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Investigation of Aggravating Risk Factors in COVID-19 Infection

Dilek YEKENKURUL [1], Nevin INCE [1], Mustafa YILDIRIM [1], Mehmet Ali SUNGUR [2], Elif EŞCAN [1], Fatih DAVRAN [3], Hasan Baki ALTINSOY [4], Betül DÖNMEZ [5], Güleser AKPINAR [6]

ABSTRACT

Aim: Coronavirus disease-2019 caused an epidemic that started in China about two years ago but affected the whole world. It was aimed to evaluate patients followed up with coronavirus disease-2019 infection, to determine risk factors and indicators for severe infection.

Material and Methods: Patients who received treatment as inpatient with coronavirus disease-2019 infection between March 15- June 01 2020 were investigated. Patients were divided into two groups according to their oxygen saturation; patients with oxygen saturation over 90% were group 1, patients with 90% or less were determined as group 2. This two groups were compared in terms of aggravating risk factors.

Results: In this study, 90 patients (46 female, 44 male) were included. Moderate-severe pneumonic involvement in computed tomography of thorax (p=0.002) and high fever (p<0.001) were thought to be indicators for severe infection. Presence of chronic disease (p=0.018) and asthma (p=0.041) were found to be aggravating risk factors. High levels of tests such as C-reactive protein, erythrocyte sedimentation rate, ferritin, neutrophil-lymphocyte ratio, lactate dehydrogenase (p<0.001), procalcitonin, D-dimer, creatine kinase, triglyceride, and low levels of tests such as lymphocytes, hemoglobin were thought to indicate severe disease.

Conclusion: Parameters such as low level of lymphocyte and high level of C-reactive protein, D-dimer, ferritin are frequently used as indicators of poor prognosis. However, we also believe that high level of procalcitonin, lactate dehydrogenase, erythrocyte sedimentation rate, creatine kinase and triglyceride, low level of hemoglobin, in addition the presence of asthma and high fever may be indicators of poor prognosis.

Keywords: Coronavirus disease-2019; aggravating factors; oxygen saturation.

COVID-19 Enfeksiyonunda Ağırlaştırıcı Risk Faktörlerinin Araştırılması

ÖZ

Amaç: Koronavirüs hastalığı-2019, yaklaşık iki yıl önce Çin'de başlayan ancak tüm dünyayı etkisi altına alan bir salgına neden olmuştur. Koronavirüs hastalığı-2019 enfeksiyonu ile takip edilen hastaların değerlendirilmesi, ciddi enfeksiyon için risk faktörlerinin ve göstergelerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Koronavirüs hastalığı-2019 enfeksiyonu ile 15 Mart- 01 Haziran 2020 tarihleri arasında yatarak tedavi gören hastalar araştırıldı. Hastalar oksijen satürasyonlarına göre iki gruba ayrıldı; oksijen satürasyonu % 90'ın üzerinde olan hastalar grup 1, % 90 ve altı olan hastalar grup 2 olarak belirlendi. Bu iki grup ağırlaştırıcı risk faktörleri açısından karşılaştırıldı.

Bulgular: Bu çalışmaya 90 hasta (46 kadın, 44 erkek) dahil edildi. Bilgisayarlı toraks tomografisinde orta-şiddetli pnömonik tutulum (p=0,002) ve yüksek ateş (p<0,001) ciddi enfeksiyon belirteçleri olarak düşünüldü. Kronik hastalık (p=0.018) ve astım (p=0.041) varlığı ağırlaştırıcı risk faktörleri olarak bulundu. C-reaktif protein, eritrosit sedimentasyon hızı, ferritin, nötrofil-lenfosit oranı, laktat dehidrogenaz (p<0,001), prokalsitonin, D-dimer, kreatin kinaz, trigliserid gibi testlerin yüksek ve lenfosit, hemoglobin gibi testlerin düşük olmasının şiddetli hastalığı gösterdiği düşünüldü.

Sonuç: Lenfosit düşüklüğü ve C-reaktif protein, D-dimer, ferritin yüksekliği gibi parametreler kötü prognoz göstergesi olarak sıklıkla kullanılmaktadır. Ancak prokalsitonin, laktat dehidrogenaz, eritrosit sedimentasyon hızı, kreatin kinaz ve

1 Department of Infectious Diseases and Clinical Microbiology, Düzce University Faculty of Medicine, Düzce, Turkey
2 Department of Biostatistics and Medical Informatics, Düzce University Faculty of Medicine, Düzce, Turkey
3 Department of Medical Biochemistry, Düzce University Faculty of Medicine, Düzce, Turkey
4 Department of Radiology, Düzce University Faculty of Medicine, Düzce, Turkey
5 Department of Medical Microbiology, Düzce University Faculty of Medicine, Düzce, Turkey
6 Department of Emergency Medicine, Düzce University Faculty of Medicine, Düzce, Turkey

Sorumlu Yazar / Corresponding Author: Dilek YEKENKURUL, e-mail: dr.dilekakinci@gmail.com
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trigliserid seviyelerinin yüksek, hemoglobin düzeylerinin düşük olmasının yanında astım ve yüksek ateş varlığının da kötü prognoz göstergesi olabileceği kanaatindeyiz.
Anahtar Kelimeler: Koronavirüs hastalığı 2019; ağırlaştırıcı faktörler; oksijen satürasyonu.

INTRODUCTION

In December 2019, cases of pneumonia of unknown cause were observed in Wuhan, China, and SARS-CoV2 (2019-nCoV) was isolated in these patients on January 7, 2020 (1). It was later named coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO) in February 2020 (2). Later on time, it has become an epidemic that affects the whole world in the form of person-to-person transmission (3). COVID-19 progresses in some patients and causes acute respiratory distress syndrome (ARDS). Respiratory failure and shortness of breath are more prominent in these patients (4,5).

Patients are categorized according to the clinical course of the disease. Although there are some differences but generally; patients without pneumonia or with mild lung involvement and who have mild symptoms are examined in the mild disease group. Patients with hypoxia and dyspnea, who have severe symptoms or wider lung involvement, are examined in the severe disease group. Patients with clinical tables such as shock, respiratory failure, multiorgan failure requiring intensive care follow-up are examined in the critical disease group (6). Besides, there are laboratory markers of patients that should be followed such as leukopenia, thrombocytopenia, lymphopenia, the elevation of C-reactive protein (CRP), and elevation of D-dimer (5). In the course of infection, cytokine storm caused by activation of the immune system increases morbidity and mortality by causing uncontrolled organ damage and death in patients (7). Since there is still no standard treatment for COVID-19, it is very important to identify prognostic risk factors (8).

There are studies on mortality risk factors in the literature; however, few studies are examining aggravating risk factors. In our study; patients were investigated who received treatment as an inpatient in our hospital's Infectious Diseases and Clinical Microbiology Clinic between 15 March-01 June 2020. It was aimed to determine the aggravating risk factors and indicators in terms of severe infection.

MATERIAL AND METHODS

Study Setting

Patients who have positive Polymerase Chain Reaction (PCR) and/or thoracic computed tomography (CT) findings interpreted in favor of COVID-19 and who were clinically diagnosed and given COVID-19 treatment were chosen for this study. Ninety patients who were hospitalized with the diagnosis of COVID-19 infection, between 15 March-01 June 2020, at the Infectious Diseases and Clinical Microbiology Clinic of Düzce University Research and Practice Hospital, a tertiary university hospital, were retrospectively evaluated. Our university hospital, located in the northwest of Turkey has a 316-bed capacity, and serves a region with a population of approximately 370,000. Patients under 18 years of age and outpatients were excluded from the study. Nine patients with an additional admission diagnosis such as bacterial pneumonia or myocardial infarction were not included to the study, because of increased disease severity and acute phase reactants. This study was approved by Düzce University Research and Application Hospital Medical Ethics Committee (Date: 20.07.2020; No: 2020/144).

COVID-19 Diagnosis

COVID-19 was first seen in our country in March 2020. Since that date, the follow-up and treatment of the COVID-19 patients have been carried out under the leadership of the guidelines published and frequently revised by the Republic of Turkey Ministry of Health. For this reason; patients, with positive PCR results taken in the form of oropharyngeal and nasopharyngeal swabs or thoracic CT findings were interpreted in favor of COVID-19, were diagnosed with COVID-19 following the guidelines of the Ministry of Health of the Republic of Turkey (3). Thoracic CT results of the patients were reported according to the severity of findings. Some patients with positive PCR did not show signs of pneumonia in the lung. While evaluating thorax CT results, it has been reported as non-pneumonia or as mild, moderate, or severe involvement. Again, with the recommendation of the guide, hydroxychloroquine sulfate 200 mg tablets were given for five days with 12-hour intervals in all our patients.

Study Group

The patients were divided into two groups according to severity of diseases. For the first group (group 1); patients were selected with room air oxygen saturation (sO2) above 90% and respiratory rate below 30/min on admission or during hospitalization. For the second group (group 2); patients were selected who with room air oxygen saturation (sO2) below 90% or 90% on admission or during hospitalization. Patients' demographic characteristics, comorbidities, habits, clinical complaints, vital signs (fever, respiratory rate, pulse, blood pressure arterial), oxygen saturation, drugs they use chronically, blood parameters, PCR results, thorax CT findings were examined.

Statistical Analysis

The distribution of the data was examined with the Kolmogorov-Simirnov test, and group comparisons for continuous variables with normal distribution were made using independent samples t-test and One-Way ANOVA, and for continuous variables not normally distributed, Mann-Whitney U test and Kruskal-Wallis test were used. Cut-off values were calculated by ROC curve analysis for parameters that differ significantly in group comparisons in terms of the course of the disease (mild/severe). Relationships between categorical variables were examined using the Pearson chi-square or Fisher's exact and Fisher-Freeman-Halton tests. Categorical variables were summarized by number (percentage), while numerical variables were given as mean ± standard deviation or median (interquartile width) [minimum-maximum] depending on the distribution pattern. Statistical analyzes were made with the SPSS v.22 package program and the level of significance was taken into account as 0.05.

RESULTS

A total of 90 patients 46 (51%) women and 44 (49%) men whom were inpatient with the diagnosis of COVID-19 in the Infectious Diseases and Clinical Microbiology Clinic were included to the study. The mean age of patients was 55.63 ± 14.95 years. Group 1 consists of 34 (52.3%) male, 31 (47.7%) female total 65 patients (72%); group 2 consists of 10 (40%) male, 15 (60%) female, total 25 patients (28%). In the statistical analysis made between the groups; there was no difference in terms of smoking and demographic characteristics such as age, age over 65 and gender (Table 1).

Table 1. Patients' demographic features, chronic diseases and chronic drug use information

Features	**Group 1 (n=65)**	**Group 2 (n=25)**	**p value**
Demographic features			
Age (years)	54.22±15.83	59.32±11.89	0.148
>65 years old(n,%)	19 (29.2)	8 (32)	0.797
Gender (n,%)			0.295
Female (n,%)	31 (47.7)	15 (60)	
Male (n,%)	34 (52.3)	10 (40)	
Smoking (n=59 vs 25,%)			0.522
No	52 (88.1)	20 (80)	
Yes	5 (8.5)	3 (12)	
Old smoking	2 (3.4)	2 (8)	
Chronic diseases n (%)			**0.018**
Yes	44 (67.7)	23(92)	
No	21 (32.3)	2 (8)	
Number of diseases (n=44 vs 23)	2 (2) [1-6]	2 (3) [1-9]	0.270
Diseases n (%)			
Hypertension	31 (47.7)	10 (40)	0.512
Anemia	15 (23.1)	10 (40)	0.108
Diabetes mellitus	9 (13.8)	8 (32)	0.070
CAD	9 (13.8)	2 (8)	0.721
Asthma	6 (9.2)	7 (28)	**0.041**
Cancer	2 (3.1)	2 (8)	0.308
CHF	2 (3.1)	3 (12)	0.129
Epilepsy	2 (3.1)	3 (12)	0.129
Depression	2 (3.1)	1 (4)	1.000
Immunosuppression	2 (3.1)	2 (8)	0.308
COPD	1 (1.5)	0 (0)	1.000
CRF	1 (1.5)	0 (0)	1.000
CVD	1 (1.5)	1 (4)	0.481
Chronic hepatitis	1 (1.5)	1 (4)	0.481
Obesity	1 (1.5)	3 (12)	0.063
Other diseases	8 (12.3)	9 (36)	**0.016**
Using chronic drug n (%)			0.223
Yes	35 (53.8)	17 (68)	
No	30 (46.2)	8 (32)	
Number of drug using chronically (n=35 vs 17)	1 (1) [1-6]	2 (2) [1-8]	**0.046**
Using drug n (%)			
Hypertension drug	25 (38.5)	9 (36)	0.829
DM drug	9 (13.8)	7 (28)	0.132
Psychiatric drug	4 (6.2)	1 (4)	1.000
Epilepsy drug	2 (3.1)	3 (12)	0.129
Cancer drug	0 (0)	1 (4)	0.278
Other drug	12 (18.5)	11 (44)	**0.013**

COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, CVD: Cerebrovascular disease, CAD: Coronary artery disease, CHF: Congestive heart failure, DM: Diabetes mellitus

Table 2. Vital signs, symptoms, last status, PCR and CT results of the patients

Features	Group 1 (n=65)	Group 2 (n=25)	p value
Vital signs			
Pulse / minute	83 (20)[60-122]	90 (14) [65-111]	**0.024**
SBP mm/Hg	110(23)[80-180]	110(20)[90-200]	0.212
DBP mm/Hg	70 (13) [50-100]	70 (10) [50-100]	0.085
RR/min	22 (0) [20-28]	24 (3) [20-32]	**<0.001**
Fever ^{o}C	37.46±0.86	38.38±0.79	**<0.001**
Oxygen sat.	95.26±1.96	86.68±4.49	**<0.001**
Presence of symptoms n (%)	57 (87,7)	25 (100)	0.100
Number of symptoms	2 (1) [1-8]	6 (4) [1-10]	**<0.001**
Symptoms: n (%)			
Fever	23 (35.4)	21 (84)	**<0.001**
Cough	39 (60)	24 (96)	**0.001**
Shortness of breath	13 (20)	14 (56)	**0.001**
Chills	11 (16.9)	20 (80)	**<0.001**
Weakness	23 (35.4)	22 (88)	**<0.001**
Nasal congestion	0 (0)	1 (4)	0.278
Headache	9 (13.8)	12 (48)	**0.001**
Sputum	0 (0)	0 (0)	
Loss of appetite	6 (9.2)	12 (48)	**<0.001**
Abdominal pain	0 (0)	2 (8)	0.075
Diarrhea	3 (4.6)	1 (4)	1.000
Loss of smell	1 (1.5)	2 (8)	0.186
Throat ache	2 (3.1)	2 (8)	0.308
Nausea-vomiting	4 (6.2)	1 (4)	1.000
Muscle pain	8 (12.3)	2 (8)	0.720
Joint pain	6 (9.2)	2 (8)	1.000
Impaired consciousness	1 (1.5)	0 (0)	1.000
Loss of taste	5 (7.7)	2 (8)	1.000
PCR results n (%)			0.189
Positive	37 (56.9)	18 (72)	
Negative	28 (43.1)	7 (28)	
CT results n (%)			**0.002**
No pneu.	7 (10.8)[a]	0 (0.0)[a]	
Mild pneu.	39 (60.0)[a]	7 (28.0)[b]	
Modarate pneu.	16 (24.6)[a]	13 (52.0)[b]	
Severe pneu.	3 (4.6)[a]	5 (20.0)[b]	
Last status n (%)			**0.022**
Healing	62 (95.4)	22 (88)	
Enthusiasm	3 (4.6)	0 (0)	
Exitus	0 (0)	**3 (12)**	

PCR: Polymerase Chain Reaction, CT: Computed Tomography,
SBP: Systolic blood pressure, DBP: Diastolic blood pressure,
Min: Minute, RR: Respiratory rate, Pneu: Pneumonia, Sat: Saturation
[a, b]: Different subscript letters denote a significant difference between column proportions at the 0,05 level

In terms of vital signs, body temperature measurement ($p < 0.001$), respiratory rate per minute ($p < 0.001$) and pulse ($p = 0.024$) were significantly higher in group 2. It was observed that patients had more symptoms in group 2 than in group 1 ($p < 0.001$). Complaints of fever, chills, cough, shortness of breath, headache, weakness, and anorexia were more common in group 2 compared to group 1. It was noteworthy that there was no sputum complaint in both groups. When the thorax CT results were examined, it was seen that the lung involvement of the patients in group 2 was more severe than in group 1 ($p = 0.002$) and the mortality rate was higher in group 2 ($p = 0.022$) (Table 2).

Table 3. Laboratory results of patients

Laboratory test	**Group 1 (n=65)**	**Group 2 (n=25)**	**p value**
CRP mg/dL	2.32 (6.42) [0.03-16.00]	7.81 (6.67) [0.58-49.00]	**<0.001**
ESR mm/h (n=48 vs 24)	32.5 (34) [5-119]	68.5 (32) [26-105]	**<0.001**
Procalcitonin ng/mL (n=53 vs 24)	0.06 (0.06) [0.01-1.05]	0.10 (0.25) [0.02-1.23]	**0.007**
≥0.5 ng/mL Procalcitonin (n=53 vs 24)	1 (1.9)	4 (16.7)	**0.031**
D-Dimer µg/mL (n=58 vs 24)	0.38 (0.36) [0.20-1.44]	0.58 (1.35) [0.20-5.18]	**0.001**
≥0.5 µg/mL D-Dimer (n=58 vs 24)	17 (29.3)	16 (66.7)	**0.002**
Ferritin ng/mL (n=54 vs 24)	153 (124) [13-834]	556 (774) [60-2000]	**<0.001**
≥500 ng/mL Ferritin (n=54 vs 24)	2 (3.7)	14 (58.3)	**<0.001**
White blood cell /uL	4500 (2100) [2000-14100]	4100 (2450) [2600-15000]	0.430
Hemoglobin g/dL	12.63±1.67	11.74±1.98	**0.035**
Neutrophil /uL	2880 (1935) [1140-10500]	3670 (5340) [1680-10870]	0.115
Lymphocyte /uL	1200 (640) [380-2850]	790 (275) [330-2080]	**<0.001**
<800 /uL Lymphocyte	14 (21.5)	14 (56.0)	**0.002**
NLR	2.78 (3.29) [0.73-23.00]	5.99 (5.58) [1.71-25.42]	**<0.001**
Platelet $x10^3$/uL	208 (99) [68-442]	185 (89) [52-305]	0.119
Triglyceride mg/dL (n=55 vs 24)	132 (64) [57-752]	154 (123) [64-377]	**0.048**
Prothrombin time sc (n=62 vs 25)	10.92±3.18	10.61±2.21	0.656
INR (n=62 vs 25)	1.16±0.21	1.17±0.23	0.761
aPTT sc (n=62 vs 25)	33.33±7.12	35.20±5.19	0.237
LDH U/L	256 (97) [152-652]	332 (135) [217-582]	**<0.001**
CK mg/Dl	92 (85) [37-819]	130 (202) [50-1046]	**0.008**
Rule of five	2 (3.1)	17 (68.0)	**<0.001**

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil/lymphocyte rate, INR: International normalized ratio, aPTT: Activated partial thromboplastin time, LDH: Lactate dehydrogenase, CK: Creatine kinase, sc=second, Rule of five: If four-fifths were positive (D-Dimer≥0,5 µg/mL, NLR≥5, CRP≥5 mg/dL, ESR ≥50 mm/h, Ferritin≥500 ng/mL)

In about three months, our three patients who were aged 46, 56, and 73, died. One of them was female and two were male. Our overall mortality rate was 3%.

CRP (p <0.001), erythrocyte sedimentation rate (p <0.001), neutrophil lymphocyte ratio (NLR) (p <0.001), lactate dehydrogenase (LDH) (p <0.001), ferritin (p<0.001), procalcitonin (p = 0.007), D-dimer (p = 0.001), creatine kinase (p = 0.008) and triglyceride (p = 0.048) levels were found to be significantly higher in group 2. Lymphocyte (p <0.001) and hemoglobin (p = 0.035) levels were significantly lower in patients in group 2. While the white blood cell count was over 11,000 / uL in only three patients, it was below 4000 / uL in 37 (56.9%) patients. However, there was no difference (p = 0.430) between the groups in terms of white blood cell count (Table 3).

Table 4. ROC analysis data for some laboratory tests

Laboratory test	AUC	95% CI	p value	Cut-off	Sensitivity	Specificity
CRP	0.786	0.687 – 0.884	**<0.001**	≥5.01	84.0	69.2
ESR	0.805	0.704 – 0.906	**<0.001**	≥61.5	70.8	83.3
Procalcitonin	0.693	0.566 – 0.820	**0.007**	≥0.075	70.8	60.4
D-Dimer	0.724	0.598 – 0.851	**0.001**	≥0.49	66.7	70.7
Ferritin	0.774	0.636 – 0.913	**<0.001**	≥393	66.7	94.4
Hemoglobin	0.637	0.507 – 0.767	**0.045**	≤12.35	68.0	58.5
Lymphocyte	0.778	0.676 – 0.880	**<0.001**	≤905	88.0	72.3
NLR	0.750	0.639 – 0.861	**<0.001**	≥3.69	76.0	67.7
Triglyceride	0.641	0.504 – 0.777	**0.048**	≥160.5	45.8	78.2
LDH	0.765	0.662 – 0.867	**<0.001**	≥277.5	80.0	66.2
CK	0.633	0.501 – 0.765	**0.050**	≥186	40.0	86.2

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil/lymphocyte rate, LDH: Lactate dehydrogenase, CK: Creatine kinase

In the ROC analysis performed to predict poor prognosis in patients, it was seen that the cut-off values for CRP was 5.01 mg/dL (AUC: 0.786; 95% CI: 0.687 - 0.884; p <0.001), for erythrocyte sedimentation rate (ESR) 61.5 mm/h (AUC: 0.805; 95% CI: 0.704 - 0.906; p <0.001), for D-dimer 0.49 µg/mL (AUC: 0.724; 95% CI: 0.598 - 0.851; p: 0.001) , for ferritin 393 ng/mL (AUC: 0.774; 95% CI: 0.636 - 0.913; p <0.001), for NLR 3.69 (AUC: 0.750; 95% CI: 0.639 - 0.861; p <0.001); and above these levels. On the other hand, it was seen that the lymphocyte cut-off value was 905/µL (AUC: 0,778; 95% CI: 0,676 – 0,880; p<0,001), and the hemoglobin cut-off value was 12.35 g/dL (AUC: 0,637; 95% CI: 0,507 – 0,767; p=0,045) or less these levels (Table 4, figure 1).

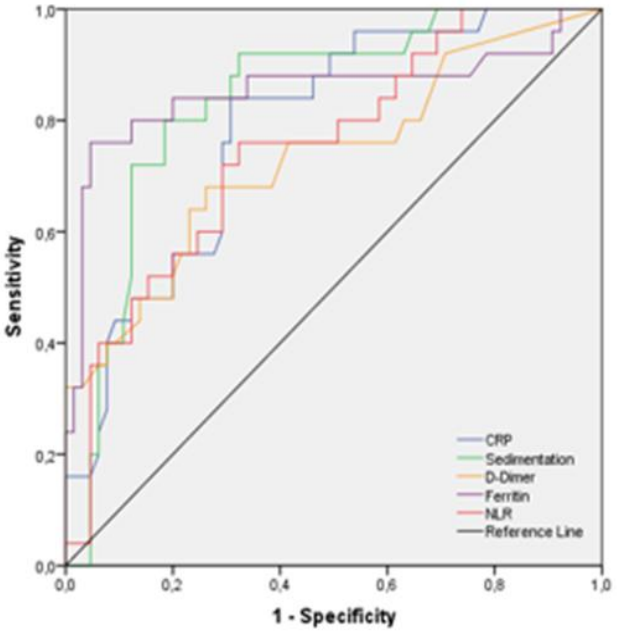

Figure 1. ROC analysis of five laboratory parameters (CRP: C-reactive protein, Sedimentation: Erythrocyte sedimentation rate, NLR: Neutrophil/lymphocyte rate)

For our study to add a difference to the literature; some boundaries were drawn considering the statistically calculated cut-off values and clinical features. For this, the results of CRP, ESR, NLR, D-dimer, and ferritin which had highest separation success according to ROC analysis were selected. Some levels were determined as five and their multiples. Levels ≥ 0.5 µg/mL for D-dimer, ≥ 5 mg/dL for CRP, ≥ 5 for NLR, ≥ 50 mm/h for ESR and finally ≥500 ng/mL for ferritin were considered positive. Patients, whose four of these five parameters were positive, were determined. Four of five parameters were found to be positive in only two patients (3.1%) in group 1, and 17 patients (68%) in group 2. It was observed that this classification was statistically significantly different (p<0.001) (rule of five, Table 3).

DISCUSSION

COVID-19, a new type of coronavirus, has affected the whole world and caused a pandemic and great losses. In some studies, risk factors of patients have been tried to be determined. One of these; was a meta-analysis made by Yang et al. In this study, the researchers reported that; diabetes mellitus, hypertension, respiratory system, and cardiovascular system diseases were the most common diseases in COVID-19 patients and comorbid disease, advanced age were associated with severe disease (9). Our study showed that the presence of chronic disease increased the severity of the disease in COVID-19 patients. However, not the most common diseases such as diabetes mellitus and hypertension; asthma (p = 0.041) and other (p=0.016) diseases were seen more in the severe group (group 2).

Since the beginning of the COVID-19 pandemic, some studies have stated that the neutrophil-lymphocyte ratio (NLR) is a parameter that provides information about the patient's condition, and the NLR has been evaluated as data indicating the patient's inflammatory status (10,11). In our study, NLR (p<0.001) was also found to be a poor prognostic indicator. Zhou et al. in their study which

examining mortality risk factors; thought that high Sequential Organ Failure Assessment (SOFA) score, advanced age, and D-dimer results higher than 1 µg/mL might be risk factors (12). In our study, age was not seen as a factor and D-dimer cut-off value was found lower as 0.49 µg/mL (AUC: 0.724; 95% CI: 0.598 - 0.851; p: 0.001). In a similar study, it was concluded that the presence of diabetes mellitus, age, high body temperature, high SOFA score, high D-dimer, high CRP, and low albumin values may indicate severe disease (13).

In a large meta-analysis, it was seen that patients admitted to the intensive care unit had higher leukocyte count, lactate dehydrogenase, and procalcitonin (14). Leukocytosis was rare in our patients and the incidence of leukopenia was higher; however, when the white blood cell averages were evaluated, there was no difference between the two groups (p = 0.430). Besides, although those with bacterial infection were not included, our procalcitonin values were found to be higher in the desaturated group and the procalcitonin cut-off value was 0.075 ng/mL (AUC: 0.693; 95% CI: 0.566 - 0.820; p: 0.007).

In a study conducted in our country, hypertension was reported as the most common comorbid disease with COVID-19, and it was shown that intensive care patients were significantly different from other patients in terms of advanced age, male gender, and diabetes mellitus (15). During the pandemic period, in our hospital, patients who met the criteria of intensive care were not followed up in our clinic. But, unlike the studies conducted, although our patients had similar chronic diseases between the groups, it was observed that the number of drugs they used due to chronic disease was significantly higher (p = 0.046) in the group with severe disease (group 2).

In the guidelines published by our Ministry of Health, lymphocyte count (<800/µl), CRP (>10mg/L), ferritin (>500ng/ml) and D-dimer (>1000 ng/ml) are emphasized as poor prognostic indicators (16). However, in our study, other than these parameters; high levels of ESR, procalcitonin, NLR, triglyceride, LDH, creatinine kinase and low levels of hemoglobin were also found to be poor prognostic indicators. In addition, in our study, the predictive values of these four indicators (lymphocyte count, CRP, ferritin, D-dimer) for poor prognosis were different from the levels specified in the guidelines published by our Ministry of Health. Lymphocyte count <905/uL, CRP >5.01 mg/dL (50.1 mg/L), ferritin >393 ng/ml, and D-dimer >0.49 µg/mL (490 ng/ml) were found to be predictive values for poor prognosis. Considering that some innovations are needed in the process of COVID-19 disease, which is difficult to manage, five parameters with a high prediction of the severe disease have been determined to contribute to the literature. Some levels were determined as five and their multiples. Levels ≥ 0.5 µg/mL for D-dimer, ≥ 5 mg/dL for CRP, ≥ 5 for NLR, ≥ 50 mm/h for ESR and finally ≥500 ng/mL for ferritin were considered positive. Patients separated who were positive four of these five parameters. It has been observed that this classification is statistically significantly different (p<0.001) (rule of five). Scoring methods have been used frequently in some diagnoses or units from past to present and provide convenience in patient follow-up. For example, in the follow-up of patients admitted to intensive care units, various scoring systems such as Acute Physiology and Chronic Health Evaluation-II (Apache-II) and SOFA are used, as a means of defining the degree of organ failure or as a mortality risk determinant (17). However, large-scale studies are needed to make this practical scoring method (rule of five) definite.

According to the data from the World Health Organization, the global mortality rate has been approximately 2% for COVID-19 infection; the reported death rate in our country is 2.67% (18,19). In our study, our mortality rate was found to be 3% similar to the literature. Three of our patients who were followed up died. All three of these patients did not smoke; however, it was observed that they had at least two chronic diseases. Besides, although there was no significant difference between the groups (p = 0.129); it was remarkable that two male patients (46 and 56 years old) who died, had epilepsy as a chronic disease and used antiepileptic drugs. In all patients followed, the compatibility of drugs used chronically with drugs used for COVID-19 was controlled and provided following the guidelines of the Ministry of Health (20). Nevertheless; of the five patients using antiepileptic drugs, two died, one had a severe illness, and one was referred. There were case reports on epilepsy, but no data on mortality risk or disease severity in patients with epilepsy were found (21,22). More studies are needed on this topic.

Statistical analysis of rare diseases such as epilepsy and rheumatoid arthritis could not be performed separately due to insufficient numbers. Research with a wide range of patients is needed, where individual analyses of all diseases are carried out. Besides, the absence of intensive care patients and the lack of SOFA score in our study were other shortcomings.

CONCLUSION

In conclusion, there is a need for studies that can be path guides in the follow-up of patients with COVID-19 infection, which has caused the death of thousands of people all over the world and whose effective treatment has not yet been found for about two years. We believe that knowing the aggravating risk factors of this disease and the parameters, that may be signs of severe disease will guide this fight. Some poor prognostic indicators have been reported in studies and in our Ministry of Health COVID-19 guide. It should be considered that apart from those known as poor prognostic indicators; the presence of asthma, high fever, high level of procalcitonin, lactate dehydrogenase, ESR, creatine kinase, triglyceride, and low level of hemoglobin may indicate poor prognosis. These patients should also be followed closely. The poor prognosis levels of some tests such as D-dimer, ferritin and lymphocyte should be reconsidered. In addition, we believe that not only one parameter should be evaluated, but all parameters should be evaluated and some facilitating tables such as the scoring system should be added to the guides.

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