



Importance of Eosinopenia in COVID-19 Infection

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Abstract

Objective: Dynamic changes in the number of eosinophils are observed during the diagnosis and follow-up in coronavirus disease-2019 (COVID-19). Our aim was to show the role of the absolute eosinophil count in the diagnosis of COVID-19 and the relationship with disease severity and prognosis.

Methods: In this study, 191 patients (130 inpatients, 61 outpatients) diagnosed with COVID-19 pneumonia with the polymerase chain reaction test and lung computed tomography; and 22 patients with positive influenza test were included as the control group. All demographic, biochemical data, clinical and radiological characteristics were recorded.

Results: The mean eosinophils on first day of the inpatient COVID-19 group were found to be statistically lower than the influenza group and the ambulatory groups ($p=0.001$, $p=0.0001$).

Conclusion: A low eosinophil count in complete blood count, can aid in the early diagnosis of infection. Persistent eosinopenia progresses with disease severity and may help determine the prognosis of the disease.

Keywords: COVID-19, eosinophils, risk factors, severe acute respiratory syndrome, coronavirus 2

INTRODUCTION

Upon detection of pneumonia cases of unknown source of origin in Wuhan, China in December 2019, World Health Organization reported a virus called the coronavirus disease-2019 (COVID-19) virus as the cause of pneumonic cases (1). Coronaviruses (CoVs) are single-stranded positive RNA viruses. The mutation rate is higher than that of DNA viruses (2). The epidemic started from wild animals at the live animal market in Wuhan (3).

Eosinophils consist about 1%-3% of peripheral blood leukocytes. Their presence in tissues is several hundred times greater than in

blood (4) and they are found in the spleen, lymph nodes, thymus, gastrointestinal mucosal surfaces (5). Eosinophil numbers do not alter much in the body, except for some diseases (6). Eosinophils are leukocytes with pro-inflammatory action. When eosinophils are activated, they can release eosinophil cationic protein, eosinophil neurotoxin, eosinophil peroxidase. Eosinopenia may develop because of accumulation in the inflammation area, suppression in the bone marrow (7). Additionally, decreased chemokine receptor expression, eosinophil apoptosis caused by type 1 interferons released during acute infection may be the cause of eosinopenia (8). Eosinopenia can be seen in sepsis, and



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typhoid fever (9,10). It has been shown that IL1B, IFN γ , IP10, and MCP values are elevated in COVID-19 patients, leading to helper T1-cell responses (11).

In the literature, eosinopenia has been seen in COVID-19 pneumonia, especially in the early stages of the disease, even in asymptomatic cases (3,8,12-20). Although the role of eosinophils in the pathogenesis of COVID-19 patients has not been clearly explained, CLC (Galectin-10), RNASE2 (EDN), and the eosinophil chemokine CCL11 (eotaxin-1) levels were elevated, and eosinophils were thought to play a role in the pathogenesis of COVID-19 (21,22).

Low eosinophil levels have been shown to be associated with poor outcomes in critical illness in many studies (13,16).

Symptoms, frequently seen in the disease such as fever, dry cough and shortness of breath, are not specific and can be seen in other non-bacterial pneumonia (23). Additionally, severe lymphopenia and eosinopenia are less common in other viral pneumonia, but frequently seen in COVID-19 pneumonia (8). Therefore, early isolation and diagnosis of the virus is important to terminate the pandemic (24). *In vitro* laboratory tests are widely used to assess disease severity, to monitor and treat patients, and to determine the prognosis (25). Studies show that there are significant changes in some hematological parameters in patients with COVID-19 pneumonia (26); normal or increased leukocyte count, decreased lymphocyte count, thrombocytopenia, decreased albumin value, high transaminase, bilirubin, lactate dehydrogenase, creatine kinase, myoglobin, procalcitonin, C-reactive protein (CRP), D-dimer values, increased prothrombin time, erythrocyte sedimentation rate values were detected (11).

In some studies, it was found that there was a significant decrease in absolute eosinophil counts in COVID-19 pneumonia, predicting that eosinopenia could be used among the early diagnostic criteria (12-16,27,28).

In this study, we showed the role of the absolute eosinophil count in the diagnosis of the disease during COVID-19 and the relationship between the number of eosinophils and disease severity and prognosis.

METHODS

Ethical Consideration

This study was approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee and all procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards (decision no: 2020/514/179/11, date: 11 June 2020).

Study Population

The data of 191 patients (94 males, 97 female) aged between 18 and 90 years who were admitted to the hospital between March 15, 2020 and May 14, 2020 with the diagnosis of COVID-19 pneumonia; outpatient (n=130) and inpatient (n=61) were retrospectively included in this study (Figure 1).

In the study, the 2019-COV polymerase chain reaction (PCR) test (VIROSWAB UMF) studied on the combined nose and throat swab sample of 167 patients were found to be positive, while 24 patients were negative. This was accepted as COVID-19 pneumonia due to clinical and radiological findings.

Vulnerable populations (children, pregnant women) were excluded from the study. Only the data of patients who received the diagnostic methods and treatments specified in the COVID-19 guidelines of the Ministry of Health were retrospectively analyzed (29).

Statistical analysis were performed by recording age, gender and clinical characteristics, biochemical data, complete blood count (CBC) parameters, lung computed tomography (CT) findings, PCR tests and treatments of all patients.

The study population was grouped as outpatient and inpatient. CBC findings, including changes in eosinophil count with clinical and radiological course were examined. Additionally, as the control group, the eosinophil counts in the hemogram data of 22 patients admitted with positive influenza test and negative 2019-COV-PCR test results were compared retrospectively. Thus, the place of absolute eosinophil count in the diagnosis of the disease, its relationship with disease severity and prognosis were compared with patients diagnosed with COVID-19.

Inpatients diagnosed with COVID-19 pneumonia were divided into two groups as severe and non-severe patients according to the laboratory criteria, the number of days of hospitalization, the clinical course, the involvement prevalence score in chest CT and the ratio of multiple drug use (plaquenil, favipravir, lopinavir-ritonavir).

CT Protocol

Chest CT imaging was performed on a 16-detector CT scanner (Emotion; SIEMENS). Patients were scanned in the supine position, during breath hold, from the lung apices down to the costophrenic angles. The acquisition parameters were as tube voltage: 130 kV, tube current: 25 mAs, pitch: 1.5, FOV: 512 mm, and slice thickness: 0.6 mm. Thick images (3 mm) were

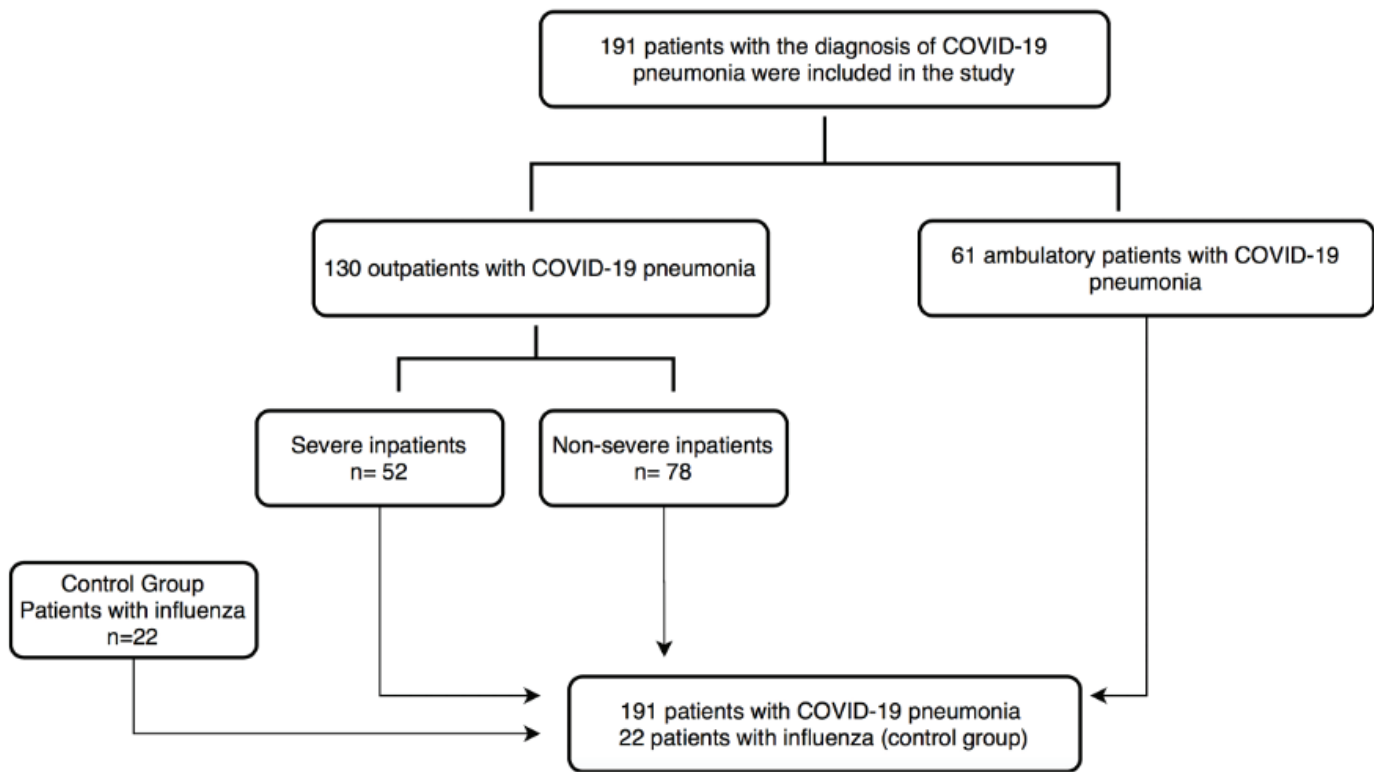


Figure 1. Diagram of the patient's population
COVID-19: Coronavirus disease-2019

reconstructed using a high-frequency reconstruction algorithm, and lung windowing and stored in the picture archiving and communicating system. A contrast material was used in none of the patients.

Chest CT Image Analysis

The initial images and chest CT scan obtained from 191 patients were reviewed by (8 years) experienced radiologists. All Digital Imaging and Communications in Medicine images were analyzed from CT studies without access to patients' clinical findings.

On each CT scan, lung lobe involved, the location of lesion categorized as central, peripheral, or both were recorded. The extent of the involvement in the lesions was classified as either focal or multifocal. The predominant pattern was categorized as ground glass opacities (GGO, defined as hazy areas of increased attenuation without obscuration of the underlying vascular markings), consolidation (parenchymal opacities obscuring underlying vessels), and both patterns. Additionally, the margin definition, interlobular septal thickening, crazy paving (thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacity) (30) air bronchogram, bronchiolectasis, cavitation, thickening of interlobular septa, parenchymal bands, tree-in-bud, pleural

effusion and lymphadenopathy (defined as lymph node with a short-axis dimension of >1.0 cm) were also recorded (31).

Chest CT Severity Score Assessment

Each of the five lung lobes was assessed for the degree of involvement and classified as follows: None (0%) corresponded to a lobe score of 0, mild (1%-25%) corresponded to a lobe score of 1, moderate (26%-50%) corresponded to a lobe score of 2, severe (51%-75%) corresponded to a lobe score of 3 and critical (76%-100%) corresponded to a lobe score of 4. The "total severity score" was determined by summing all five lobes' scores (range of possible scores, 0-20) (31).

Statistical Analysis

Statistical analyses were performed using statistical software (NCSS: Number Cruncher Statistical System 2007, Utah, USA). In addition to descriptive statistical methods (mean, standard deviation), the distribution of variables was examined with the Shapiro-Wilk normality test, One-Way analysis of variance paired in time comparisons of normally distributed variables, Newman-Keuls multiple comparison test was used in subgroup comparisons, One-Way variance in intergroup comparisons, independent t-test for comparison of paired groups, Friedman test for time comparisons of variables that do not show a normal

distribution, Dunn's multiple comparison test for subgroup comparisons, Kruskal-Wallis test for intergroup comparisons, Mann-Whitney U test for the comparison of paired groups, chi-square and Fisher's Exact test reality for comparisons of qualitative data. Pearson correlation test was used to determine the relationship between variables. Results were evaluated at the level of significance $p < 0.05$.

RESULTS

Demographic Data

A total of 191 patients diagnosed with COVID-19 pneumonia, including 130 inpatients and 61 outpatients, and 22 influenza test positive control group were included in this study. In the study 94 (49.3%) were female and 97 (50.7%) were male. The mean age of 191 patients diagnosed COVID-19 pneumonia was 50. The mean age of the inpatient COVID-19 group was 54.87 ± 12.43 while the mean age of the outpatient COVID-19 group was 39.9 ± 11.62 ($p = 0.0001$). The mean age of the influenza group was 42.5 ± 21.49 .

Characteristics of Severe Hospitalized COVID-19 Patients

The ratio of male/female patients in the severe inpatient group was 63.46/36.54 percent. While the mean age was found to be 56.83 ± 10.18 in the severe group, the mean age was found to be 53.56 ± 13.63 in the non-severe group. Neutrophil counts in the severe group mean CRP on the 1st and 3rd days, >10 days of hospitalization, intensive care (5 patients), intubation, death (5 patients), more than one drug use (plaquenil, favipravir,

lopinavir-ritonavir) was seen. In lung CT scoring, the score of 5 out of 20 and above were found to be statistically significantly higher than the non-severe group ($p = 0.002$).

Hemoglobin, lymphocyte and eosinophils 1st day averages of the inpatient group were found to be statistically significantly lower than the outpatient group (Table 1).

The prevalence of male patients was 63.46% in the severe group and 43.59% in the non-severe group. In the severe group, the mean CRP on the 1st and 3rd days, the number of days of hospitalization >10, the use of more than one drug that went to intensive care were found statistically significantly higher than the non-severe group. In the severe group, the number of those who scored 5 out of 20 in the lung CT scoring was significantly higher than that in the non-severe group.

In the severe group, compared to the non-severe group, on the 3rd day lymphocyte and eosinophils were lower and neutrophil and neutrophil to lymphocyte ratio was higher (Table 2 and 3).

In this study, as a control group, the 1st day hemogram data of 22 patients positive influenza test (2019-COV-PCR test result negative) were compared COVID-19 patients. The mean age of the inpatient COVID-19 group was found to be statistically significantly higher than the Influenza and outpatient COVID-19 groups (Table 4).

DISCUSSION

The study population consisted of 191 patients diagnosed with COVID-19 pneumonia with mean age 50. It was lower

Table 1. Comparison of day 1 and day 14 hemogram parameters of inpatient COVID-19 and outpatient COVID-19 patients

		COVID-19 inpatients	COVID-19 outpatients	p
Hemoglobin (g/dL)	1 st day	13.40±1.63	13.98±1.65	0.022
	14 th day	13.72±1.61	13.60±1.44	0.75
Platelets (10 ³ /μL)	1 st day	226615.38±85221.59	239177.05±75928.07	0.327
	14 th day	312485.29±119456.54	323833.33±88392.24	0.672
Leukocytes (10 ³ /μL)	1 st day	6656.92±3427.7	6218.03±2225.5	0.362
	14 th day	7094.12±2096.19	7183.33±1581.32	0.85
Neutrophils (10 ³ /μL)	1 st day	4658.46±3208.03	3772.95±1807.29	0.046
	14 th day	4123.53±1571.97	4195.83±1306.66	0.84
Lymphocytes (10 ³ /μL)	1 st day	1439.23±723.85	1785.25±785.46	0.003
	14 th day	2205.88±1014.8	2320.83±826.72	0.619
NLR	1 st day	4.21±5.42	2.53±1.86	0.01
	14 th day	2.34±2.01	2.01±0.9	0.442
Eosinophils (10 ³ /μL)	1 st day	17.19±57.92	72.13±133.08	0.0001
	14 th day	155.15±126.12	95.88±95.42	0.039

NLR: Neutrophil to lymphocyte ratio, COVID-19: Coronavirus disease-2019

Table 2. Comparison of inpatients with severe and non-severe inpatients at admission

		Severe	Non-severe	p
Age		56.83±10.18	53.56±13.63	0.143
Sex	Female	36.54% (19)	56.41% (44)	-
	Male	63.46% (33)	43.59% (34)	-
CRP (mg/L)	1 st day	63.16±48.8	29.55±27.01	0.0001
	3 rd day	88.43±56.21	30.52±26.03	0.0001
Hospitalization days	<3 day	5.77% (3)	17.95% (14)	-
	3-10 day	53.85% (28)	79.49% (62)	-
	>10 day	40.38% (21)	2.56% (2)	0.0001
More than one drug	Yes	23.08% (12)	94.87% (74)	-
	No	76.92% (40)	5.13% (4)	0.0001
Intubation	No	88.46% (46)	100% (78)	-
	Yes	11.54% (6)	0	0.002
Clinical course	Intensive care	9.62% (5)	0	-
	Exitus	9.62% (5)	0	0.0001
Lung CT	>10	23.53% (12)	8.11% (6)	-
	5-10	58.82% (30)	47.3% (35)	-
	<5	17.65% (9)	44.59% (33)	0.002

CRP: C-reactive protein, CT: Computed tomography

Table 3. Comparison of hemogram parameters of severe and mild inpatients with COVID-19

		Severe n=52	Non-severe n=78	p
Hemoglobin (gr/dL)	1 st day	13.56±1.7	13.29±1.59	0.348
	3 rd day	12.97±1.71	12.67±1.75	0.349
	14 th day	13.86±1.54	13.61±1.67	0.516
Neutrophils (10 ³ /μL)	1 st day	4363.46±2036.53	4855.13±3794.28	0.467
	3 rd day	5417.31±3090.83	3420.29±2139.03	0.0001
	14 th day	4080±1607.18	4157.89±1564.41	0.786
Lymphocytes (10 ³ /μL)	1 st day	1417.31±804.09	1453.85±670.08	0.413
	3 rd day	1250±674.03	1616.81±624.76	0.0001
	14 th day	2070±1096.75	2313.16±946.16	0.192
NLR	1 st day	3.58±1.93	4.63±6.81	0.18
	3 rd day	5.84±4.86	2.31±1.39	0.0001
	14 th day	2.68±2.56	2.07±1.41	0.6
Eosinophils (10 ³ /μL)	1 st day	18.27±66.44	16.47±51.92	0.521
	3 rd day	39.23±79.41	82.17±120.79	0.006
	14 th day	166.67±149.33	146.05±105.51	0.785

NLR: Neutrophil to lymphocyte ratio, COVID-19: Coronavirus disease-2019

than the studies by Wang et al. (15) (56 years), Zhang et al. (12) (57 years), Chen et al. (32) (55 years), but higher than that by Huang et al. (11) (49 years). In our study, the mean age of the inpatient COVID-19 group (54.87±12.43) and the severe group in the hospitalized patients (56.83±10.18) were higher. Older

people are more likely to get COVID-19 pneumonia and more hospitalizations are required over the age of 50 and the disease is more severe in inpatients. This may be due to older people having more comorbidity and a weaker immune response to diseases. These data are similar to the study of Zhang et al. (12).

Table 4. Comparison of demographic characteristics and day 1 hemogram parameters of COVID-19 inpatients and outpatients and control group influenza patients

		Influenza		COVID-19 inpatients		COVID-19 outpatients		p
Age		42.5±21.49		54.87±12.43		39.9±11.62		0.0001
Sex	Male	15	68.18%	63	48.46%	31	50.82%	0.231
	Female	7	31.82%	67	51.54%	30	49.18%	
Hemoglobin (gr/dL) 1 st day		12.44±1.59		13.4±1.63		13.98±1.65		0.001
Neutrophils (10 ³ /μL) 1 st day		3640.91±1807.3		4658.46±3208.03		3772.95±1807.29		0.231
Lymphocytes (10 ³ /μL) 1 st day		1077.27±418.54		1439.23±723.85		1785.25±785.46		0.0001
NLR 1 st day		3.7±1.99		4.21±5.42		2.53±1.86		0.0001
Eosinophils (10 ³ /μL) 1 st day		1.25±2.07		0.28±0.76		1.08±1.69		0.0001

NLR: Neutrophil to lymphocyte ratio, COVID-19: Coronavirus disease-2019

In our study, 97 (50.7%) of the patients diagnosed with COVID-19 pneumonia were male. This rate was found to be the same as the study of Zhang et al. (12) (50.7%). It was found to be lower than the data of reports from China's Center for Disease Control and Prevention (51.4%) (33) Wang et al. (15) (54.3%), Chen et al. (32) (73%), Huang et al. (11) (66%). In our study, the rate of male patients (51.54%) was higher in outpatients (49.1%). Additionally, the rate of male patients in the severe group (63.4%) in hospitalized patients was higher than that in the non-severe group (43.59%).

In our study, 2019-COV PCR test of 167 patients diagnosed with COVID-19 pneumonia was found to be positive. Although 24 of the inpatients were negative for 2019-COV PCR results, they were accepted as COVID-19 pneumonia according to their clinical and radiological findings. A similar study also had patients diagnosed clinically (18).

Except for 4 patients in the inpatient group, all patients in the study underwent lung CT at the time of admission to the hospital for early diagnosis (the other 4 patients were diagnosed at an external center and referred to our hospital). The most common involvement in lung CT was bilateral GGO and consolidation, and there was no difference in the number of lobes involved between the groups. These data were similar to the data in the literature (30).

Neutrophil counts in the severe group the averages of CRP in the 1st and 3rd days, days of hospitalization more than 10 days, going to intensive care mortality rate, the overuse of medication were found to be higher than the non-severe group (Table 2). Additionally, patients in the severe group scored higher than

the distribution score on the lung CT (5 of 20 points) compared to the non-severe group. In the literature, as in our study, the prevalence of GGO involvement in lung CT was correlated with disease progression (17).

a) As in our study, in the study by Wang et al. (15) in patients with severe disease, inflammatory cells such as neutrophils and leukocytes were higher at the time of diagnosis, while lymphocyte and eosinophil counts were lower (12,16-18). Similar to the data in the literature, eosinophil counts were similar to lymphocyte counts in severe and mild patients (12,15,16). The number of eosinophils at the time of presentation is important in early diagnosis and seems to be related to disease severity. Additionally, the increase in eosinophil counts after treatment indicates that eosinophils can also be used to evaluate the response to treatment. Similarly, in the study by Jesenak et al. (17), normalization of eosinophil count in severe patients correlated with improvement in clinical condition.

In the literature, eosinopenia has been seen in COVID-19 pneumonia, especially in the early stages of the disease, even in asymptomatic cases (8,12-17,27,28,34). Especially in the study by Li et al. (27), eosinopenia and high hs-CRP combination had 67.9% sensitivity and 78.2% specificity in early diagnosis of disease and the area under the eosinopenia curve had a sensitivity of 0.717 to 74.7% and specificity of 68.7%.

b) In our study, eosinophil counts were found to be lower in the severely ill group compared to the non-severe group and were found to be persistent for a long time. In the study by Jesenak et al. (22), normalization of eosinophil count in severe patients correlated with clinical improvement, while severe and

persistent eosinopenia was observed in fatal COVID-19 patients. In the study by Zhang et al. (12), blood eosinopenia was observed in more than half of the patients in severe cases. Additionally, there was a correlation between eosinophil and lymphocyte counts at hospitalization and after 3 days in severe and non-severe patients. In our study, while there was a correlation between eosinophil and lymphocyte count in the mild patient group, it was not observed in the severe group. In the study by Azkur et al. (8), severe COVID-19 pneumonia was associated with a low eosinophil count. Tanni et al. (13) also showed that low eosinophil count is associated with early diagnosis and prognosis of the disease. Many studies have shown that low eosinophil levels are associated with poor outcome in critical illnesses (15,16).

In our study, the eosinophil count was found to be lower in severe patients who scored higher than the prevalence scoring in lung CT. Decreased blood eosinophil counts in severe patients may have early diagnostic value, particularly in patients with GGO in bilateral lungs. Even eosinopenia can occur before radiological findings. In this way, perhaps many patients can be diagnosed early and quickly prevent pandemics without performing lung CT. Thus, it can be cost-effective and unexposed to unnecessary radiation. In the study by Jesenak et al. (17), decreased eosinophil counts were associated with radiological changes such as GGO findings and respiratory symptoms, especially in the bilateral lung.

c) In this study, although eosinophil values were low in all groups, the mean eosinophil 1st day of the inpatient COVID-19 group was found to be significantly lower than the influenza group and outpatient COVID-19 groups. Although eosinopenia is not specific to COVID-19 infection, we believe that eosinopenia is a common finding in both COVID-19 and influenza. However, eosinophil values were found to be lower in COVID-19 patients than in patients with influenza. First day eosinophil counts were 0 in 156 (81%) of 191 patients in COVID-19 patients and in 13 (59%) of 22 patients in the influenza group. Its lower rate, especially in inpatients, supports the that it is also associated with disease severity. A published article in 2003 reported that approximately 90% of SARS-CoV patients had eosinopenia (35). In the study of Tanni et al. (13) as in our study, eosinophil values were found to be lower in COVID-19 patients than in patients with influenza. Additionally, Tanni et al. (13) showed that eosinophil values decreased in COVID-19 patients, particularly in the first 48 h. Wu et al. (36) reported a case in which COVID-19 and influenza virus coexisted in China and they mentioned the difficulties in diagnosis and the similarities between the two

diseases. In the study of Andreozzi et al. (19), it was stated that eosinopenia could be a potential indicator of influenza or SARS-CoV-2 infections (27).

The small number of patients in the influenza group can be considered a limiting factor of the study.

CONCLUSION

The presence of a low or no eosinophil count in CBC can help early isolation of the individuals infected with potential COVID-19 virus. While waiting for confirmatory test results, CBC can be a useful tool in deciding whether to immediately isolate a patient and initiate certain treatments. Considering that the 2019-COV PCR test may result in false negative results, which is important to prevent real patients from being sent home without treatment and prevent the further expansion of the pandemic. Also, by using an inexpensive CBC test, it is possible to prevent the unnecessary exposure of the patients to radiation without the need for more lung CT.

Persistent eosinopenia after admission was associated with high disease severity and low cure rates. In addition to the diagnosis of eosinopenia, it can guide us in distinguishing severe and non-severe patients, preventing intensive care and evaluating the disease prognosis. Although eosinopenia is not specific to COVID-19 infection and can also be seen in other viral infections, eosinophil values are lower in COVID-19 patients than in patients with influenza.

Ethics

Ethics Committee Approval: This study was approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee and all procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (decision no: 2020/514/179/11, date: 11 June 2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.U., Design: Z.T., Data Collection or Processing: T.N., B.Y., S.S., N.Ü.Ö., Analysis or Interpretation: N.E., Literature Search: N.U., P.Ö.E., R.D.K., H.S., Writing: N.U., N.E.

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