Non-comunicable disease

Eosinophil count and clinical outcome in patients with acute exacerbation of Chronic obstructive pulmonary disease

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Keywords

Eosinophil count • Clinical outcome • Acute exacerbation • COPD

Summary

Introduction. *We examined the association of blood eosinophil counts at the time of AECOPD hospitalization with the risk of ICU admission as well as the hospital lengths of stay and mortality.*

Methods. *In the current retrospective study, the association between blood eosinophil counts in COPD patients at the time of AECOPD hospitalization and the risk of subsequent ICU admission as well as mortality was assessed. The chi-squared test and t-test were used to compare categorical and continuous variables. The statistical significance level was set at 0.05. Kaplan-Meier curves for mortality as well as ICU admission up to 40 days after discharge from the index hospitalization were constructed using the determined optimal eosinophil threshold derived above and for the predetermined ≥ 300 vs < 300 cells/μL threshold. All analyses were performed using SPSS version 19.*

Results. *Antibiotic prescription was significantly associated with increased ICU admission (OR = 1.57; confidence interval [95% CI] = 1.02-2.42. Patients with higher FEV1 had decreased ICU admission (OR = 0.98, 95% CI = 0.97-1.01, p = 0.1) as well as all-cause mortality compared (OR = 0.98, 95% CI= 0.92-1.04, p = 0.58). There were significantly greater mortality rates for patients with higher ESR (OR = 1.02, CI =1.01-1.03, p = 0.01) and CRP (OR = 1.02, 95% CI = 1.01-1.03, p = 0.01). There were significantly lower ICU admission rates for patients with higher FVC (OR = 0.97, 95% CI = 0.95-0.98, p = 0.002).*

Conclusions. *Blood eosinophil count could help determine the risk of ICU admission as well as mortality in COPD patients at the time of hospitalization.*

Introduction

Chronic obstructive pulmonary disease (COPD) has different phenotypes and prognoses (1). Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the most common respiratory problems, which is associated with serious complications and consequences such as reduced quality of life and high attenuation. It defined as the sudden worsening in airway function and respiratory symptoms in patients with COPD [2]. It is crucial to diagnose patients with a severe prognosis to treat and prevent disease from exacerbating as well as their deaths [3, 4]. Blood eosinophil counts have been used as a biomarker of airway inflammation [5]. There are conflicting reports on whether elevated blood eosinophil counts predict an increased risk of intensive care unit (ICU) admission [5-9]. There is also evidence of the relationship between the number of eosinophils and the possibility of hospitalization, hospital mortality, and the length of stay in the hospital [10, 11]. Nevertheless, using a single cut-off of blood eosinophil level to predict clinical outcome has been challenged [12, 13]. Studies reported that the within-subject variation of hourly blood eosinophil counts was more than 20%. Between-subject variation was even greater [14]. In COPD patients, blood eosinophil counts are associated with severe AECOPD [8]. Exacerbations associated with blood eosinophil counts >2% (approximately >150 cells/mL) are associated with shorter hospitalization in severe AECOPD [5, 15]. We hypothesized that monitoring blood eosinophils could be helpful in managing treatment. The current study aimed to assess the association of blood eosinophil count at the time of AECOPD hospitalization with subsequent risk of ICU admission, as well as increased length of stay and in-hospital mortality.

Materials and methods

This was a retrospective study on COPD patients during AECOPD hospitalization in Imam Khomeini Hospital between January 1, 2017, and Dec 31, 2019. The data source was the electronic medical records. Age, gender,

and comorbidity status were determined. Based on Hegewald et al study, the highest blood eosinophil count was measured 7 days before the index admission until 24 hours after the index admission (The first AECOPD-related hospitalization in the study period) [16] and before the administration of systemic corticosteroids (oral or intravenous). Laboratory variables including WBC count, FEV1 (%), FVC (%), ESR, and CRP were measured.

Study Patients

The hospitalized AECOPD patients aged >40 years with a secondary diagnosis related to asthma were included. All patients who were included in the study met the inclusion criteria. Overall, 1196 AECOPD hospitalizations were recognized; after excluding ineligible patients, 477 AECOPD patients were identified. Only subjects with a confirmed diagnosis of exacerbation of COPD were studied. An exacerbation of COPD was defined by a new onset of two or more events of dyspnea, coughing, increased sputum production or chest tightness that led to a change in treatment with systemic glucocorticoids or antibiotics for at least 3 days Diagnoses of COPD, chronic asthma, bronchiectasis, or interstitial lung disease were made based on previously confirmed spirometry or imaging by a physician. The first AECOPD-related hospitalization in the study period was selected as the index admission. Patients who died during the index admission, patients without blood eosinophil counts, pregnant cases, patients who had a known malignancy, and hospitalizations occurring after the index hospitalization were excluded.

Statistical Analyses

The primary outcomes were ICU admission as well as death due to all causes. For the primary outcomes, a blood eosinophil count ≥ 300 cells/μL was used to stratify patient groups. Multiple logistic regression analyses adjusted for age, sex comorbidities, and corticosteroid use were performed. The statistical significance level was set at 0.05. Kaplan-Meier curves for mortality as well as ICU admission up to 40 days after discharge from the index hospitalization. All analyses were performed using SPSS version 16.

Results

The mean and standard deviation of blood eosinophil count at the time of admission for understudied patients was 319.77 ± 200.78 cells/μL. Overall, the blood eosinophil count in 45 (9.4%) of patients was < 100 cells/μL. Also, the blood eosinophil counts in 198 (41.5%) and 234 (49.1%) cases were 100-300 cells/μL and counts ≥ 300 cells/μL (eosinophilic) respectively. Compared to patients with eosinophil counts ≥ 300 cells/μL, Cases who had eosinophil counts < 300 cells/μL were generally older (P: 0.22) with a higher rate of male patients (P: 0.03) and higher forced expiratory volume in one second (FEV1) value (P: 0.007) (Tab. I).

Regarding comorbidities, there were not statistical significant differences in the prevalence of diabetes (P: 0.82), hypertension (P: 0.40), cerebrovascular disease (P: 0.28), and apnea-hypopnea syndrome (OSAHS) (P: 0.70). More than thirty-four percent of patients had hypertension, with a non-significant difference between the high and low eosinophil groups (P: 0.40). A history of bronchodilator use was 74.2% with no -significant difference between the eosinophil groups (P:0.84). The

Tab. I. Comparison Different factors by eosinophil count.

Variable	Total (n = 477)	EOS < 100 cells/μjnL (n = 45)	EOS = 100-300 cells/μL (n = 198)	EOS ≥ 300 cells/μL (n = 234)	P
Age	66.16 ± 11.18	68.42 ± 10.21	66.50 ± 11.90	65.44 ± 10.70	0.22
Male Gender	329 (69)	25 (55.6)	132 (66.7)	172 (73.5)	0.03
Hypertension	163 (34.2)	18 (40.0)	71 (35.9)	74 (31.6)	0.4
Diabetes	89 (18.7)	10 (22.2)	36 (18.2)	43 (18.4)	0.82
Cerebrovascular disease	52 (10.9)	2 (4.4)	25 (12.6)	25 (10.7)	0.28
Pulmonary disease	25 (5.2)	5 (11.1)	6 (3.0)	14 (6.0)	0.07
OSAHS	6 (1.3)	0(0.0)	3 (1.5)	3 (1.3)	0.7
Bronchodilator	354 (74.2)	35 (77.8)	146 (73.7)	173 (73.9)	0.84
Antibiotic	149 (31.2)	16 (35.6)	71 (35.9)	62 (26.5)	0.09
ICU Admission	147 (30.8)	12 (26.7)	55 (27.8)	80 (34.2)	0.30
Death	28 (5.9)	3 (6.7)	11 (5.6)	14 (6.0)	0.95
Hospital Stay(Day)	8.05 ± 4.35	8.20 ± 4.49	8.07 ± 4.36	8.02 ± 4.25	0.96
WBC count	9539.97 ± 3823.69	7654.44 ± 3721.18	8433.38 ± 2922.98	10838.93 ± 4075.33	0.001
FEV1(%)	51.31 ± 19.31	55.52 ± 16.02	55.07 ± 19.85	47.49 ± 18.85	0.007
FVC(%)	68.00 ± 19.87	69.41 ± 19.58	71.21 ± 19.92	65.17 ± 19.63	0.07
ESR	22.53 ± 26.61	27.02 ± 23.34	24.57 ± 29.50	19.94 ± 24.37	0.09
CRP	27.98 ± 34.67	25.91 ± 33.89	24.93 ± 28.62	27.50 ± 36.66	0.72

* Those with P value < 0.05 were highlighted using the bold font. Data are presented as the number of patients (%), mean ± SD. FEV1% predicted from the stable stage of the patients.

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; EOS: eosinophils; SD: standard deviation; BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; OSAHS: obstructive sleep apnea-hypopnea syndrome.

mean and standard deviation of hospital length of stay was 8.05 ± 4.35 days, with a non-significant difference between the eosinophil group (P:0.40). A total of 147 patients (30.8%) were admitted to ICU and the admission rate was not significantly different between eosinophil groups. Mortality during hospitalization for all cases was 5.9% (28 of 477 patients). Mortality was not significantly different between the eosinophil groups (6.7, 5.6, and 6.0%). Kaplan-Meier curves for mortality, as well as ICU admission based on eosinophil value of ≥ 300 cells/μL, are shown in figure 1. There was no significant difference in the of hospital length of stay between eosinophil groups using a threshold of 300 cells/μL. In terms of laboratory tests, the white blood cells (WBC), were significantly higher in the patients with eosinophilic AECOPD (P: 0.001) and conversely, erythrocyte sedimentation rate (ESR) was lower in the patients with eosinophilic AECOPD; the differences between the groups was not statistically significant (Tab. I).

In addition, Antibiotic prescription was significantly associated with increased ICU admission (OR = 1.57; confidence interval [95% CI] = 1.02-2.42) (Tab. II). There was no significant difference in the primary outcome of ICU admission between the high eosinophil and low eosinophil groups using a threshold of 300 cells/μL, Odds ratio [OR] =1.45, 95% confidence interval [95% CI] = 0.98-2.17) (Tab. II).

However, patients with higher FEV1 had decreased ICU admission (OR = 0.98, 95% CI = 0.97-1.01, P: 0.10) as well as all-cause mortality compared (OR = 0.98, 95% CI = 0.92-1.04, P: 0.58). There were significantly greater mortality rates for patients with higher ESR (OR = 1.02, CI = 1.01-1.03, P: 0.01) and CRP (OR = 1.02, 95% CI = 1.01-1.03, P:0.01). There were significantly lower ICU admission rates for patients with higher FVC (OR = 0.97, 95% CI = 0.95-0.98, P: 0.002).

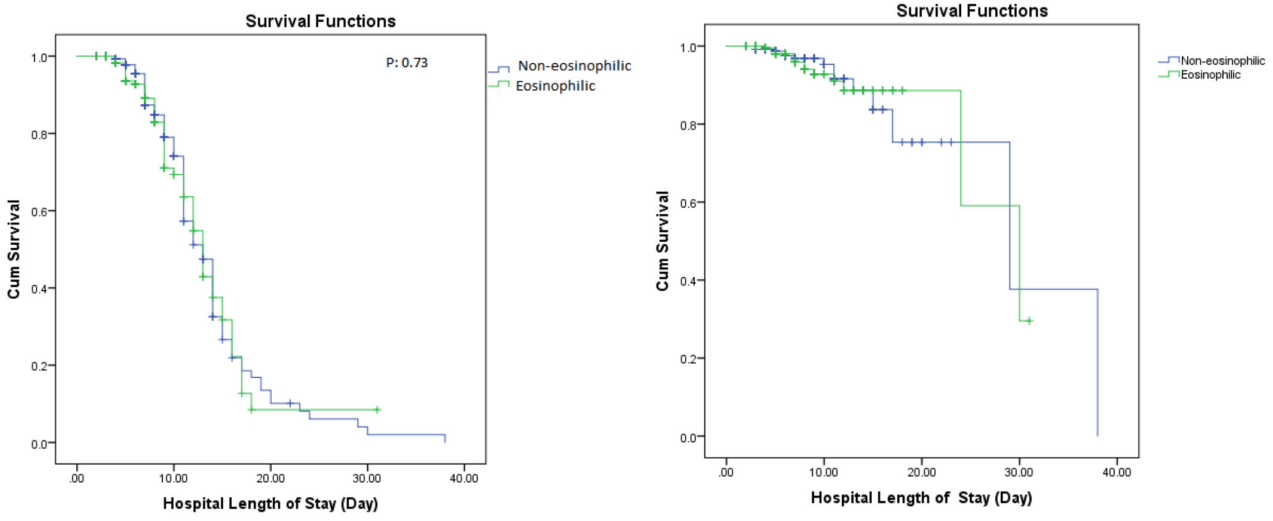
Discussion

The available evidence indicates the importance of blood eosinophil levels in predicting the severity of COPD disease, the response rate of patients to treatment, and the proper management of these patients [17-19]. However, there is still not much agreement on the threshold used to define the eosinophilic phenotype [16]. Although studies have used varying thresholds to define eosinophilic phenotype [5, 20], thresholds used to define the eosinophilic phenotype are not yet standardized. We found that blood eosinophil counts of ≥300 cells/μL are common, occurs in 49% of patients.

There was no statistically significant association between eosinophilic AECOPD and ICU admission. Various studies have evaluated blood eosinophils in AECOPD. However, results in different populations with AECOPD are inconsistent [5, 8, 16, 20]. Some studies have shown an increased risk of readmission with increased eosinophils [6, 21]. A study [6] showed that high eosinophilia was associated with COPD-related readmission [9]. Other studies showed a negative association [5], or even no association [7] between blood eosinophils and re-admission. One of the possible reasons for the different results is the use of corticosteroids before eosinophil measurement in some studies [5, 6] may play a role in the different results. Eosinophils play an important role in the type 2 immune response pathway and are also associated with allergic, rheumatological, infectious, and rare idiopathic disorders [22]. Also, the relationship between high blood eosinophils and readmission in patients with COPD may be partially explained by the presence of comorbidities [16].

Our results showed that higher eosinophil is not significantly associated with mortality. Many studies have shown that eosinopenia is associated with mortality in AECOPD patients [15, 23-27]. This discrepancy

Fig.1. Comparison of Hospital lengths of stay by eosinophil status.



Tab. II. Effective factors on Mortality and ICU admission of understudied cases.

Variables	Mortality	P	ICU admission	P
	OR (95% CI)		OR (95% CI)	
Age	1.04 (1-1.08)	0.06	1.01 (99-1.03)	0.22
Sex(males)	1.45 (0.60-3.47)	0.41	1.06 (0.69-1.65)	0.78
Antibiotics	1.28 (0.57-2.89)	0.55	**1.57 (1.02-2.42)**	**0.04**
Bronchodilators	1.23 (0.44-3.46)	0.69	0.78 (0.49-1.25)	0.31
EOS < 300 cells/μL	1.08 (0.49-2.35)	0.85	1.45 (0.98-2.17)	0.07
Comorbidity	1.71 (0.66-4.44)	0.27	0.88 (0.57-1.36)	0.57
WBC count	1.03 (1.01-1.09)	0.03	1.0 (0.99-1.01)	0.1
FEV1(%)	0.98 (0.92-1.04)	0.58	0.98 (0.97-1.01)	0.1
FVC(%)	1.02 (0.86-1.20)	0.45	**0.97 (0.95-0.98)**	0.002
ESR	**1.02 (1.01-1.03)**	0.01	0.99 (0.98-1.01)	0.07
CRP	**1.02 (1.01-1.03)**	0.01	1.0 (0.99-1.01)	0.25

may be due to patient selection. On the contrary, some studies have shown that the number of blood eosinophils is not related to in-hospital mortality in AECOPD patients [28, 29], For example, Chen et al concluded that the number of eosinophils on admission in patients with AECOPD is not related to mortality in patients requiring hospitalization in the intensive care unit [10].

The possibility of an association between eosinophil count and risk of death is still unclear [30]. In the present study, AECOPD patients with lower eosinophils tended to have increased ESR levels, which may indicate that they are more susceptible to infection [30]. Some studies have shown a correlation between low eosinophils and infection [31, 32]. We also observed that non-eosinophilic patients were older, which suggested that they may be more prone to infection. Therefore, the relationship between mortality in patients with eosinopenia may be due to severe infection. Eosinophil count was associated with ICU admission, and length of stay, which was in agreement with previous reports [29, 33, 34].

The use of bronchodilators for AECOPD has also been evaluated in various studies. The results of these studies indicate that the use of bronchodilators, especially in patients with a history of frequent exacerbations and an increase in the number of eosinophils, has been associated with a reduction in AECOPD [35-37].

High blood eosinophil counts were not associated significantly with mortality. Similarly, a clinical study involving COPD patients found that elevated blood eosinophil counts (≥200, 300, 400 cells/μL) were not associated with mortality when compared with patients with decreased eosinophil counts [38]. This observation is not consistent with other studies. Discrepancies between study results may be due to differences in COPD severity. Some beneficial factors such as better FEV1, fewer symptoms, less dyspnea, and less emphysema [35], may be present in patients with high eosinophil counts [39]. In addition, higher eosinophil counts may influence mortality because there is an association between improved response to corticosteroids and eosinophil counts [36, 40, 41]. Another point to consider when interpreting study results is that, eosinophil cutoff may influence the results.

The present study had limitations. First, the present study was an observational study and its results do not imply causal relationships. Second, the lack of follow-up of patients prevented further evaluation of long-term outcomes. Another limitation was related to the uncertainty regarding the diagnosis of COPD. Finally, there is an increasing body of evidence linking eosinophil counts to clinical outcomes in COPD patients. As such, further evaluation in future studies is essential.

Conclusions

The current study presents evidence of the association between blood eosinophils and clinical outcomes of AECOPD. Our data further support the use of blood eosinophils levels on admission as a prognostic biomarker for hospitalized COPD patients. Blood eosinophil count could help determine the risk of ICU admission as well as mortality of COPD cases, although further studies are necessary to identify the prognostic value of blood eosinophils in COPD patients.

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Data availability statement

The data presented in this study are available on request from the corresponding author.

Informed consent statement

Not applicable.

Ethical consideration

This study approved by ethics' committee of Tehran university of medical sciences with ID: IR.TUMS.IKHC.REC.1400.427.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' Contributions

NF, FM: conceptualization, Methodology, validation, project administration, supervision. IHB: data curation, formal analysis, investigation. HH, HK, MA and AN: writingoriginal draft preparation and editing. All authors have read and agreed to the published version of the manuscript.

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