SUBMITTED 9 MAR 21
REVISIONS REQ. 29 APR & 2 JUN 21; REVISIONS RECD. 30 APR & 7 JUN 21
ACCEPTED 29 JUNE 21
ONLINE-FIRST: AUGUST 2021
DOI: https://doi.org/10.18295/squmj.8.2021.099

Elevated Peripheral Blood Eosinophils (PBE) During Acute Exacerbation of COPD (AECOPD)

Prevalence and clinical significance

Mitha Al Sibani,[1,2] *Abdullah M. Al Alawi,[1,2] Jamal Al Aghbari[1,2]

[1]Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman; [2]Oman Medical Specialty Board, Muscat, Oman

**Corresponding Author's e-mail: dr.abdullahalalawi@gmail.com*

Abstract

Objectives: An elevated peripheral blood eosinophil (PBE) count during acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a potential predictor of treatment responsiveness and future exacerbation risk. This study aimed to evaluate the prevalence and clinical significance of elevated PBE counts in hospitalized patients with AECOPD in Oman. ***Methods:*** This single-center retrospective study included all patients with AECOPD who were admitted to Sultan Qaboos University Hospital between January 2017 and July 2019. The patients were classified as having eosinophilic or noneosinophilic AECOPD based on blood eosinophil counts. An elevated eosinophil count was defined as a blood eosinophil count > 0.3×10^9 cells/L on admission. The length of hospital stay, use of oral and inhaled steroids, number of readmissions in a year, and use of mechanical ventilation on admission were compared between the eosinophilic and non-eosinophilic AECOPD groups. ***Results:*** Of the 102 patients included in the study, 42.2% had eosinophilic AECOPD. The eosinophilic AECOPD group had a reduced length of hospital stay ($P = 0.02$) but an increased risk of readmission in a year ($P = 0.04$). Most patients in both the groups were treated with inhaled and oral steroids. The need for mechanical ventilation did not differ between the groups. ***Conclusion:*** Eosinophilia is highly prevalent in patients with AECOPD and is associated with a reduced length of hospital stay but an increased risk of readmission in a year. It can be

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used as a surrogate marker to predict the health outcomes of patients with AECOPD and select treatment options.

Keywords: Chronic Obstructive Pulmonary disease (COPD); Eosinophils; Steroids; length of stay; hospital readmission.

Advances in Knowledge

- Eosinophilia is highly prevalent in patients with acute exacerbation of COPD.
- Eosinophilic exacerbation of COPD is associated with a reduced length of hospital stay but an increased risk of readmission in a year.

Application to Patient Care

- Peripheral blood eosinophil count can be used as a surrogate marker to predict the treatment response.
- Peripheral blood eosinophil count can be used to guide the treatment choices for patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation. Patients with COPD suffer from exacerbation, reduced quality of life, and increased morbidity and mortality.[1-3]

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is mainly associated with neutrophilic inflammation; however, predominant eosinophilic airway inflammation has been reported in a subset of patients with COPD.[4-6] Up to 40% of patients with COPD have an eosinophilic phenotype of COPD, defined as peripheral blood eosinophil (PBE) counts $\geq$ 2%.[4] Several studies have shown that patients with elevated PBE counts are at an increased risk of frequent exacerbations but show a good response to steroid therapy.[1, 4] Evidence suggests that circulating eosinophils can be recruited to the lungs and can increase inflammation by the actions of cytokines, immunoregulatory cells, and other proinflammatory mediators.[7] Accordingly, PBE count has been suggested to be useful as a surrogate marker to direct the use of oral steroid therapy in patients with AECOPD and as a predictor of future exacerbation and disease stability.[6] The data assessing the role of PBE on mortality outcome are inconsistent.[8, 9] Overall, the role of PBEs in the clinical manifestation

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of COPD remains highly debatable.[10, 11] No prior study has been conducted in the Middle East to assess the prevalence and clinical significance of eosinophilia during AECOPD. The present study aimed to evaluate the prevalence and clinical significance of elevated PBE counts in hospitalized patients with AECOPD.

Methods

This retrospective cohort study was conducted at Sultan Qaboos University Hospital (SQUH), a 500-bed multi-specialty tertiary hospital that provides health care for Muscat and Al-Batinah governorates' residents. It is also considered a major referral center for many specialties that provide high-quality care for patients referred from the entire country of Oman.[12]

All patients with AECOPD admitted to SQUH between January 2017, and July 2019 were included in the study. We have used the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria to ascertain COPD diagnosis for all included patients. In addition, we have included the most recent lung function test before the index hospitalization when there is more than one lung function test. Data were collected from electronic patient records using a standardized electronic data collection sheet. The patients were classified as having eosinophilic or non-eosinophilic AECOPD based on their blood eosinophil counts. An elevated eosinophil count was defined as a blood eosinophil count greater than 0.3×10^9 cells/L at the time of admission. In addition, the length of hospital stay, use of oral and inhaled steroids, number of readmissions in a year, and use of mechanical ventilation on admission were compared between the eosinophilic and non-eosinophilic AECOPD groups.

Categorical variables were reported as numbers and percentages, while continuous variables were expressed as means ± standard deviations (SDs) for normally distributed data and as medians and interquartile ranges (IQRs) for non-normally distributed data. Continuous variables between the groups were compared using Student's t-test for normally distributed data and Wilcoxon's rank-sum test for non-normally distributed data. Fisher's exact test was used to assess the association between categorical variables (given the small sample size). A 2-sided p-value < 0.05 was considered statistically significant. Statistical calculations were performed using the Stata v. 16.1 software package (StataCorp LLC, USA).

The study was approved by the Medical Research Ethics Committee of the College of

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Medicine and Health Sciences of Sultan Qaboos University.

Results

A search of the hospital database revealed 128 patients with AECOPD who were hospitalized during the study period. Twenty-three patients were found to be asthmatic, while three patients were lost to follow-up. Thus, 102 patients were included in the study. The mean age of the patients was 72.9 ± 10.9 years, and 79.4% of the patients were male. Approximately 93.1% of the patients had a history of smoking (current or ex-smoker). Both the groups had a severely reduced forced expiratory volume in one second (FEV1) (43.8 ± 17.8 %). In total, 42.2% of the patients had eosinophilic AECOPD. Patients with non-eosinophilic AECOPD stayed in the hospital for a longer duration than those with eosinophilic AECOPD (p = 0.02). Patients with eosinophilic AECOPD had a significantly higher number of readmissions in a year than those with non-eosinophilic AECOPD (*P* = 0.04). Most patients in both groups received systemic steroids (92.2%) and were on inhaled steroids (78.4%) before admission. There was no significant difference in the need for mechanical ventilation between the groups (*P* = 0.32). Moreover, the eosinophil count before discharge did not differ significantly between the groups (*P* = 0.43).

Discussion

The present study is the first to assess the prevalence and clinical significance of eosinophilia in hospitalized COPD patients in the Middle East, where most patients are of Arabic ethnicity. We found that patients with eosinophilic AECOPD have a reduced length of hospital stay but are at an increased risk of readmission in a year.

The prevalence of eosinophilic AECOPD ranged from 10% to 37% in previous studies. [13-15] These differences in the prevalence of eosinophilia during AECOPD could be explained by the difference in patients' ethnicity, use of corticosteroids before admission, and difference in cut-off values used to define eosinophilia.[1, 16-18] The most commonly used cut-off value to define eosinophilic COPD is 2%, which corresponds to 150 cells/μL. However, the absolute eosinophil count might be more accurate because the white cell count can differ significantly for various reasons.[1] In the present study, we used a cut-off value greater than 300 cells/μL to define eosinophilic AECOPD, which has been validated in previous studies.[1, 7, 16, 19, 20] The prevalence of eosinophilic AECOPD in our cohort was 42.2%, which is higher than most of the previously reported values. This higher prevalence of eosinophilic AECOPD could be

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related to the high prevalence of smoking in our cohort.

In patients with COPD and under certain circumstances, the PBEs are recruited to the lungs prompting cascades of inflammatory responses, including secretion of chemokines, cytokines, and cytotoxic granular products.[21] Most patients in both the groups were treated with inhaled and oral steroids; however, patients with elevated PBE counts showed a better response, as evidenced by a reduced length of hospital stay ($p = 0.02$), which could be explained by the anti-inflammatory role of corticosteroids on patients with eosinophilic AECOPD. Our finding of reduced length of hospital stay of eosinophilic AECOPD is similar to that of previous studies.[16, 22]

About 40% of patients with eosinophilic AECOPD required mechanical ventilation compared to 50.9% of patients with non- eosinophilic AECOPD, which may be explained by the poor response of non-eosinophilic AECOPD to corticosteroids. Also, previous studies demonstrated that non-eosinophilic AECOPD is strongly associated with infections and worse outcomes, which may be explained by the higher need for mechanical ventilation.[21]

There were no significant differences in age, sex, FEV1, and smoking status between the groups (Table 1). In addition, before discharge from the hospital, the eosinophil count did not differ significantly between eosinophilic and non-es eosinophilic AECOPD, which could be explained by a high percentage of patients who were treated with steroids in both groups.

This finding may provide insight into using oral and inhaled steroids in patients with AECOPD based on the eosinophil count to avoid risks associated with the indiscriminate use of steroids in such patients.[23] There was no difference in the need for mechanical ventilation between the groups ($p = 0.32$). In the present study, the mortality outcome was not assessed because of the small sample size; however, previous studies have suggested that eosinophilic AECOPD is associated with a lower inpatient mortality rate, but the data are conflicting.[8, 9, 22] In contrast, patients with eosinophilic AECOPD had an increased number of readmissions in a year ($p = 0.04$); this is similar to previous findings.[17, 22]

The present study is the first to assess the prevalence of eosinophilia in patients of Arabic ethnicity. The results confirmed that eosinophil count could be used as a surrogate marker to predict the treatment response and risk of readmission in inpatients with AECOPD. This

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finding supports the 2020 GOLD recommendation regarding the role of PBE in guiding the treatment choice for patients with COPD.[10]

There are several limitations to the present study. First, it was a single-center retrospective study. Second, the inpatient mortality rate in the groups could not be assessed because of the small sample size. Third, the study included hospitalized patients with AECOPD; however, it did not include patients with mild and moderate exacerbations who were managed in the outpatient setting. Moreover, potential cofounders, including heart failure, ischemic heart disease, and hypertension, were not considered.

Conclusion

Eosinophilia is highly prevalent in hospitalized patients with AECOPD. It is associated with a reduced length of hospital stay and an increased risk of readmission in a year. In addition, the eosinophil count can be used as a surrogate marker to predict the health outcomes of patients with AECOPD and select treatment options, including corticosteroid use.

Authors' Contribution

MS, AA and JA contributed to the research design. MS collected the data. MS and AA analysed the data and manuscript writing. AA and JA revised the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

No funding was received for this study.

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Table 1: Eosinophilic and non-eosinophilic COPD exacerbation: characteristics, treatment options, and outcomes

Characteristics	**Total cohort n = 102**	**Normal eosinophil count n = 59**	**High eosinophil count n = 43**	***P* value**
Age (years), mean±SD	72.9 ± 10.9	73.0 ± 12.3	72.4 ± 8.8	0.17
Male (n)	81 (79.4%)	50 (84.8%)	31 (72.1%)	0.10
Smoking (n)	95 (93.1%)	56 (94.9%)	39 (90.7%)	0.40
Eosinophil count on admission (cells × 10^9/L), median (IQR)	0.3 (0.0–0.6)	0.1 (0–0.2)	0.6 (0.5–1.2)	<0.001
FEV1* (%),mean±SD	43.8 ± 17.8	44.3 ± 17.2	43.1 ± 18.7	0.52
Treatment				
Oral steroids (n)	94 (92.2%)	55 (93.2%)	39 (90.7%)	0.72
Inhaled steroids (n)	80 (78.4%)	44 (74.6%)	36 (83.7%)	0.33
Need for mechanical ventilation (n)	47 (46.1%)	30 (50.9%)	17 (39.5%)	0.32
Outcomes				
Length of hospital stay (days), median (IQR)	4 (3-7)	5 (4-7)	4 (6-3)	0.02
Eosinophil count on discharge (× 10^9/L) median (IQR)	0.1 (0.0–0.3)	0.1 (0–0.3)	0.2 (0.0–0.5)	0.43
Readmission in a year (n),median (IQR)	0 (0–2)	0 (0–1)	1 (0–3)	0.04

**forced expiratory volume in one second.*

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