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Prognostic Factors for COVID-19 Patients and Role of Eosinophils

COVID-19 Hastaları İçin Prognostik Faktörler ve Eozinofillerin Rolü

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ABSTRACT

Objective: We planned to investigate the relationship of blood eosinophil level with disease severity and its effect on prognosis in coronavirus disease 2019 (COVID-19) patients.

Material and Methods: Four hundred and thirty-four COVID-19 patients who were hospitalized in the ward and admitted to our hospital between March 11, 2020, and May 15, 2020, and whose diagnosis was confirmed by real-time-polimerase chain reaction were included in the study.

Results: Lymphocyte, eosinophil count, and percentage were found to be significantly lower in mortal group (p=0.004, p=0.043, p<0.001, respectively). The blood c-reactive protein (CRP) value was also found to be high in mortal group (p<0.001). When the radiological findings accompanied by pleural effusion were more fatal (p<0.001). In addition, significantly more lobe involvement (mean 4.5) was observed in mortal group (p=0.009). According to the results of multivariate logistic regression analysis, 50–64 age range (p=0.028), shortness of breath (p=0.011), complaints of nausea-vomiting (p=0.007), low number and percentage of eosinophils in the blood count (p=0.001), and radiological findings accompanied by pleural effusion (p=0.026) were determined as important risk factors for mortality.

Conclusion: The presence of eosinopenia and elevated CRP with lymphopenia at admission in COVID-19 patients is an indicator of poor prognosis and has been found to be associated with mortality.

Keywords: COVID-19, eosinopenia, mortality, pneumonia, prognosis.

ÖZ

Amaç: Çalışmamızda koronavirüs hastalığı (COVID-19) olan hastalarda kan eozinofil düzeyinin hastalık şiddeti ile ilişkisi ve prognoza etkisinin araştırılması amaçlanmaktadır.

Gereç ve Yöntemler: Çalışmaya, 11 Mart 2020-15 Mayıs 2020 tarihleri arasında hastanemizde klinikte yatmış olan ve ayaktan başvuran gerçek zamanlı polimeraz zincir reaksiyonu (PCR) ile tanısı doğrulanmış 434 COVID-19 hastası dahil edildi.

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Bulgular: Lenfosit sayısı, eozinofil sayısı ve yüzdesinin mortal grupta anlamlı şekilde düşük olduğu görüldü (sırasıyla p=0,004, p=0,043, p<0,001). Kan C-reaktif protein (CRP) değeri de mortal grupta yüksek saptandı (p<0,001). Radyolojik bulgulara bakıldığında plevral efüzyonun eşlik ettiği tabloların daha mortal seyrettiği görüldü (p<0,001). Ayrıca mortal seyreden hastalarda anlamlı şekilde daha fazla lob tutulumu (ortalama 4,5) gözlendi (p=0,009). Çok değişkenli lojistik regresyon analizi sonuçlarına göre 50-64 yaş aralığı (p=0,028), nefes darlığı (p=0,011), bulantı kusma (p=0,007) şikayetlerinin olması, kan tablosunda eozinofil sayı ve yüzdesindeki düşüklük (p=0,001) ve radyolojik bulgularda plevral efüzyonun (p=0,026) eşlik ettiği durumlar mortalite için önemli risk faktörleri olarak belirlendi.

Sonuç: COVID-19 hastalarında başlangıçta lenfopeni ile birlikte eozinopeni ve CRP yüksekliğinin eşlik etmesi kötü prognoz göstergesi olup, mortalite ile ilişkili bulundu.

Anahtar kelimeler: COVID-19, eozinopeni, mortalite, pnömoni, prognoz.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), which was reported at the end of 2019 in Wuhan, China, is a highly contagious infectious disease that causes severe acute respiratory syndrome.[1,2] This virus which belongs to the same genus as severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus, named SARS-CoV-2 by the international virus taxonomy committee, is more contagious than both of them.[3] The first COVID-19 case in Türkiye was detected on March 11, 2020.[4]

Early identification of risk factors in this disease is important to shape a more appropriate and timely treatment because it can be fatal. Many biomarkers such as d-dimer and neutrophil-lymphocyte ratio that serve this purpose have been emphasized.[5] It has also been shown that eosinophils have a variety of other functions, including immunoregulation and antiviral activity.[6] For many years, eosinopenia has already been used as a biomarker in bacterial infections.[7] Some studies associate low eosinophil count with poor prognosis in COVID-19 infection.[8,9]

After eosinophils are released from the bone marrow, they migrate to the tissue by circulating for a few days.[9] Eosinopenia due to immune collapse, increased eosinophil migration from the blood to the infected organ, sustained and efficient Type-1 response that antagonizes the Type-2 response involving IL-5 that supports eosinophil survival and activation, interruption of eosinophilopoiesis as well as decreased eosinophil transfer from the bone marrow to the blood. The chemokine receptor stimulated by the release of Type-1 interferon during acute infection can be observed due to decreased release of adhesion factors as well as increased eosinophil apoptosis.[10]

Eosinopenia was also observed in the majority of COVID-19 patients, and its effect on prognosis has not been adequately investigated.[11] The aim of this study was to investigate the poor prognostic factors in COVID-19 patients, especially the relationship between blood eosinophil level and disease severity and its effect on prognosis.

MATERIAL AND METHODS

Four hundred and thirty-four COVID-19 patients who admitted to the hospital between March 11, 2020, and May 15, 2020, received outpatient or inpatient treatment and whose diagnosis was confirmed by real-time-polimerase chain reaction (PCR) were included in the study. Patients' symptoms, comorbidities, radiological features (chest X-ray and thorax computed tomography [CT]), blood lymphocyte, eosinophil and c-reactive protein (CRP) levels, and surveys at the admission were recorded retrospectively using the hospital information network.

The study approved by the Ethics Committee of the hospital with the 5th decision number at the meeting dated June 12, 2020, and conducted in accordance with the Helsinki Declaration. An informed consent form is not required due to the fact that it is a retrospective study.

Statistical Analysis

Data were analyzed with SPSSV.21.0 (SPSS Inc., Chicago, IL, USA). After the normality test using Kolmogorov–Smirnov and Shapiro–Wilk test, Student's T test was used to compare normally distributed continuous variables, and Mann–Whitney U test was used to compare non-normally distributed continuous variables. Continuous variables were expressed as the mean±standard deviation or as the median (range).

Chi-square and Fisher's exact test were used for the comparison of categorical parameters. Categorical variables were given as a number (%). Multivariate logistic regression analysis was performed to identify the risk factors. P<0.05 was considered statistically significant.

RESULTS

Of the 434 patients followed for COVID-19, 249 (57.4%) were male. There were 197 (45.4%) patients in the 15–49 age group, 143 (32.9%) patients in the 50–64 age group, and 94 patients were aged 65 and over. A total of 222 (60.5%) had no smoking history.

The most common symptoms were cough (62.7%), malaise (37.6%), fever (37.4%), shortness of breath (37.1%), and myalgia (20.7%), respectively. Posteroanterior chest X-ray of 291 (67.1%) patients showed signs of disease, and thorax CT had signs of disease in 360 (89.3%) of 417 patients. On CT images, 89.3% of the patients had ground glass opacities, 64% of them had infiltrations, 31.4% of them had consolidation, and 7.2% of them had pleural effusion. The mean number of lobes involved was 2.8±2.3, and the hospital stay was 8.1±0.4 days. Four hundred and four (93.1%) patients had recovered and 30 (6.9%) patients had died. Detailed demographic and clinical characteristics of the patients are shown in Table 1.

Table 1: Clinical features of the patients

	n	%		n	%
Age groups			Eosinophil mean±SD (min-max)	102.5±144.0 (0–1100)	
15–49	197	45.4	Eosinophil % mean±SD (min-max)	1.5±1.7 (0.0–11.8)	
50–64	143	32.9	CRP mean±SD (min-max)	16.8±43.4 (0–377.5)	
≥65	94	21.7	Findings in chest X-ray n(%)		
Gender			Unilateral	105	36.1
Female	185	42.6	Bilateral	186	63.9
Male	249	57.4	Ground glass opacities in thorax CT		
Comorbidity	219	50.5	Unilateral	74	20.6
Smoking history			Bilateral	286	79.4
No	222	60.5	Infiltrations		
Yes	145	39.5	Local	125	48.4
Fever	162	37.4	Diffused	133	51.6
Cough	272	62.7	Consolidation	126	31.4
Sore throat	80	18.4	Pleural effusion	29	7.2
Weakness	163	37.6	Number of lobes involved mean±SD (min-max)	2.8±2.3 (0–6)	
Dyspnea	161	37.1	Hospital stay (days) mean±SD (min-max)	8.1±0.4 (1–95)	
Myalgia	90	20.7	Results		
Leukocyte mean±SD (min-max)	7661.3±4159.0 (1200–31900)		Survival	404	93.1
Neutrophil % mean±SD (min-max)	69.4±12.2 (26.3–98.1)		Exitus	30	6.9
Lymphocyte mean±SD (min-max)	1412.7±839.1 (100–9600)				

SD: Standard deviation, CRP: C-reactive protein, CT: Computed tomography.

When the characteristics of the patients who died and survived due to COVID-19 were examined detailly, 90% of the patients who died were over 50 years old (p<0.001). Most (86.7%) of them had at least one comorbidity (p<0.001). Furthermore, we found that smoking history played a statistically significant effective role on the mortality of COVID-19 disease (p<0.001) (Table 2).

While the symptoms of sputum production, shortness of breath, nausea-vomiting, and loss of appetite, which were mostly seen during the course of the disease were strongly associated with the risk of mortality (p<0.001, p<0.001, p=0.010, and p=0.005, respectively), fatigue and anosmia were also to a certain extent (p=0.026, p=0.029) was found to be related to mortality.

Considering the hemogram parameters, the elevation of leukocytes and neutrophils was in parallel with the risk of mortality (p=0.001, p<0.001), while the risk of mortality was increased as the values of lymphocytes and eosinophils decreased (p=0.004, p<0.001). The elevation in CRP, which is an acute phase reactant, was also found to be directly proportional to the risk of death (p<0.001).

When the radiological images of the patients were evaluated, the presence of lesions in chest X-ray was found to be significantly associated with the risk of death (p=0.002). The presence of infiltration on thorax CT was (p=0.029) associated with the mortality rate, especially consolidation, pleural effusion, and the increase in the number of involved lobes significantly associated with mortality (p=0.002, p<0.001, and p=0.009, respectively).

According to the results of multivariate logistic regression analysis, it was observed that the age range of 50–64 (p=0.028), shortness of breath (p=0.011), and presence of pleural effusion (p=0.026) were risk factors for mortality, while nausea-vomiting (p=0.007), low eosinophil count (p=0.001), and percentage (p=0.001) were determined as very strong risk factors for mortality (Table 3).

DISCUSSION

COVID-19 is a global pandemic infectious disease that affects the whole world and causes severe acute respiratory syndrome with high mortality. It can cause severe disease through various immune mechanisms such as abnormal and overactivated immunity and cytokine storms caused by SARS-CoV-2. Biomarkers that can provide information about the prognosis of the disease will guide clinicians.[2]

In this retrospective study, we evaluated 434 real-time PCR-confirmed COVID-19 patients, 45.4% of the patients were in the

Table 2: Comparison of demographic and clinical findings of alive and dead patients

	Mortal (n=30)		Alive (n=404)		p
	n	%	n	%	
Age group					
15–49 years	3	10.0	194	48.0	**<0.001**
50–64 years	14	46.7	129	31.9	
≥65 years	13	43.3	81	20.0	
Gender					
Male	20	66.7	229	56.7	0.286
Female	10	33.3	175	43.3	
Comorbidity	26	86.7	193	47.8	**<0.001**
Smoking history					
No	8	28.6	214	63.1	**<0.001**
Yes	20	71.5	125	36.9	
Weakness	17	56.7	146	36.2	**0.026**
Sputum	11	36.7	38	9.4	**<0.001**
Dyspnea	25	83.3	166	33.7	**<0.001**
Nausea-vomiting	7	23.3	31	7.7	**0.010**
Anosmia	4	13.3	14	3.5	**0.029**
Anorexia	10	33.3	52	12.9	**0.005**
Leukocyte	10000 (3500–31900)		6550 (1200–30900)		**0.001**
Neutrophil percentage %	80.9 (62.0–96.2)		69.4 (26.3–98.1)		**<0.001**
Lymphocyte	950 (200–3000)		1300 (100–9600)		**0.004**
Eosinophil	0 (0–600)		100 (0–1100)		**0.043**
Eosinophil percentage %	0.1 (0.0–5.3)		1.0 (0.0–11.8)		**<0.001**
CRP	17.2 (1.6–340.5)		3.5 (0.0–377.5)		**<0.001**
Findings in chest x-ray					
Yes	28	93.3	263	65.1	**0.002**
No	2	6.7	141	34.9	
Ground glass opacities in thorax CT					
Unilateral	2	7.4	72	21.6	0.079
Bilateral	25	92.6	261	78.4	
Infiltration	24	82.8	234	62.6	**0.029**
Consolidation	17	56.7	108	29.4	**0.002**
Pleural effusion	10	33.3	19	5.1	**<0.001**
Number of lobes involved median (min-max)	4.5 (0–6)		2 (0–6)		**0.009**

CRP: C-reactive protein, CT: Computed tomography.

15–49 age group, 32.9% of them in the 50–65 age group, and 21.7% of them in the ≥65 age group. When we looked at the age groups of the patients who died, 14 patients (46.7%) in the 50–64 age group and 13 patients (43.3%) in the ≥65 age group were found. Most (86.7%) of them had at least one comorbidity in mortal group. Mortality was strongly associated in patients with advanced age and higher comorbidity in our study, similar to other studies (p<0.001 for both).[3,12] In this study, we found no effect of gender on mortality. However, in the study of Du et al.,[3] the mortality rate was higher in males. The mortality rate increased significantly with the presence of a smoking history (p<0.001). Alqahtani et al.,[13] also found that smoking increases the mortality rate similar to our study.

While cough was the most common symptom in patients, dyspnea was significantly more common in mortal group (p<0.001). The reason why dyspnea was associated with high mortality as a clinical reflection of serious complications such as pulmonary embolism and multilobar involvement of lung or pleural effusion. In this study, fatigue, sputum production, nausea, and vomiting were also found to be associated with mortality (p=0.026, p<0.001, and

Table 3: Multivariate logistic regression analysis of risk factors for mortality

	OR	%95 CI	p
Age group			0.088
15–49 versus 50–65	7.40	1.235–44.387	**0.028**
15–49 versus ≥65	4.68	0.828–26.476	0.081
Comorbidity	1.49	0.324–6.820	0.610
Sputum	2.91	0.647–13.126	0.164
Dyspnea	5.84	1.490–22.908	**0.011**
Nausea-vomiting	10.15	1.861–55.392	**0.007**
Anosmia	13.80	0.885–215.551	0.061
Anorexia	0.88	0.219–3.557	0.861
Leukocyte	1.00	0.999–1.001	0.925
Neutrophil	1.00	0.999–1.001	0.694
Neutrophil percentage %	1.08	0.962–1.218	0.189
Eosinophil	1.04	1.014–1.057	**0.001**
Eosinophil percentage %	0.17	0.002–0.180	**0.001**
Lymphocyte	1.00	0.998–1.001	0.580
CRP	1.00	0.997–1.014	0.197
Findings in chest X-ray	4.38	0.474–40.562	0.193
Infiltration	0.83	0.196–3.546	0.805
Consolidation	1.55	0.449–5.326	0.490
Pleural effusion	5.26	1.214–22.822	**0.026**
Number of lobes involved	1.08	0.832–1.411	0.553

According to the results of multivariate logistic regression analysis; the presence of shortness of breath and nausea-vomiting, a low number and percentage of eosinophils, and the presence of pleural effusion were determined as important risk factors for mortality. OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein.

p=0.010, respectively). In a Spain study in which elderly patients were included, the effect of dyspnea on mortality was also observed.[12] However, the relationship between other symptoms and mortality could not be demonstrated both in the same study and in the study of Martos Pérez et al.[14]

There was a significant correlation between the extent of lung involvement and mortality. In the study of Hejazi et al.[15] on intensive care patients in Iran, they found that multilobar involvement was associated with comorbidity and poor prognosis, but they could not associate it with mortality. However, the study of Aydemir et al.[16] was similar to ours, they found a relationship between multilobar involvement and the severity and mortality of the disease. In addition, mortality was found to be significantly higher in patients with accompanying pleural effusion. We think that both multilobar involvement and pleural effusion will contribute to the development of respiratory failure more easily in the patient and have an effect on mortality because the patient also had other comorbidities, especially involving the lungs. Wei et al.[17] also defined pleural effusion as a poor prognostic factor in their study.

Eosinopenia is a marker that correlates with the severity of the disease in acute infections, especially in bacterial infections. The decrease in the number of eosinophils in the blood during acute infections was first described by Zappert in 1983 and has been used as a useful diagnostic marker since its definition.[7] Although the exact mechanism of eosinopenia is not known, the effect of stress on the bone marrow due to adrenal, glucocorticoid, and epinephrine is emphasized in acute infection.[6,7,18] Moreover, it has been stated that eosinophil granule proteins can neutralize the virus. Therefore, a decrease in the number of eosinophils may be associated with viral load.[3] In addition, there are studies showing that the PCR results of the patients become negative in an average of 5 days after the eosinophil count returns to normal, and that the increase in eosinophils may be associated with clinical improvement.[1] Considering these mechanisms, it may be a factor that COVID-19 infection does not show a worse prognosis as expected in patients with asthma and similar allergic comorbidities.[2,6] In our study, the number and the percentage of eosinophils were significantly lower in mortal group (respectively, p=0.043, p<0.001). As a result, in this study, similar to previous studies, eosinopenia was found to be associated with mortality. Sun[19] and Chen[8] also found that the severity of the disease increased as the number of eosinophils decreased.

In our study, the lymphocyte count was found to be significantly lower in mortal group, similar to previous studies (p=0.004). Terpos et al.[20] and Sun et al.[19] also found a relationship between lymphopenia and disease severity.

Lymphopenia and eosinopenia are helpful markers in the diagnosis of the disease and also associated with the prognosis and mortality of the disease.[21,22]

Furthermore, a direct correlation was found between high CRP value and mortality (p<0.001). Although there are many similar studies, the study of Li et al.[22] also supports this study.

Study Limitations

The limitation of this study is that it was a retrospective design.

CONCLUSION

Eosinophil count is a simple and inexpensive method that can be used to determine the prognosis in COVID-19 patients. We believe that it can guide the clinician at the time of diagnosis in the treatment planning phase. We can reduce mortality by early diagnosis and early treatment of patients with poor prognostic factors.

Disclosures

Ethics Committee Approval: The study was approved by The University of Health Sciences, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee (date: 12.06.2020, number: 5).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.Ç., N.K.; Design – N.K.; Supervision – P.Ç.; Materials – P.Ç.; Data Collection and/or Processing – Ç.A.; Analysis and/or Interpretation – N.K., P.Ç.; Literature Search – N.K., Ç.A., P.Ç.; Writing – N.K., Ç.A., P.Ç.; Critical Reviews – N.K., P.Ç.

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