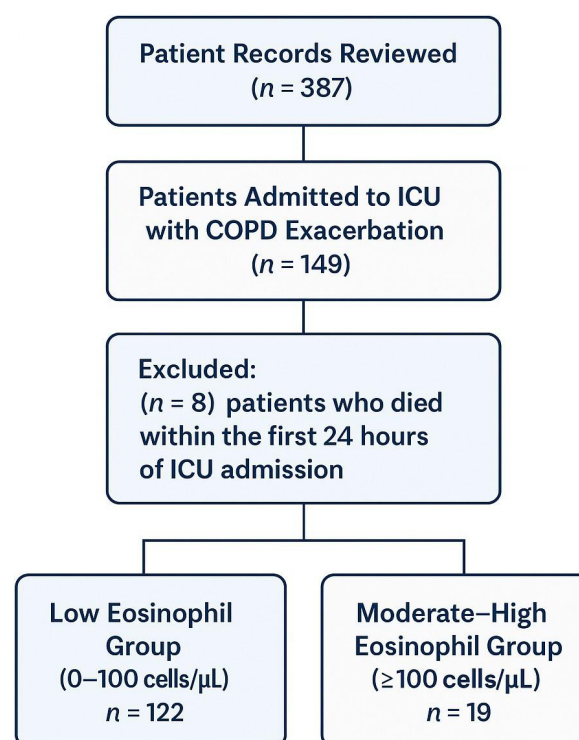


Figure 1. Flowchart of patient selection and eosinophil-based grouping

Further data collected included ICU length of stay (LOS), ICU mortality, and the need for intubation. To compare comorbidity profiles, mortality risk, and infection severity between the groups, the Charlson Comorbidity Index, APACHE II scores, and SOFA scores were also recorded at ICU admission.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Version 27 (IBM Corp., Armonk, NY, USA). Categorical nominal variables were summarized as frequencies and percentages (n, %). Ordinal variables and numerical data that did not follow a normal distribution were reported as medians with their corresponding ranges (min-max). Numerical data with a normal distribution were expressed as mean $\pm$ standard deviation (SD). In the patient groups, for categorical variables, the Chi-square test was used if each cell contained more than 5 patients. If any cell contained fewer than 5 patients, Fisher's exact test was applied.

Numerical data were analyzed using the student's T test when normally distributed, and the Mann-Whitney U test when not. The normality of numerical data was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests, skewness and kurtosis values, histograms, and proximity of outliers to each other. For bivariate correlation analyses, Spearman's correlation test was applied if at least one of the variables did not follow a normal distribution, while Pearson's correlation test was used if both variables were normally distributed.

A confidence interval of 95% was adopted for all statistical tests, with a significance threshold set at $p < 0.05$. For normally distributed numerical variables with significant differences between means, effect sizes were calculated using Cohen's d.

RESULTS

Among the 141 patients included in the study, 91 were male and 50 were female. Of these, 122 were assigned to the low eosinophil group, while 19 were categorized into the moderate-high eosinophil group. The average age in the low eosinophil group was 71.13 ± 0.87 years, compared to 68.42 ± 2.05 years in the moderate-high eosinophil group. No significant differences were identified between the two groups in terms of age, APACHE II scores, SOFA scores, Charlson Comorbidity Index (CCI), or glasgow coma scores (GCS) (Table 1).

When comparing infective parameters, patients in the low eosinophil group had significantly higher neutrophil counts, NLR, PLR, and procalcitonin levels, while their lymphocyte counts were significantly lower (p-values: 0.009, <0.001, <0.001, 0.026, and 0.002, respectively). However, no significant difference was observed between the groups in terms of CRP levels (p: 0.461) (Table 1).

Additionally, among patients admitted to the ICU with COPD exacerbation, no significant differences were identified between the low eosinophil and moderate-high eosinophil groups in terms of sex, mortality, intubation requirement during ICU stay, inotropic support, or tracheostomy needs (p-values: 0.892, 0.365, 0.574, 1, and 1, respectively, based on Chi-square or Fisher's exact test as appropriate).

Correlation analyses conducted between eosinophil levels and other quantitative variables across both groups revealed a moderate, significant negative correlation between eosinophil levels and both PLR and NLR ($p < 0.001$, r : -0.300, 95% CI: -0.448 to -0.137; $p < 0.001$, r : -0.330, 95% CI: -0.474 to -0.169, respectively, Spearman) (Figure 2, 3). Additionally, a moderate, significant positive correlation was observed between eosinophil levels and lymphocyte counts ($p < 0.001$, r : 0.311, 95% CI: 0.149 to 0.457). Furthermore, a weak but significant positive correlation was identified between eosinophil levels and partial carbon dioxide pressure (pCO_2) (p: 0.004, r : 0.238, 95% CI: 0.071 to 0.392, Spearman). Similarly, eosinophil levels exhibited a weak but significant positive correlation with ICU length of stay (p: 0.016, r : 0.203, 95% CI: 0.034 to 0.361, Spearman). Among all variables,

intubation duration showed the strongest positive correlation with ICU length of stay ($p < 0.001$, r : 0.511). However, when partial correlation analysis was performed by controlling for intubation duration, the correlation between eosinophil levels and ICU LOS was no longer significant (p: 0.220) (Table 2).

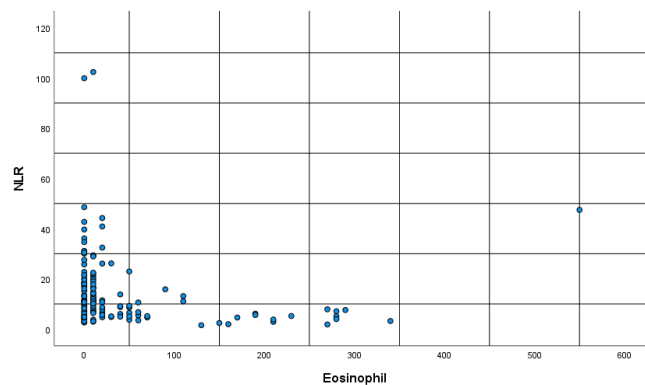


Figure 2. Correlation between eosinophil and NLR

NLR: Neutrophil/lymphocyte ratio

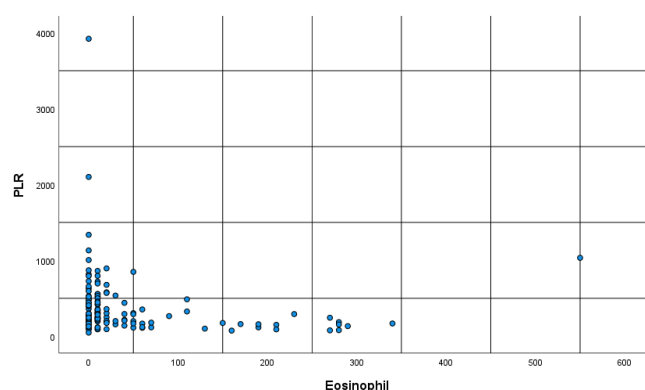


Figure 3. Correlation between eosinophil and PLR

PLR: Platelet/lymphocyte ratio

DISCUSSION

COPD represents a heterogeneous group of disorders, and over the years, efforts have been made to define its subtypes based on distinct clinical and pathological characteristics. Identifying these subtypes is crucial for developing personalized

Table 1. Comparison of quantitative values between patient groups

Parameter	Low eosinophil group [mean $\pm$ SD or median (min-max)]	Moderate-high eosinophil group [mean $\pm$ SD or median (min-max)]	p-value
Age (years)	71.13 $\pm$ 0.87	68.42 $\pm$ 2.05	0.253 ^a
APACHE II score	17.3 $\pm$ 6.9	15.7 $\pm$ 6.9	0.373 ^a
SOFA score	4.5 $\pm$ 3.5	4.2 $\pm$ 3.2	0.784 ^a
CCI	3.8 $\pm$ 1.5	3.8 $\pm$ 2.4	0.969 ^a
GCS	15 (3-15)	15 (3-15)	0.713 ^a
Lymphocyte count (cells/ μ l)	894 $\pm$ 571	1557 $\pm$ 796	0.002 ^{a*}
Neutrophil count (cells/ μ l)	9786 $\pm$ 4954	7374 $\pm$ 3258	0.009 ^{a*}
Procalcitonin (ng/ml)	6 (1-155)	4 (1-21)	0.026 ^{b*}
Neutrophil/lymphocyte ratio	11.22 (2.6-102.3)	5.09 (1.5-47.4)	<0.001 ^{b*}
Platelet/lymphocyte ratio	284.8 (47.01-3921.3)	157.8 (74.06-1033.3)	<0.001 ^{b*}

^a: Student's T test, ^b: Mann-Whitney U test, ^{*}: Significant values at 95% confidence interval, SD: Standard deviation, min: Minimum, max: Maximum, APACHE: Acute physiology and chronic health evaluation, CCI: Charlson Comorbidity Index, GCS: Glasgow coma score, SOFA: Sequential organ failure assessment

Table 2. Correlation analysis of eosinophil levels with clinical and laboratory variables

Variables	Correlation coefficient (r)	p-value	95% CI	Test type
Eosinophil-PLR	-0.3	<0.001	-0.448 to -0.137	Spearman
Eosinophil-NLR	-0.33	<0.001	-0.474 to -0.169	Spearman
Eosinophil-lymphocyte count	0.311	<0.001	0.149 to 0.457	Spearman
Eosinophil-pCO ₂	0.238	0.004	0.071 to 0.392	Spearman
Eosinophil-ICU LOS	0.203	0.016	0.034 to 0.361	Spearman
Intubation duration-ICU LOS	0.511	<0.001	0.373 to 0.627	Spearman
Eosinophil-ICU LOS (Partial, controlled for intubation duration)	0.104	0.220		Partial Spearman

CI: Confidence interval, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, pCO₂: partial carbon dioxide pressure, ICU: Intensive care unit, LOS: Length of stay

treatment strategies in disease management. For instance, beyond the classical subtypes such as chronic bronchitis and emphysema, recent years have seen the emergence of phenotypic variations like Asthma-COPD Overlap Syndrome (ACOS) and eosinophilic COPD. The recognition of these subtypes is not only essential for understanding the natural course of the disease but also plays a pivotal role in optimizing therapeutic responses.

In recent years, studies have explored the relationship between peripheral blood eosinophil levels and COPD exacerbations, as well as their impact on treatment response. A study by Pavord et al.⁸ demonstrated that COPD patients with higher eosinophil levels significantly benefitted more from inhaled corticosteroid (ICS) therapy. By analyzing various eosinophil thresholds, the study highlighted that eosinophil levels above 300 cells/μl were particularly associated with higher response rates to treatment.

In patients monitored in the ICU due to COPD exacerbation, eosinophil levels have been reported to yield differing outcomes in terms of infectious and inflammatory processes. A retrospective study conducted by Singh et al.⁹ involving 200 ICU patients observed that those with low eosinophil levels (<100 cells/μl) were more frequently associated with infectious causes and required mechanical ventilation for longer durations. In our study, while no significant difference was found between the groups in terms of ICU length of stay, a weak but significant positive correlation was identified between eosinophil count and ICU length of stay across all patients. In our analysis, where the need for mechanical ventilation was determined to be the most significant factor prolonging ICU stays, partial correlation analysis neutralized this effect, revealing that eosinophil levels had no independent impact on ICU length of stay. The imbalance in sample sizes between the two patient groups emerged as a limitation of our study. This imbalance may have contributed to findings that, while inconsistent with the literature, were deemed coincidental. In a study by Christenson et al.¹⁰ involving 120 patients, it was demonstrated that those with the ACOS phenotype had significantly higher eosinophil levels and responded better to corticosteroid therapy. These findings underscore the potential impact of phenotypic differentiation on tailoring individualized treatment strategies.

Analyses based on low, moderate, and high eosinophil levels provide valuable insights into the treatment and prognosis of COPD patients. For instance, in the WISDOM study by

Watz et al., it was observed that discontinuing ICS therapy in patients with eosinophil levels >300 cells/μl significantly increased the risk of exacerbations.¹¹ These findings suggest that eosinophil levels may serve not only as a predictor of treatment response but also as an effective biomarker for forecasting clinical outcomes.

In our study, we found that as eosinophil levels increased, the partial carbon dioxide pressure (pCO₂) measured at ICU admission also rose significantly. This finding could indicate that higher eosinophil counts in patients are associated with more severe inflammatory processes, potentially leading to greater bronchoconstriction. Similarly, a prospective study by Wang et al.,¹² conducted on 300 ICU-admitted COPD exacerbation patients, reported that low eosinophil levels (<100 cells/μl) were associated with higher mortality rates. However, in our study, no significant differences in mortality rates were observed between the groups.

One of the most notable findings of our study is the observation that patients with lower peripheral blood eosinophil levels exhibited significantly higher levels of infection-related inflammatory markers such as NLR, PLR, and procalcitonin. This finding strongly supports the hypothesis that non-eosinophilic COPD exacerbations may be primarily driven by infectious etiologies. Several studies in the literature have suggested that eosinopenia in critically ill patients reflects acute physiological stress and impaired immune response, and is associated with worse prognosis.¹³ In the context of COPD, low eosinophil levels may indicate infection-related exacerbations and suggest that this phenotype may require a different treatment approach than eosinophilic exacerbations.^{14,15} Moreover, previous research has shown that ratios such as NLR and PLR are significant predictors of 30-day mortality in patients with severe COPD exacerbations requiring intensive care.¹⁶

In the 2018 review by Kostikas et al.,¹⁷ it was discussed that blood eosinophil count can influence treatment strategies in both asthma and COPD. In asthma, elevated blood eosinophil levels have gained importance in identifying patients who may be candidates for biologic therapies. In COPD, higher eosinophil counts have been associated with a better response to inhaled corticosteroid (ICS) therapy, particularly in patients with frequent exacerbations. While a cut-off value of 300 cells/μl is generally accepted in asthma to define eosinophilia, there is still no consensus on a universal threshold or optimal measurement frequency for blood eosinophils in COPD.

Recent studies increasingly recommend the use of blood eosinophil levels as a biomarker in patients with COPD. Their value is progressively recognized both in guiding treatment decisions and in predicting treatment response.^{18,19} When evaluated alongside the findings of our study, the admission of a patient with a COPD exacerbation and elevated eosinophil levels to the ICU should prompt the ICU physician to consider the following questions:

- Could this exacerbation likely be non-infectious in nature?
- Does the patient currently use inhaled corticosteroids? Have they discontinued them? How is their treatment adherence?
- Is a favorable response to treatment likely? Should anti-inflammatory therapies be prioritized?

Considering all these aspects, we believe that in critically ill COPD patients admitted to the ICU with acute exacerbations, in addition to leukocyte, neutrophil, lymphocyte, and platelet counts in complete blood count, eosinophil levels should also be taken into account to develop more personalized and phenotype-specific treatment strategies.

Future Research Recommendations

Future studies should aim to validate the findings of this study in larger, prospective, and multicenter cohorts to improve generalizability and statistical robustness. In particular, further research should focus on the longitudinal behavior of blood eosinophil levels during different phases of COPD exacerbation and recovery, as well as their dynamic relationship with infectious markers and respiratory function. Moreover, incorporating data on prior corticosteroid use, treatment adherence, and environmental exposures could offer deeper insight into the pathophysiological basis of eosinophilic versus non-eosinophilic exacerbations. A more refined phenotypic classification of COPD patients in the ICU setting may facilitate the development of personalized therapeutic strategies and improve clinical outcomes.

Limitations

This study has several limitations that should be acknowledged. First and foremost, there was a notable imbalance in group sizes, with a considerably larger number of patients in the low eosinophil group (n=122) compared to the moderate-high eosinophil group (n=19). This disproportion may have reduced the statistical power of group comparisons and limited the generalizability of the findings. Additionally, due to the retrospective design, potential confounding factors such as prior corticosteroid use, medication adherence, and the precise etiology of exacerbations (e.g., bacterial vs. viral) could not be fully assessed.

CONCLUSION

Although peripheral blood eosinophil levels are not yet a primary determinant in decision-making models for managing and predicting prognosis in patients admitted to the ICU with a diagnosis of COPD exacerbation, they should undoubtedly be considered in clinical practice. In our study,

we did not evaluate parameters such as the use of ICS or treatment adherence prior to ICU admission. However, future ICU-based studies should focus on these factors to better understand the triggers of COPD exacerbations between ICU admissions. Large-scale prospective studies are needed to analyze the relationships between ICS usage, treatment adherence, blood eosinophil levels, and infectious processes to improve patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 11.12.2024, Decision No: 2024-BÇEK 185).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Use of Artificial Intelligence

Artificial intelligence was utilized for English grammar checking after the manuscript was written.

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