Eosinophil count can predict dyspnea level in patients with acute exacerbation of chronic obstructive pulmonary disease

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Резюме

Blood eosinophil count is associated with measurements have been used as biomarkers for eosinophil-related airway inflammation. Eosinophils are found in the airways, tissues, and blood during stable disease or acute exacerbations of COPD (AECOPD). The modified Medical Research Council dyspnea scale (mMRC) and COPD assessment test (CAT) scores have been shown to be useful as novel tools for evaluating these aspects of COPD. **The aim.** This study aimed to investigate the relation of blood eosinophil count with the assessment scales and the number of emergency department (ED) admissions in patients with acute exacerbations COPD. **Study Design.** Cross-Sectional Study. **Methods.** Based on eosinophil count, the patients were divided into two groups: < 300 cells μL^{-1} and $\geqslant 300$ cells μL^{-1}. For these two groups, the relationship between acute exacerbation and the number of admissions to ED, the number of hospitalizations in the last one year, CAT score, mMRC score, and comorbid diseases were analyzed. **Results.** 166 patients was mean age 69.0, 126 (75.9%) male. Patients with high eosinophil count had fewer ED admission compared with those with low eosinophil count(5 and 10, respectively), Median mMRC score of patients with low eosinophil count was significantly higher compared with that of patients with high eosinophil count($p = 0.022$).The difference between the median CAT scores of the two groups was not statistically significant. A statistically significant, negative relationship was found between the eosinophil count and mMRC scores ($r = -0.219$; $p = 0.005$). **Conclusion.** High levels of eosinophilia in patients presenting with AECOPD are associated with low mMRC score. Also, although not statistically significant, the number of admissions to the ED may be lower.
Key words: risk scores; chronic obstructive pulmonary disease; dyspnea; eosinophils.

Число эозинофилов как возможный предиктор определения степени тяжести одышки у пациентов с обострением хронической обструктивной болезни легких

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Abstract

Число эозинофилов в крови уже используется в качестве биомаркера эозинофильного воспаления дыхательных путей. Эозинофилы обнаруживаются в дыхательных путях, тканях и крови во время стабилизации заболевания или обострений хронической обструктивной болезни легких (ХОБЛ). Полезными и проверенными новыми инструментами для оценки этих аспектов ХОБЛ являются модифицированная шкала одышки Комитета медицинских исследований (*The modified Medical Research Council dyspnea scale* – mMRC) и оценочный тест по ХОБЛ (COPD *Assessment Test* – CAT). **Целью** перекрестного исследования явилось изучение связи числа эозинофилов в крови с результатом оценки с помощью указанных шкал и количеством госпитализаций в отделение неотложной помощи у пациентов с обострениями ХОБЛ. **Материалы и методы.** Пациенты с ХОБЛ (*n* = 166: 126 (75,9 %) мужчин; средний возраст – 69,0 года) были распределены в 2 группы – в 1-ю группу вошли больные ХОБЛ, число эозинофилов у которых составило < 300 клеток / мкл⁻¹, 2-ю – ⩾ 300 клеток / мкл⁻¹. В обеих группах проанализирована взаимосвязь между обострениями и числом госпитализаций в отделения неотложной помощи за последний год, оценкой по CAT и mMRC и сопутствующими заболеваниями. **Результаты.** У пациентов с более высоким числом эозинофилов отмечено меньшее количество госпитализаций по сравнению с таковым при низком уровне эозинофилов (5 и 10 соответственно); установлена также значимо более высокая средняя оценка по mMRC у пациентов с низким числом эози-

нофилов по сравнению с таковой у лиц с высоким числом эозинофилов ($p = 0,022$). Разница средней оценки по CAT между группами не являлась статистически значимой. Выявлена статистически значимая отрицательная взаимосвязь между числом эозинофилов и оценками по mMRC ($r = -0,219$, $p = 0,005$). **Заключение.** Установлено, что у пациентов с обострениями ХОБЛ и высоким числом эозинофилов показатель по mMRC обычно низкий. Кроме того, такие больные реже госпитализируются в отделения неотложной помощи, хотя это различие не являлось статистически значимым.

Ключевые слова: шкалы для оценки риска, хроническая обструктивная болезнь легких, одышка, эозинофилы.

Exacerbations in chronic obstructive pulmonary disease (COPD) are important causes of worsening of lung functions, impairment of the quality of life, overuse of emergency health services, and mortality [1]. Airway inflammation and etiology are heterogeneous in acute exacerbations of COPD (AECOPD). In addition, causes or triggers of AECOPD may vary according to underlying mechanisms and acute treatment [2, 3]. Although the strongest predictor of AECOPD is known to be the number of acute attacks in the previous year, one of the other potential predictors is the blood eosinophil count [4]. Although COPD is considered a neutrophil-mediated inflammatory disease, eosinophils are found in the airways, tissues, and blood during stable disease or AECOPD [5]. Blood eosinophil count is associated with increased sputum eosinophil count, and both measurements have been used as biomarkers for eosinophil-related airway inflammation [6]. In addition, high sputum eosinophil count is associated with a decrease in pathogenic bacteria in the airway [7]. Furthermore, studies have shown that the risk of exacerbation is reduced with inhaled corticosteroids in patients with high blood eosinophil counts in stable COPD but there are conflicting results regarding the increase or decrease in the number of acute exacerbations [8 − 11].

Respiratory function tests are important components of the diagnosis of COPD; however, they are not descriptive enough to understand the health status and quality of life of patients [2]. Therefore, the modified Medical Research Council dyspnea scale (mMRC) and COPD assessment test (CAT) scores have been shown to be useful as novel tools for evaluating these aspects of COPD [12, 13]. The CAT score is calculated using an eight-item questionnaire and covers several aspects of the quality of life, whereas the mMRC score is determined by only one question about dyspnea [14]. However, the mMRC scale is used more frequently in clinical practice [15]. Good communication between the patient and the doctor is an important component of good clinical practice, and this can be achieved by the application of these questionnaires. Especially, when compared to the mMRC score, CAT score is a more difficult assessment to obtain, considering the age and sociocultural level of the patients.

Owing to the conflicting results in the literature, this study aimed to investigate the relation of blood eosinophil count with the assessment scales and the number of emergency department (ED) admissions in patients with AECOPD.

Materials and methods

Study design

This was a prospective cross-sectional study conducted in the emergency department (ED) of a tertiary training and research hospital where 300 000 patients apply annually. Patients who presented to the emergency department with the diagnosis of AECOPD between October 2018 and September 2019 were included in the study. To confirm the diagnoses of the patients, only those patients were examined who had a previous diagnosis of COPD from pulmonary diseases outpatient clinics screened through the hospital information processing system or who were diagnosed with COPD and issued a drug report through the electronic report system of the Ministry of Health. Among these patients, those with one or a few of the criteria mentioned in the Global Initiative for Chronic Obstructive Lung Disease COPD 2019 guideline for the diagnosis of acute exacerbation (e.g., fever, increased sputum, change in sputum character, and increased dyspnea) were included in the study [2]. Patients who did not have a diagnosis of COPD in their past records, did not want to have a complete blood count, could not answer the questions in the scoring assessments, and had hematological malignancies were excluded from the study.

Data collection and questionnaires

The demographic characteristics of the patients and their comorbid diseases, eosinophil counts of the patients whose complete blood count was studied, number of ED admissions, and number of hospitalizations because of AECOPD in the last one year were recorded. Eosinophil counts was obtained when patients visiting emergency department. The mMRC scale and CAT scores were obtained at the time of admission. The CAT score comprises eight questions; each is presented as a semantic 6-point ($0 − 5$) differential scale, providing a total score out of 40. Scores of $0 − 10$, $11 − 20$, $21 − 30$, and $31 − 40$ represent mild, moderate, severe, or very severe clinical impact, respectively [16]. The mMRC dyspnea score is a 5-point ($0 − 4$) scale based on the severity of dyspnea [17].

Outcome

On the basis of eosinophil count, the patients were divided into two groups: < 300 cells μL^{-1} and $\geqslant 300$ cells μL^{-1}. For

these two groups, the relationship between acute exacerbation and the number of admissions to the emergency department, the number of hospitalizations in the last one year, CAT score, mMRC score, and comorbid diseases were analyzed.

Statistical analysis

To summarize the data obtained from the study, descriptive statistics were presented for continuous variables as mean ± standard deviation or median and interquartile range, depending on the distribution. Categorical variables were summarized as numbers and percentages. Normality of numerical variables was tested with the Kolmogorov − Smirnov test. In the comparison of the two groups, independent sample t-test was used for numerical variables with normal distribution and the Mann−Whitney U test was used for variables without normal distribution. To compare the differences between categorical variables, Pearson's chi-squared test was used for 2 × 2 tables with expected cells of ⩾ 5 and Fisher's exact test was used for tables with expected cells < 5. Spearman's rank correlation coefficient was used to examine the relationships between numerical variables. Statistical analysis was performed with the jamovi project (2020) jamovi (Version 1.2) and JASP team (2020). JASP (Version 0.12.2) programs were used, and the significance level was considered at $p < 0.05$ in all analyses.

Results

The mean age of 166 patients included in the study was 69.0 (± 11.6) years. Of them, 126 (75.9%) were male and 40 (24.1%) were female. Although the eosinophil count of 128 patients with COPD presenting with acute exacerbation (77.1%) was $< 300 \times 10^9$ L^{-1}, it was $\geqslant 300 \times 10^9$ L^{-1} in 38 (22.9%) patients. The median number of annual emergency visits because of AECOPD was 8.0 [3.0 − 15.0]. The median mMRC score of the patients was 3.0 [2.0 − 3.0], and the median CAT score was 24.5 [20.0 − 27.0]. Comorbidities of the patients are given in Table 1.

Groups were compared according to their demographic and clinical characteristics. Age and gender showed similar distribution between the groups ($p = 0.229$ and $p = 0.777$, respectively; Table 2). Conversely, although patients with high eosinophil count had fewer ED admission compared with those with low eosinophil count (5 and 10, respectively), the differences between the median ED admissions and hospitalizations were not statistically significant ($p = 0.649$ and $p = 0.554$, respectively; Table 2).

Median mMRC score of patients with < 300 cells μL^{-1} eosinophil count was significantly higher compared with that of patients with $\geqslant 300$ cells μL^{-1} eosinophil count (Figure 1, $p = 0.022$). The difference between the median CAT scores of the two groups was not statistically significant ($p = 0.242$). When the rates of comorbidity were compared between the groups, no statistically significant difference was found ($p > 0.05$ for all).

The relationship between eosinophil count and age, the number of admissions to the emergency department, the number of hospitalizations, and mMRC score was investigated in the patients admitted to the emergency department

Variables	
Age, *Mean ± SD*, years	69.0 ± 11.6
Gender, *n* (%):	
• Male, *n* (%)	126 (75.9)
• Female, *n* (%)	40 (24.1)
Eosinophil count (cells µL⁻¹), *n* (%):	130.0 (52.5 − 260.0)
• Low (< 300 cells µL⁻¹)	128 (77.1)
• High (≥ 300 cells µL⁻¹)	38 (22.9)
No of admissions ED, median (IQR)	8.0 (3.0 − 15.0)
No of hospitalization, median (IQR)	0.0 (0.0 − 1.0)
mMRC score, median (IQR)	3.0 (2.0 − 3.0)
CAT score, median (IQR)	24.5 (20.0 − 27.0)
Comorbidity, *n* (%):	
• Hypertension	93 (56.0)
• Diabetes Mellitus	30 (18.1)
• Dyslipidemia	23 (13.9)
• Coronary Artery Disease	70 (42.2)
• Chronic renal failure	6 (3.6)
• Cerebrovascular disease	5 (3.0)
• Other	40 (24.1)

Note: ED, Emergency Department; IQR, Inter Quantile Range; mMRC, The modified Medical Research Council dyspnea scale; CAT, COPD assessment test.

for AECOPD (Table 3). Consequently, a statistically significant, negative, and weak relationship was found between the eosinophil count and mMRC scores of the patients ($r = -0.219$, $p = 0.005$). It can be said that, as the eosinophil count of the patients increases, their mMRC scores decrease (Figure 2). No statistically significant relationship was found between eosinophil count and other variables ($p > 0.05$ for all).

Discussion

Although COPD is a disease characterized by increased macrophages and activated neutrophils, an increase in eosinophil count is observed in some patients [18]. Eosinophil-associated airway inflammation can be detected in both stable COPD and AECOPD [5, 19], and some studies in the literature show a correlation between sputum and blood eosinophil counts [6, 11, 20]. *A.Jabarkhil et al.* conducted a real-life retrospective cohort study and found that patients with eosinophilic AECOPD were clinically less severe and their in-hospital and 3-year mortality rate was lower [21]. Similarly, *C.Casanova et al.* examined the relationship between high eosinophil count and clinical outcome and found that high eosinophil count was associated with better clinical outcome [22]. In the present study, a statistically significant and negative correlation was found between the eosinophil counts of the patients and the mMRC score, and considering that the mMRC score can be used to predict future poor outcome, this

Characteristic	Eosinophil Count, cells μL⁻¹		p
	< 300 (*n* = 128)	≥ 300 (*n* = 38)	
Age, years	69.6 ± 11.7	67.1 ± 11.3	0.229*
Gender, *n* (%):			
• Male, *n* (%)	96 (75.0)	30 (78.9)	0.777**
• Female, *n* (%)	32 (25.0)	8 (21.1)	
No of admissions ED, median (IQR)	10.0 (3.0 – 20.0)	5.0 (4.0 – 14.2)	0.649***
No of ospitalization, median (IQR)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	0.554***
mMRC score, median (IQR)	3.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	**0.022***
CAT score, median (IQR)	23.0 (19.5 – 27.0)	26.0 (25,0 – 27.0)	0.242***
Comorbidity, *n* (%):			
• Hypertension	72 (56.2)	21 (55.3)	0.999**
• Diabetes Mellitus	24 (18.8)	6 (15.8)	0.860**
• Dyslipidemia	15 (11.7)	8 (21.1)	0.232**
• Coronary Artery Disease	56 (43.8)	14 (36.8)	0.569**
• Chronic renal failure	5 (3.9)	1 (2.6)	0.999**
• Cerebrovascular disease	5 (3.9)	0 (0.0)	0.590**
• Other	32 (25.0)	8 (21.1)	0.777**

Note: IQR, Inter Quantile Range; ED, Emergency Department; mMRC, The modified Medical Research Council dyspnea scale; CAT, COPD assessment test; *, T-test was used for independent groups. Descriptive statistics were given as mean ± standard deviation; **, Pearson's χ^2 test or Fisher Exact test was used. Descriptive statistics were given as *n* (%);***, Mann – Whitney U-test was used. Descriptive statistics are given as the median (Inter Quantile Range); *p* values indicated in bold were considered statistically significant (*p* < 0.05).

Примечание: * – для сравнения независимых групп использовалмя Т-критерий; описательные статистические показатели включали среднее ± стандартное отклонение; ** – использовался критерий χ^2 Пирсона или точный критерий Фишера; описательные статистические показатели включали число (%); *** – использовался U-критерий Манна–Уитни. Описательные статистические показатели включали медиану (межквартильный размах). Значения *p*, выделенные жирным шрифтом, считались статистически значимыми (*p* < 0,05); IQR – межквартильный размах.

result is consistent with the results of the aforementioned studies.

One of the topics of interest about COPD and eosinophils is the relationship between eosinophilia and acute exacerbation risk. There are various opinions on this subject in the literature. *S.Couillard et al.* reported an increased risk of exacerbation in eosinophilic patients with COPD in their study with 167 patients [23], whereas *D.Duman et al.* conducted a retrospective study with 1704 patients and suggested that high eosinophil count
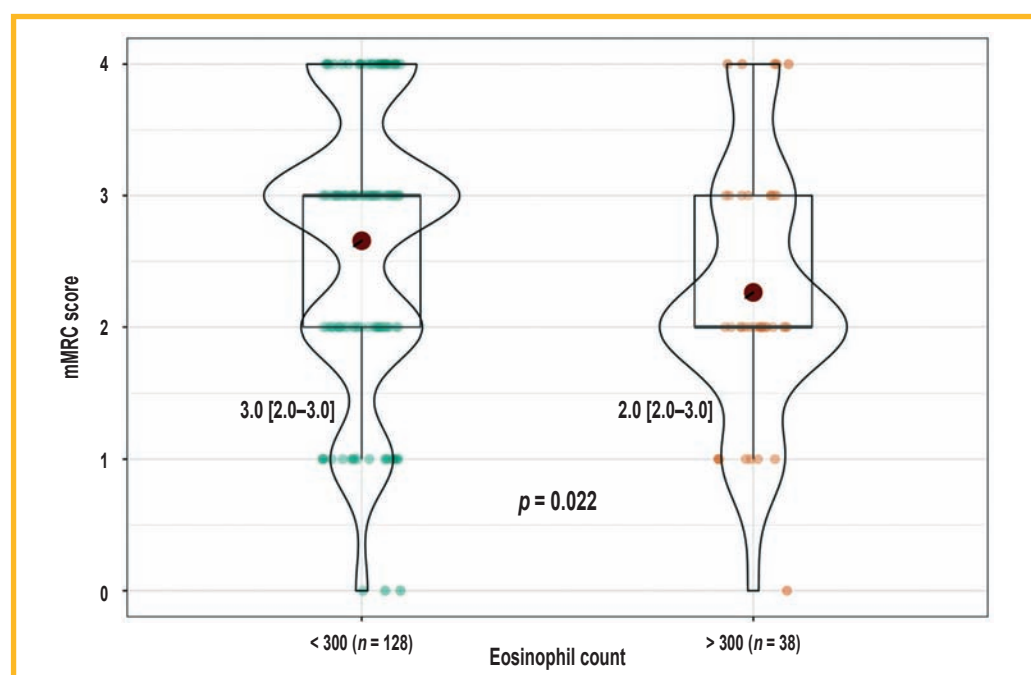

Figure 1. Relationship between groups and mMRC score
Note: mMRC, The modified Medical Research Council dyspnea scale.

Рис. 1. Различия между группами при оценке по mMRC

Table 3
Comparison of patients' eosinophil levels with some parameters
Таблица 3
Взаимосвязь числа эозинофилов с некоторыми параметрами

Parameter	Spearman's ρ	p
Age	−0.114	0.145
No of admissions ED	−0.003	0.969
Hospitalization	−0.045	0.565
mMRC score	−0.219	0.005
CATs score	−0.060	0.711

Note: ED, Emergency Department; mMRC, The modified Medical Research Council dyspnea scale; CAT, COPD assessment test; Spearman' ρ correlation coefficient was used.

Примечание: использовался коэффициент корреляции Спирмена ρ.

score focuses on some chronic factors that greatly affect the quality of life rather than acute changes, which may have led to this result.

There are certain limitations to this study. First, the number of patients can be increased. Small sample size may result from using sophisticated scales to evaluate the patients. Second, there was no long-term follow-up of the patients. Third, the change in eosinophil count as response to treatment or the treatment the patients received was not investigated.

Conclusion

High levels of eosinophilia in patients presenting with AECOPD are associated with low mMRC score and, although not statistically significant, the number of admissions to the ED may be lower.
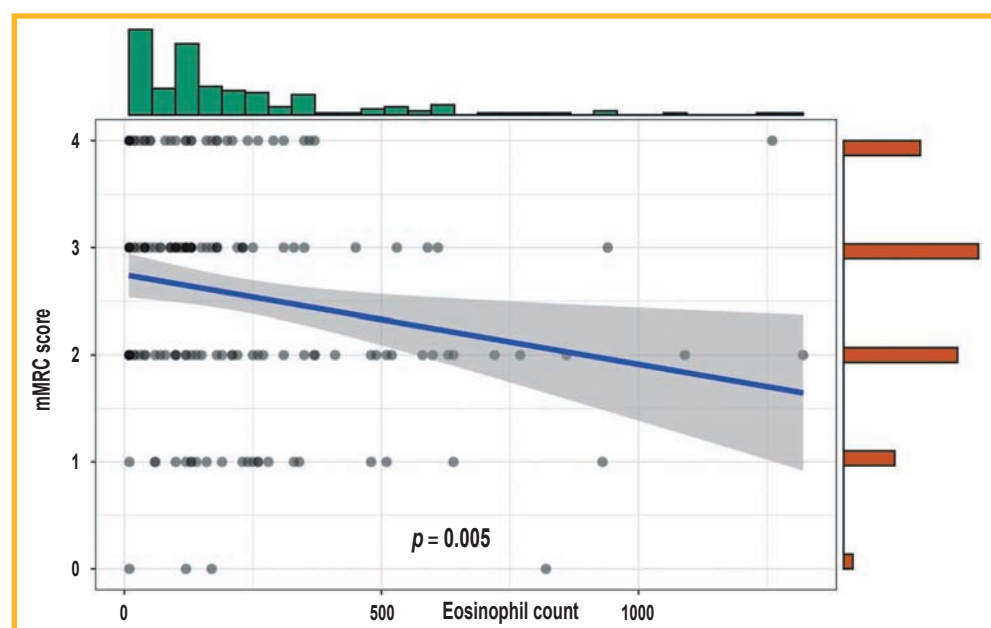

Figure 2. Correlation between eosinophil count and mMRC score
Note: mMRC, The modified Medical Research Council dyspnea scale.

Рис. 2. Корреляция между числом эозинофилов и оценкой по mMRC

was protective against exacerbation [24]. In the present study, although the number of admissions to the emergency department was not significantly different in patients with high eosinophil count, it was lower compared with patients with low eosinophil count. To address the confusion created by the different results obtained in the literature, comprehensive studies with larger patient populations are needed.

CAT score is an eight-question test used to determine the impact of COPD on the patient's life and current health status [25]. It is often used to evaluate the current health status of patients with stable COPD, and its importance in evaluating the effectiveness of treatment in patients treated for AECOPD has been discussed recently [26]. The mMRC score is a short but effective scoring that determines health status through dyspnea [25]. It is used more frequently in clinical practice because of its advantages such as rapid applicability and being unaffected by sociocultural differences. In the present study, a statistically significant and negative correlation was found between eosinophil count and the mMRC score, but no significant correlation was found with the CAT score. CAT

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