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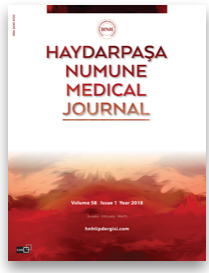

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ORIGINAL ARTICLE

The Importance of Eosinophils in the Course of Diseases: Eosinopenia, COVID-19 and Mortality

Burcu Bayramoğlu, İsmail Tayfur

Department of Emergency Medicine, University of Health Sciences Türkiye, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Istanbul, Türkiye

Abstract

Introduction: Eosinophils are involved in many metabolic events, such as the provision of homeostasis in the organism, host cell defense, and tissue repair and regeneration. Despite these important roles, eosinophils can be overlooked during the examination of blood tests performed in daily clinical practice. This study aimed to investigate the role of eosinophils in the clinical course of COVID-19.

Methods: In this study, patients who presented to the emergency department with symptoms of COVID-19 and had a positive polymerase chain reaction test or typical COVID-19 involvement on thoracic computed tomography were evaluated retrospectively. The patients' demographic data and blood parameters were obtained. In addition, the patients' outcomes, requirements for admission to inpatient wards or the intensive care unit, mechanical ventilation requirements, and in-hospital mortality were recorded and statistically analyzed.

Results: The study included a total of 3,845 patients. The eosinophil count was found to be lower in cases requiring hospitalization, intensive care, or mechanical ventilation, and in those with in-hospital mortality. In addition, the eosinophil count was found to be the most significant prognostic factor among all investigated parameters.

Discussion and Conclusion: Although eosinophil count is often overlooked, it is one of the factors that determines the prognosis in critically ill patients, as in the case of COVID-19. To the best of our knowledge, this is the first study to investigate the effect of eosinophil count on the course of COVID-19 and compare the utility of eosinophil count with other complete blood count parameters for this purpose.

Keywords: COVID-19; eosinopenia; eosinophil; mortality; prognostic markers.

In a healthy adult, eosinophils are differentiated from leukocytes and constitute 1-5% of peripheral leukocytes[1]. An eosinophil count below 50 cells/mm^3 is defined as eosinopenia[2]. Eosinophils are involved in the provision of homeostasis, host cell defense against infectious agents, and tissue repair and regeneration. They have antimicrobial, antiviral, anti-inflammatory, and antitumoral effects[1]. Eosinophils enable the recognition of viruses by the organism, the production of cytokines, the production of superoxide and nitric oxide, and increase cellular survival. Eosinophils show their antiviral effect along with the production of cytokines[3]. Despite these important roles, eosinophils can still be overlooked during the examination of blood tests performed in daily clinical practice.

Correspondence: Burcu Bayramoğlu, M.D. Department of Emergency Medicine, University of Health Sciences Türkiye, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Istanbul, Türkiye
Phone: +90 216 606 33 00 **E-mail:** drburcubayramoglu@gmail.com
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Coronavirus disease 2019 (COVID-19), which emerged in 2019 and resulted in a global pandemic in a short time, was reported to affect approximately 762 million individuals and cause 6.9 million deaths as of April 2023 [4]. Various clinical and laboratory data are used to make the hospitalization decision for COVID-19 cases and to predict the prognosis. Cases with a poor prognosis and those requiring hospitalization are specified in the "Guidance to COVID-19 Outbreak Management and Working" published by the Turkish Ministry of Health. According to this guideline, a lymphocyte count above 800/µl, a C-reactive protein (CRP) 10 times higher than the laboratory reference value, a ferritin value above 500 ng/ml, a d-dimer value above 1,000 ng/ml, a respiratory rate over 24/min, an oxygen saturation below 93% in room air, and involvement of more than 50% in lung imaging indicate a poor prognosis and require hospitalization[5]. To date, many markers have been investigated to predict prognosis in COVID-19, including calprotectin, serum amyloid A, carcinoembryonic antigen, von Willebrand factor antigen, interleukin 18, Krebs von den Lungen-6, and long pentraxin 3[6–10]. However, these markers are neither in clinical use nor easily accessible. In addition, the lymphocyte-to-mean platelet volume ratio, ferritin-to-lymphocyte percentage ratio, red cell distribution width (RDW), prolonged prothrombin time, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio have been investigated as possible prognostic markers[11–17]. Eosinophil count is another marker evaluated for this purpose[1,18–20].

This study aimed to investigate and compare the utility of leukocyte, neutrophil, and eosinophil counts, NLR, and eosinophil-to-lymphocyte ratio (ELR) in predicting hospitalization, admission to inpatient wards or the intensive care unit (ICU), the number of hospitalization days, mechanical ventilation requirements, and in-hospital mortality in patients who presented to the emergency department due to COVID-19.

Materials and Methods

Patients who were admitted to a tertiary care hospital between July 2021 and December 2021 were included in the study. Data from patients who were 18 years of age or older, had a positive PCR sample for COVID-19, or had typical COVID-19 involvement on thorax CT were used in the study. At the time of the study, the hospital where the study was conducted provided care predominantly for COVID-19 cases. Permission was obtained from the Turkish Ministry of Health, and Ethics Committee approval was received from the institutional ethical committee (E-46059653-020, 17.03.2022). The study was conducted in accordance with the Declaration of Helsinki.

Patients aged below 18 years, those who left the hospital without completing their treatment after hospitalization or were referred to another center, those who used medication or had a disease that could affect eosinophil count, and pregnant women were not included in the study. The patients' demographic data and blood parameters, namely leukocyte, eosinophil, lymphocyte, and neutrophil counts, NLR, and ELR, were obtained. In addition, data on hospitalization or discharge status, inpatient ward or ICU admission, mechanical ventilation requirements, the number of hospitalization days, and in-hospital mortality were recorded. The hospitalization decision was made according to the COVID-19 diagnosis and treatment guidelines published by the Turkish Ministry of Health.

Statistical analyses of the obtained data were performed using IBM SPSS v.21. p-values<0.05 were considered statistically significant.

Results

The study included a total of 3,845 patients, of whom 1,922 were women. Of the patients included in the study, 615 were discharged, and 3,230 were hospitalized. When the age distribution of the discharged and hospitalized patients was examined, the mean age of the hospitalized patients was 56 years, and that of the discharged patients was 46 years ($p<0.001$). The mean number of hospitalization days was 9.4.

Laboratory results showed that eosinophil (10 vs 30 cell/mm^3) and lymphocyte (1110 vs 1500 cell/mm^3) counts and ELR (0.006 vs 0.022) median values were significantly lower, and NLR (4.64 vs 2.66) was significantly higher in hospitalized cases compared to discharged cases (Table 1). These parameters were included in a multivariate regression analysis model to determine which was more significant in the differentiation between the hospitalized and discharged patients. In this analysis, eosinophil count and NLR were successful in this differentiation ($p<0.001$ for both), while lymphocyte count and ELR did not provide significant results (Table 2).

According to the analysis of investigated parameters in relation to inpatient ward and ICU admissions, the median values of eosinophil (0 vs 10 cell/mm^3) and lymphocyte (925 vs 1130 cell/mm^3) counts and ELR (0.000 vs 0.007) were significantly lower, and the median value of NLR (7.89 vs

Table 1. Relationship between clinical variables and investigated parameters

Parameter	Outcome		p
	Hospitalization Median (IQR)	Discharge Median (IQR)	
Eosinophil count (cells/mm^3)	10.0 (0.0-30.0)	30.0 (10-110)	<0.001
Lymphocyte count (cells/mm^3)	1110.0 (800.0-1540.0)	1500.0 (1110.0-1980.0)	<0.001
NLR	4.64 (2.91-7.72)	2.66 (1.71-3.84)	<0.001
ELR	0.006 (0.00-0.025)	0.022 (0.00-0.065)	<0.001
	Inpatient ward or ICU admission		p
	Inpatient ward Median (IQR)	ICU Median (IQR)	
Eosinophil count (cells/mm^3)	10.0 (0.0-30.0)	0.0 (0.0-10.0)	<0.001
Lymphocyte count (cells/mm^3)	1130.0 (820.0-1540.0)	925.0 (645.0-1395.0)	<0.001
NLR	4.49 (2.85-7.38)	7.89 (4.52-12.35)	<0.001
ELR	0.007 (0.00-0.026)	0.000 (0.00-0.012)	<0.001
	Mechanic ventilation requirement		p
	Present Median (IQR)	Absent Median (IQR)	
Eosinophil count (cells/mm^3)	0.0 (0.0-10.0)	10.0 (0.0-30.0)	<0.001
Lymphocyte count (cells/mm^3)	920.0 (630.0-1327.5)	1150.0 (840.0-1560.0)	<0.001
NLR	6.81 (3.95-11.48)	4.39 (2.80-7.21)	<0.001
ELR	0.000 (0.000-0.0121)	0.008 (0.000-0.027)	<0.001
	In-hospital mortality		p
	Present Median (IQR)	Absent Median (IQR)	
Eosinophil count (cells/mm^3)	0.0 (0.0-10.0)	10.0 (0.0-30.0)	<0.001
Lymphocyte count (cells/mm^3)	920.0 (627.50-1320.0)	1140.0 (837.5-1560.0)	<0.001
NLR	6.75 (3.94-11.10)	4.41 (2.80-7.27)	<0.001
ELR	0.000 (0.000-0.012)	0.007 (0.000-0.027)	<0.001

Mann-Whitney U test was used; IQR: interquartile range; NLR: neutrophil-to-lymphocyte ratio; ELR: eosinophil-to-lymphocyte ratio; ICU: intensive care unit.

4.49) was significantly higher among the patients who were admitted to the ICU (Table 1). The multivariate regression analysis revealed that eosinophil and lymphocyte counts were significant in the differentiation of cases according to inpatient ward and ICU admissions (p=0.008 and p=0.011, respectively), but NLR and ELR did not have significant values (Table 2).

The median values of eosinophil (0 vs 10 cell/mm^3) and lymphocyte (920 vs 1150 cell/mm^3) counts and ELR (0.0 vs 0.008) were significantly lower, and NLR (6.81 vs 4.39) was significantly higher among the patients who required mechanical ventilation. In the multivariate regression analysis model performed to identify the factor that was most significant in evaluating the mechanical ventilation requirement, the eosinophil count had the highest value, followed by NLR, and the lymphocyte count was the least successful (p<0.001, p=0.003, and p=0.032, respectively). ELR was not found to be significant in this analysis (Table 2).

When in-hospital mortality was examined, eosinophil (0 vs 10 cell/mm^3) and lymphocyte (920 vs 1140 cell/mm^3) counts and ELR (0.0 vs 0.007) were significantly lower, and NLR (6.75 vs 4.41) was significantly higher among the patients with in-hospital mortality (Table 1). According to the multivariate regression analysis model, the eosinophil count had the highest significance value, followed by NLR, and the lymphocyte count was the least successful in the differentiation of cases with and without in-hospital mortality (p<0.001, p=0.004, and p=0.038, respectively). ELR was not significant in this evaluation (Table 2).

Table 2. Relationship between investigated parameters according to clinical variables

Parameter	Hospitalization or Discharge				
	B	OR	p	95% confidence interval	
				Lower	Upper
Eosinophil count (cells/mm^3)	0.004	1.004	<0.001	1.003	1.005
Lymphocyte count (cells/mm^3)	0.000	1.000	0.390	1.00	1.00
NLR	-0.145	0.865	<0.001	0.823	0.909
ELR	0.003	4.438	0.098	0.758	25.994
	Inpatient ward or ICU admission				
	B	OR	p	95% confidence interval	
				Lower	Upper
Eosinophil count (cells/mm^3)	-0.005	0.995	0.008	0.991	0.999
Lymphocyte count (cells/mm^3)	0.001	1.001	0.011	1.000	1.001
NLR	0.009	1.009	0.353	0.991	1.027
ELR	-3.392	0.371	0.134	0.004	56.577
	Mechanical ventilation requirement				
	B	OR	p	95% confidence interval	
				Lower	Upper
Eosinophil count (cells/mm^3)	0.007	1.007	<0.001	1.004	1.010
Lymphocyte count (cells/mm^3)	0.000	1.000	0.032	0.999	1.000
NLR	-0.023	0.977	0.003	0.962	0.992
ELR	2.119	10.169	0.345	0.083	1247.665
	In-hospital mortality				
	B	OR	p	95% confidence interval	
				Lower	Upper
Eosinophil count (cells/mm^3)	0.006	1.006	<0.001	1.003	1.010
Lymphocyte count (cells/mm^3)	0.000	1.000	0.038	0.999	1.000
NLR	-0.023	0.978	0.004	0.962	0.993
ELR	1.850	6.362	0.447	0.054	746.610

Multivariate regression analysis was used; OR: odds ratio; NLR: neutrophil-to-lymphocyte ratio; ELR: eosinophil-to-lymphocyte ratio; ICU: intensive care unit.

Discussion

Eosinophil count is a marker that has started to be investigated as a prognostic factor in various clinical conditions. The DECAF (dyspnea severity, eosinopenia, consolidation, acidemia, and atrial fibrillation) score, developed in 2012 by Steer et al.[21] to predict in-hospital mortality in acute exacerbations of chronic obstructive pulmonary disease (COPD), includes eosinophil count below 50 cells/mm^3 as a factor that adversely affects prognosis. Another clinical condition in which the eosinophil count is examined is sepsis, which is associated with a disproportionate response of the host to an infection and impaired organ functions. Organ dysfunction is determined based on a sequential organ failure assessment (SOFA) score of 2 or higher. In a study in which sepsis cases were evaluated, Suhendra et al.[2] found that eosinophil count was below 40 cells/mm^3 in cases with a SOFA score of 2 and above, and they suggested that this parameter could be used as a new marker in the diagnosis of bacterial sepsis. In another study, Fumagalli et al.[22] reported that among patients who presented to the emergency department, the presence of eosinopenia was a serious factor associated with an increased risk of mortality.

During the time when the COVID-19 pandemic was most prevalent, studies were conducted in which eosinophil count was used as a marker in the clinical evaluation of patients.

In one of these studies, Eijmael et al.[19] analyzed the data of 230 COVID-19 PCR (+) patients by dividing them into three groups according to the severity of their complaints (mild, moderate, and severe). The authors detected high leukocyte and neutrophil counts in patients with severe complaints. Lymphopenia was similar in all three patient groups, with no statistically significant difference being observed, but the eosinophil level was found to decrease as the severity of the disease increased. Similar results were found when age, gender, and comorbidities were taken into account. In another study evaluating 198 patients with a diagnosis of COVID-19, Tong et al.[23] reported that lymphocyte, monocyte, basophil, and eosinophil counts were lower, and neutrophil count and NLR were higher in cases that resulted in mortality. The authors also noted that the rate of mortality was higher in the group with eosinopenia. Naoum et al.[24] compared the results of 100 patients with COVID-19 (divided into discharged, admitted, and deceased groups) and 47 healthy controls. They observed that leukocyte and neutrophil counts were higher among the hospitalized and deceased COVID-19 (+) patients, lymphocyte and eosinophil counts were lower in all COVID-19 (+) groups, and the eosinophil count was lower among the deceased and severe COVID-19 (+) cases.

In a study conducted with 107 patients, Cazzaniga et al.[18] did not detect eosinophils in 75 patients (absolute eosinopenia). The authors reported that patients with eosinopenia were older, and absolute eosinopenia was observed in those who presented to the hospital with low saturation levels and had a more severe disease course. In addition, in the group with absolute eosinopenia, the respiratory support requirement and mortality were higher, and the discharge rate was lower. Absolute eosinopenia was determined to be an independent factor in the requirement for four-week respiratory support and mortality. Mertoglu et al.[25] divided 555 patients diagnosed with COVID-19 into two groups according to whether they were admitted to the ICU or patient wards. In the ICU group, leukocyte count, neutrophil count, and NLR were higher, and lymphocyte and eosinophil counts were lower. Tahir Huyut et al.[26] reported that the mortality group had a lower lymphocyte count and higher leukocyte and neutrophil counts among a total of 4,364 cases diagnosed with COVID-19. In the same study, the eosinophil count was also lower in the mortality group. Yan et al.[27], evaluating 190 patients with COVID-19, determined that the eosinophil count was lower in very severe cases than in severe and moderate cases. In addition, the eosinophil count was lower in patients with bilateral involvement on computed tomography than in those with unilateral or no involvement. The authors also noted a lower eosinophil count in patients with mortality. In a study of 39 patients, Li et al.[28] found that the eosinophil count was lower in the presence of COVID-19 PCR positivity and affected the course of the disease.

Conclusion

In the current study, eosinophil count and other complete blood count parameters were investigated and compared according to variables such as the hospitalization decision, inpatient ward or ICU admission, mechanical ventilation requirement, and in-hospital mortality in COVID-19 cases. This study differs from previous studies in terms of the large sample size and both the individual and comparative evaluations of the parameters. According to the results, eosinophil count can assist clinicians in predicting the severity of COVID-19 and the mechanical ventilation requirement. As seen in the example of COVID-19, the number of eosinophils is a parameter that should be considered in microbial diseases and in the care of other critical patient groups.

The major limitations of our study include its retrospective design and the absence of data concerning the time from symptom onset to patient presentation.

Ethics Committee Approval: Permission was obtained from the Turkish Ministry of Health, and Ethics Committee approval was received from the institutional Ethical Committee (E-46059653-020, 17.03.2022). The study was conducted in accordance with the Declaration of Helsinki.

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