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Evaluation of Biomarkers and Clinical Course in Patients Developing Neurologic Disorders due to COVID-19

COVID-19'a Bağlı Nörolojik Bozukluk Gelişen Hastalarda Biyobelirteçlerin ve Klinik Seyrin Değerlendirilmesi

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Abstract

COVID-19 is a highly contagious and deadly disease. It may present with neurologic symptoms as well as respiratory symptoms. In this study, the existence of different biomarkers in the development and evaluation of neurologic symptoms and complications in patients with COVID-19 and the relationship between clinical course and neurologic disorders were investigated. In this prospective randomized study, the study group included 133 patients with a diagnosis of COVID-19 who were admitted to the neurology clinic and intensive care unit managed by expert neurologists during the pandemic period. Patients were classified as those without neurological disorders associated with COVID-19, those with mild neurologic disorders, and those with severe neurological disorders. The demographic characteristics, laboratory values, lung tomography, and clinical features of these patients were examined and the relationship between them was investigated. Of the patients, 54.9% were male, 45.1% were female, and the mean age was 60.85±18.38 (min-max: 19-91) years. As the age increased, a moderately significant positive correlation was found between the presence of neurologic disorders and disease severity. Myalgia (39.1%) and headache (34.6%) were the most common neurologic symptoms. In patients with severe neurologic disorders, the most common neurologic symptom was unconsciousness (n=22, 64.7%). Hemoglobin levels, hematocrit, lymphocyte counts, and procalcitonin levels were decreased ($p=0.010$, $p=0.018$, $p=0.001$, and $p=0.021$, respectively) in patients with neurologic disorders, neutrophil count, C-reactive protein, D-dimer, and interleukin-6 levels were increased ($p=0.039$, $p=0.020$, $p<0.001$, and $p=0.001$, respectively). An increase in the presence and severity of neurologic disorders was observed in patients in parallel with an increase in lung computed tomography scores and O_2 requirement ($p<0.001$ and $p<0.001$, respectively). As the severity of the neurologic disorders of the patients increased, the rate of discharge decreased ($p<0.001$). Our results suggested that some biomarkers associated with the severity of the disease could also be shown in patients with neurologic disorders, and patients with COVID-19 had severe disease in the presence of neurologic disorders. To define the existence of an independent biomarker, there is a need for large-scale studies in which neurologic disorders are handled separately.

Keywords: COVID-19, Neurologic disorder, Biomarkers, Pulmonary involvement.

Özet

COVID-19 yüksek derecede bulaşıcı ve ölümcül bir hastalıktır. Solunum semptomlarının yanı sıra nörolojik semptomlarla da ortaya çıkabilmektedir. Bu çalışmada, COVID-19 hastalarında nörolojik semptom ve komplikasyonların gelişimi ve değerlendirilmesinde farklı biyobelirteçlerin varlığı ve klinik seyir ile nörolojik bozukluklar arasındaki ilişki araştırılmıştır. Bu prospektif randomize çalışmada, çalışma grubu pandemi döneminde COVID-19 kliniği haline getirilen uzman nörologlar tarafından yönetilen nöroloji klinik ve yoğun bakıma yatırılan COVID-19 tanılı 133 hastayı içeriyordu. Hastalar, COVID-19 ile ilişkili nörolojik bozukluğu olmayanlar, hafif nörolojik bozukluğu olanlar ve ciddi nörolojik bozukluğu olanlar olarak kategorize edildi. Bu hastaların demografik özellikleri, laboratuvar değerleri, akciğer tomografisi ve klinik özellikleri incelenerek ilgili parametreler ile hastalık grupları arasındaki ilişkiler araştırıldı. Hastaların %54.9'u erkek, %45.1'i kadındı ve yaş ortalaması 60.85±18.38 (minimum-maksimum: 19-91) idi. Yaş arttıkça, nörolojik bozuklukların varlığı ile hastalık şiddeti arasında orta derecede anlamlı bir pozitif korelasyon olduğu bulundu. Miyalji (%39.1) ve baş ağrısı (%34.6) en sık görülen nörolojik semptomlardı. Ciddi nörolojik bozukluğu olan hastalarda en sık görülen nörolojik semptom ise bilinç kaybıydı (n=22, %64.7). Nörolojik bozukluğu olan hastalarda hemoglobin düzeyleri, hematokrit değerleri, lenfosit sayıları ve prokalsitonin düzeyleri azalmış (sırasıyla, p=0.010, p=0.018, p=0.001 ve p=0.021), buna karşın nötrofil sayısı, C-reaktif protein, D-dimer ve interlökin-6 seviyeleri artmıştı (sırasıyla p=0.039, p=0.020, p<0.001 ve p=0.001). Akciğer bilgisayarlı tomografi skorları ve O_2 gereksinimindeki artışa paralel olarak hastalarda nörolojik bozuklukların varlığı ve şiddetinde artış olduğu gözlemlendi (sırasıyla, p<0.001 ve p<0.001). Hastalarda nörolojik bozuklukların şiddeti arttıkça, taburculuk oranlarının da azaldığı saptandı (p<0.001). Sonuçlarımız, hastalık ciddiyeti ile ilişkili bazı biyobelirteçlerin nörolojik bozukluğu olan hastalarda da gösterilebileceğini desteklemekte ve COVID-19'lu hastalarda nörolojik bozuklukların varlığında ciddi hastalık tablolarının geliştiğini göstermektedir. Bununla beraber bağımsız bir biyobelirteç varlığının tanımlanması için nörolojik bozuklukların ayrı ayrı ele alındığı geniş ölçekli çalışmalara gereksinim vardır.

Anahtar Kelimeler: COVID-19, Nörolojik bozukluk, Biyobelirteçler, Akciğer tutulumu.

Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious and deadly disease that has affected the world globally. The scientific world has focused on an unpredictable complex disease that can develop rapidly and cause serious and fatal complications. In the presence of this new infection, the determination of markers that can predict disease severity and prognosis is essential in the clinical follow-up of patients. Several hematologic, biochemical, coagulation function, and inflammatory biomarkers have been defined to identify high-risk patients in the fight against this disease. Biomarkers used to classify patients with COVID-19 include increased white blood cell and neutrophil counts; decreased lymphocyte, platelet, and eosinophil counts; increased neutrophil-lymphocyte ratio (NLR); decreased hemoglobin levels; increased D-dimer, cardiac troponin I, C-reactive protein (CRP), lactate dehydrogenase (LDH), and interleukin-6 (IL-6) levels; and prolonged prothrombin time have been associated with severe COVID-19 [1-5].

COVID-19 patients may present with respiratory symptoms such as fever, shortness of breath, cough, as well as mild neurologic symptoms such as headache, inability to taste and smell, dizziness, myalgia, and serious neurologic complications such as cerebrovascular disease, encephalopathy, encephalitis, transverse myelitis, altered consciousness, and seizures [6]. Although biomarkers have been identified to predict severe disease, there are limited studies demonstrating the existence of markers that can predict patients with neurologic disorders. These markers can be decisive in the evaluation of the development of neurologic symptoms and complications. In addition, the determination of these markers allows the recognition of patients with COVID-19 that initially present with neurologic findings. For all these reasons, in this study, we aimed to examine the existence of different biologic markers in the development and evaluation of neurologic symptoms and complications in patients with COVID-19, and their relationship with clinical status and prognosis.

Material and Method

This study was approved by the Turkish Republic Ministry of Health (Protocol No: 2020-05-19T09-44-18) and the University of Health Sciences Gulhane Faculty of Medicine Ethics Committee (09.06.2020/2020-247). The study was conducted in accordance with the principles of the revised Declaration of Helsinki.

Patients

In this prospective study, the study group included 133 consecutive patients who were aged 18 years or older, admitted with symptoms of COVID-19, hospitalized in the neurology clinic and intensive care unit (ICU), which were turned into COVID-19 clinics managed by specialist neurologists during the pandemic period, and were confirmed as having COVID-19 through laboratory tests. Patients aged under 18 years or whose COVID-19 positivity was not confirmed were excluded from the study. Throat and nasal swab samples were used for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus analysis. COVID-19 positivity was identified using real-time reverse transcription polymerase chain reaction (rRT-PCR).

Study design and data collection

Patients were evaluated during daily visits by experienced neurologists. The patients were classified as those without neurologic disorders associated with COVID-19, those with mild neurological disorders, and those with severe neurological disorders. Headache, dizziness, loss of taste and smell, and the presence of myalgia were accepted as mild neurologic disorders. Stroke, altered consciousness, seizure, transverse myelitis, and encephalitis were accepted as severe neurologic disorders.

Laboratory tests (hematologic, biochemical, coagulation, and inflammatory biologic markers) on the first day of admission to the hospital were recorded.

A computed tomography (CT) scoring system, which was a semi-quantitative evaluation method, was used to measure the degree of lung involvement. Two lungs were evaluated in a total of five lobes. First, the extent of the lesion in each lobe was visually estimated and a score between 1 and 5 was given according to the degree of involvement (0 points: no involvement, 1 point: 1-25%, 2 points: 26-50%, 3 points: 51-75%, 4 points: 76-100%). Second, the scores of the five lobes were summed to obtain a total lung score ranging from 0 to 20 [7].

The severity of acute respiratory tract infection was defined according to oxygen demand. Low-flow oxygen therapy was defined as 1-6 L/min−1 through nasal cannulas to obtain a SpO_2 level of 90-92% [8]. If the oxygen requirement was >6 L/min, it was accepted as high oxygen demand. In the follow-up of the patients, the patients were categorized as those with no oxygen need, those with low-flow oxygen requirement, and those with high oxygen requirement. The prognosis was evaluated according to death and discharge status.

According to the groups, the laboratory values of the patients, the degree of lung involvement, clinical course, and prognosis were analyzed, and statistical analysis was performed. At the endpoint, we tried to define the presence of biochemical markers, clinical and radiologic status, and differences in prognosis in patients with mild and severe neurologic disorders and patients with no neurologic disorders.

Statistical analysis

The IBM SPSS Statistics 25.0 program was used in the analysis of the data of the research. The Kolmogorov-Smirnov test was used to determine the conformity of the study data to normal distribution, and table and histogram graphics were used. For descriptive data analysis, mean ± standard deviation and minimum and maximum values were used in the evaluation of continuous variables, and the percentages and numbers of participants were used for categorical variables. The independent samples t-test was used to compare the mean of two independent groups of the quantitative variable conforming to the normal distribution. Pearson's correlation test was used to evaluate the linear relationship between quantitative variables, and simple linear regression analysis was used to reveal the relationship between dependent variables and independent variables in the data. According to the results of the tests used, the level of significance in differences between the variables was accepted as $p<0.05$.

Results

Of the total 133 patients, 54.9% (n=73) were male and 45.1% (n=60) were female. The mean age was 60.85±18.38 (range, 19-91) years.

Neurologic disorders were found in 80.5% (n=107) of the patients. Mild neurologic disorders were detected in 54.9% (n=73) of the patients, and severe disorders were seen in 25.6% (n=34) (Table 1).

The most common neurologic disorders among all patients were myalgia (n=52, 39.1%;) and headache (n=46, 34.6%), which were observed in approximately one-third of the patients (Figure 1). Headache (n=41, 56.2%) was the most common symptom in patients with mild neurologic disorders and change in consciousness was the most common in patients with severe neurologic disorders (n=22, 64.7%) (Table 1).

Table 1. Distribution of neurologic disorders in the patients.

Neurologic disorders		n	%
No neurologic disorders (n=26, 19.5%)	-	-	-
Mild neurologic disorders (n=73, 54.9%)	Headache	41	56.2
	Loss of smell	15	20.5
	Loss of taste	23	31.5
	Dizziness	21	28.8
	Myalgia	46	63.0
Severe neurologic disorders (n=34, 25.6%)	Headache	5	14.7
	Loss of smell	2	5.9
	Loss of taste	2	5.9
	Seizure	4	11.8
	Consciousness change	22	64.7
	Stroke	15	44.1
	Transverse myelitis	1	2.9
	Encephalitis	1	2.9
	Dizziness	2	5.9
	Myalgia	6	17.6

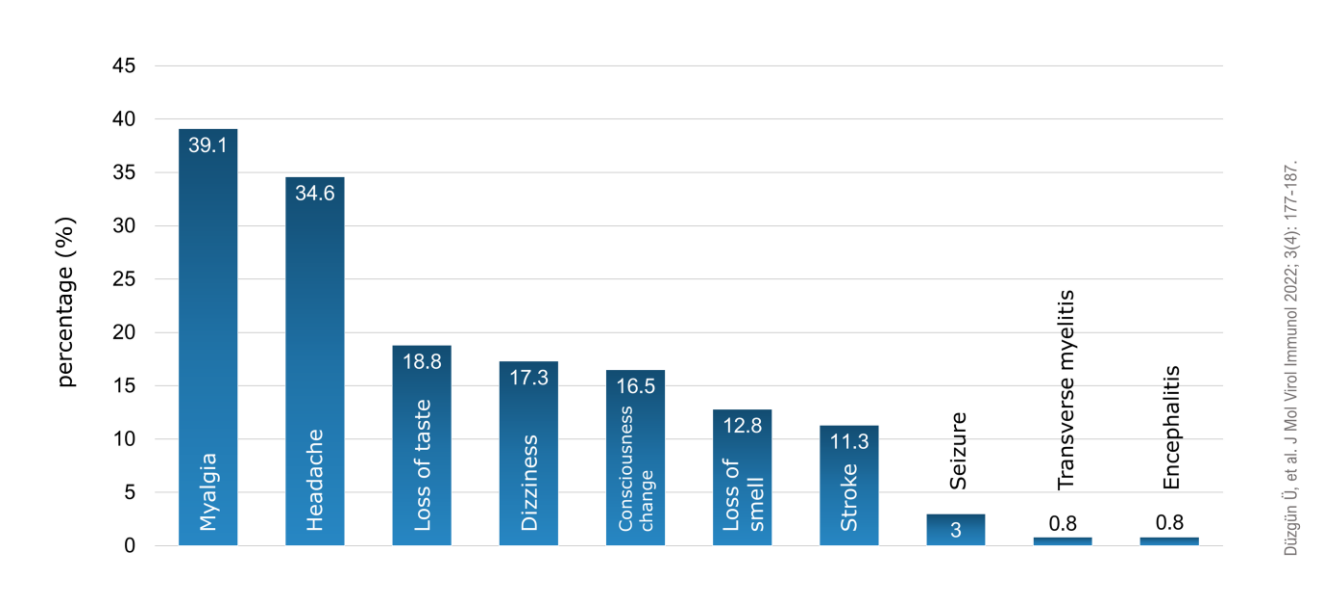

Figure 1. Neurologic findings in patients with COVID-19.

The mean age of those with neurologic disorders (n=107) (63.28±16.80 years) was statistically significantly older (p=0.002) than the mean age of those without neurologic disorders (n=26) (50.85±21.35 years). As age increased, a moderately significant positive correlation was observed between the presence of neurologic disorders and the severity of the disease (presence of neurologic disorders; r=0.318, p<0.001 and disease severity; r=0.357, p<0.001) (Table 2).

In terms of laboratory values of patients with neurologic disorders, a significant increase was found in neutrophil count and CRP, D-dimer, IL-6, and LDH levels (p=0.039, p=0.020, p<0.001, p=0.001, and p=0.005, respectively). Also, a significant decrease was found in lymphocyte counts, hemoglobin levels, hematocrit, and procalcitonin levels (p=0.001, p=0.010, p=0.018, and p=0.021, respectively) when compared with those without neurologic disorders (Table 3 and Table 4).

Table 2. Correlation between variables.

Neurologic disorders	Severity of disease		Sex		Age	
	r	p	r	p	r	p
Neurological disorder	0.402*	<0.001	0.054	0.537	0.318*	<0.001
Severity of disease			-0.135	0.121	0.357*	<0.001
Sex					-0.168	0.053

*Correlation is significant at the 0.01 level

Table 3. Comparison of the laboratory values of the patients in terms of the presence of neurologic disorders I.

Laboratory values	Neurologic disorders	Mean	SD	p
aPTT (22-38 sn)	No	25.82	2.16	0.291*
	Yes	26.90	4.22	
PT (9.7-14.3 sn)	No	11.75	1.05	0.058
	Yes	13.05	3.07	
INR (0.8-1.2)	No	1.02	0.14	0.128
	Yes	1.12	0.28	
Trop-I (0.01-17.5pg/mL)	No	158.36	506.17	0.472
	Yes	81.34	294.27	
CRP (0-5 mg/L)	No	46.26	68.69	0.020
	Yes	85.80	77.00	
D-dimer (0-0.5 mg/L)	No	0.66	0.71	<0.001*
	Yes	1.74	2.52	
IL-6 (0-5 pg/mL)	No	12.73	10.90	0.001*
	Yes	50.61	55.11	
Lactate (0.5-1.6 mmol/L)	No	2.00	0.85	0.958
	Yes	1.99	0.61	
CK (24-170 U/L)	No	76.07	48.87	0.112*
	Yes	153.88	159.51	
LDH (0-247 U/L)	No	260.90	96.62	0.005
	Yes	374.94	177.30	
Procalcitonin (0-0.65 ng/mL)	No	4.14	16.79	0.021*
	Yes	0.61	1.52	

p; independent samples t-test. *; nonparametric tests, independent samples. SD; standard deviation. aPTT; activated partial thromboplastin time. PT; prothrombin time. INR; international normalized ratio. Trop-I; troponin-I. CRP; C-reactive protein. IL-6; interleukin-6. CK; creatine kinase. LDH; lactate dehydrogenase.

Table 4. Comparison of the laboratory values of the patients in terms of the presence of neurologic disorders II.

Laboratory values	Neurologic disorders	Mean	SD	p
WBC (4.49-10.9x10^3 cells/µL)	No	6.15	2.76	0.171
	Yes	7.09	3.18	
RBC (3.92-5.08x10^6 /µL)	No	4.75	0.59	0.076
	Yes	4.49	0.69	
Hgb (11.9-14.6 g/dL)	No	14.06	1.93	0.010
	Yes	12.93	1.98	
Htc (36.6-44%)	No	41.48	5.43	0.018
	Yes	38.12	6.65	
Platelet (171-388x10^3 cells/µL)	No	211.35	56.77	0.770
	Yes	217.36	100.57	
MCV (82.9-98 fL)	No	87.24	4.50	0.277
	Yes	85.22	9.17	
MCH (27-32.3 pg)	No	29.59	2.07	0.253
	Yes	28.75	3.61	
MCHC (31.8-34.7 g/L)	No	33.87	0.87	0.562
	Yes	33.69	1.58	
MPV (7.5-11.2 fL)	No	8.76	0.81	0.609
	Yes	8.86	0.97	
RDW-SD (38.2-49.2 fL)	No	42.70	4.55	0.356
	Yes	44.20	7.58	
RDW-CV (12.1-14.3%)	No	13.77	1.44	0.122
	Yes	14.64	2.77	
Neutrophil (2.1-8.89x10^3 cells/µL)	No	3.95	2.81	0.039
	Yes	5.32	3.06	
Neutrophil percentage (42.9-74.3%)	No	60.55	14.00	0.001
	Yes	71.69	14.76	
Lymphocyte (1.26-3.35x10^3 cells/µL)	No	1.60	0.70	0.001
	Yes	1.11	0.67	
Lymphocyte percentage (18.3-45.7%)	No	29.12	12.87	<0.001
	Yes	17.85	11.16	
Monocyte (0.25-0.84x10^3 cells/µL)	No	0.53	0.25	0.900
	Yes	0.54	0.33	
Monocyte percentage (4.2-11.8%)	No	8.97	3.04	0.363
	Yes	8.13	4.42	
Eosinophil (0-0.4x10^3 cells/µL)	No	0.05	0.08	0.767
	Yes	0.05	0.10	
Eosinophil percentage (0.2-5.3%)	No	0.98	1.10	0.347
	Yes	0.73	1.24	
Basophil (0-0.27x10^3 cells/µL)	No	0.01	0.02	0.266
	Yes	0.07	0.28	
Basophil percentage (0.1-1%)	No	0.37	0.24	0.405
	Yes	0.91	3.29	

p: independent samples t-test. SD; standard deviation. WBC; white blood cell. RBC; red blood cells. Hgb; hemoglobin. Hct; hematocrit. MCV; mean corpuscular volume. MCH; mean corpuscular hemoglobin. MCHC; mean corpuscular hemoglobin concentration. MPV; mean platelet volume. RDW-CV; red cell distribution width.

As the lung CT score of the patients increased, the presence of neurologic disorders and the severity of neurologic disorders increased significantly (p<0.001) (Table 5). Likewise, the O_2 requirement of patients with neurologic disorders increased in direct proportion to the severity of the neurologic disorders (p<0.001). As the severity of neurologic disorders of the patients increased, a significant decrease was found in the rate of discharge (p<0.001). All patients without neurologic disorders were discharged; 94.5% of patients with mild neurologic disorders and 70.6% of patients with severe neurologic disorders were discharged (p<0.001) (Table 6).

In the correlation analysis examined in terms of clinical manifestations, a moderate and significant relationship was found between the lung CT score, receiving O_2 treatment, disease severity, and the prognosis of the patients, and the presence of neurologic disorders (lung CT score: r=0.383, p<0.001, O_2 treatment: r=0.362, p<0.001, disease severity: r=0.402, p<0.001, and prognosis: r= -0.353, p<0.001, respectively).

According to the regression analysis, the coefficient of determination between the lung CT score variable and the neurologic disorder variable was (r2)=0.146, the coefficient of determination between the disease severity variable and neurologic disorder variable was (r2)=0.162, and the coefficient of determination between the prognosis of the patients variable and the neurologic disorder variable was (r2)= 0.146. Accordingly, it was concluded that 14.6% of the changes in the lung CT score, 16.2% of the changes in the severity of the disease, and 12.9% of the discharge or death rates of the patients depended on the severity of the neurologic disorders.

Table 5. Comparison of patients' neurologic disorders in terms of lung CT scores.

Lung CT score		Neurologic disorders			Total	p*
		No neurologic disorders	Mild neurologic disorders	Severe neurologic disorders		
0 points	n	6	2	2	10	<0.001
	% within lung CT	60.0%	20.0%	20.0%	100.0%	
	% within neurologic disorders	26.1%	3.1%	5.9%	8.2%	
	% of total	4.9%	1.6%	1.6%	8.2%	
1-5 points	n	9	21	7	37	
	% within lung CT	24.3%	56.8%	18.9%	100.0%	
	% within neurologic disorders	39.1%	32.3%	20.6%	30.3%	
	% of total	7.4%	17.2%	5.7%	30.3%	
6-10 points	n	8	33	11	52	
	% within lung CT	15.4%	63.5%	21.2%	100.0%	
	% within neurologic disorders	34.8%	50.8%	32.4%	42.6%	
	% of total	6.6%	27.0%	9.0%	42.6%	
11-15 points	n	0	8	12	20	
	% within lung CT	0.0%	40.0%	60.0%	100.0%	
	% within neurologic disorders	0.0%	12.3%	35.3%	16.4%	
	% of total	0.0%	6.6%	9.8%	16.4%	
16-20 points	n	0	1	2	3	
	% within lung CT	0.0%	33.3%	66.7%	100.0%	
	% within neurologic disorders	0.0%	1.5%	5.9%	2.5%	
	% of total	0.0%	0.8%	1.6%	2.5%	

*Independent samples t-test. CT: computed tomography.

Table 6. Comparison of patients' neurologic disorders in terms of oxygen need and prognosis.

O_2 treatment		Neurologic disorders			Total	p*
		No neurologic disorders	Mild neurologic disorders	Severe neurologic disorders		
Not received	n	21	38	9	68	<0.001
	% within O_2 treatment	30.9%	55.9%	13.2%	100.0%	
	% within neurologic disorders	80.8%	52.1%	26.5%	51.1%	
	% of total	15.8%	28.6%	6.8%	51.1%	
Received	n	5	35	25	65	
	% within O_2 treatment	7.7%	53.8%	38.5%	100.0%	
	% within neurologic disorders	19.2%	47.9%	73.5%	48.9%	
	% of total	3.8%	26.3%	18.8%	48.9%	
No 0_2 need	n	21	38	9	68	<0.001
	% within disease severity	30.9%	55.9%	13.2%	100.0%	
	% within neurologic disorders	80.8%	52.1%	26.5%	51.1%	
	% of total	15.8%	28.6%	6.8%	51.1%	
Low-flow oxygen need	n	2	25	7	34	
	% within disease severity	5.9%	73.5%	20.6%	100.0%	
	% within neurologic disorders	7.7%	34.2%	20.6%	25.6%	
	% of total	1.5%	18.8%	5.3%	25.6%	
High-flow oxygen need	n	3	10	18	31	
	% within disease severity	9.7%	32.3%	58.1%	100.0%	
	% within neurologic disorders	11.5%	13.7%	52.9%	23.3%	
	% of total	2.3%	7.5%	13.5%	23.3%	
Mortality	n	0	4	10	14	<0.001
	% within prognosis	0.0%	28.6%	71.4%	100.0%	
	% within neurologic disorders	0.0%	5.5%	29.4%	10.5%	
	% of Total	0.0%	3.0%	7.5%	10.5%	
Discharge	n	26	69	24	119	
	% within prognosis	21.8%	58.0%	20.2%	100.0%	
	% within neurologic disorders	100.0%	94.5%	70.6%	89.5%	
	% of Total	19.5%	51.9%	18.0%	89.5%	

p*: Independent samples t-test.

Discussion

In this study, patients with COVID-19 were evaluated in terms of demographic, laboratory, and clinical characteristics, and the presence of different biomarkers in patients with neurologic disorders and the relationship between clinical course and neurologic disorders were investigated.

COVID-19 may present with respiratory symptoms as well as neurologic findings and complications [6]. A wide spectrum of neurologic disorders including headache, inability to taste and smell, dizziness, myalgia, cerebrovascular disease, encephalopathy, altered consciousness, encephalitis, transverse myelitis, and seizures were observed in the patients we studied, and the most common neurologic disorders were headache and myalgia.

The prevalence of myalgia varies widely in studies, ranging from 3.36% to 64% [9]. Headache has been shown in studies to be the fifth most common symptom of COVID-19 after fever, cough, myalgia/fatigue, and shortness of breath [6].

Several possible mechanisms have been identified that cause the neurological symptoms of COVID-19, causing the SARS-CoV-2 virus to enter the central nervous system (CNS) and produce deleterious effects. These possible mechanisms are systemic hematogenous spread, which causes neuronal cell death as a result of crossing the blood–brain barrier (BBB) due to viremia, and neuronal retrograde spread through the olfactory bulb. Although the neuroinvasiveness of SARS-CoV-2 is not fully understood, increasing evidence suggests that both the hematogenous and neuronal pathways may be used [6].

Human pathogenic coronaviruses are known to bind to target cells via human angiotensin-converting enzyme 2 (ACE2) receptors [10]. The obligate receptor of the SARS-CoV-2 virus spike protein is ACE2. It is widely expressed in epithelial cells throughout the body, including the CNS. Therefore, SARS-CoV-2 can facilitate the direct invasion of cerebrovascular endothelial cells, neurons, and glial cells expressed in the CNS, causing apoptosis and necrosis [6,11-13]

SARS-CoV-2 infection has been associated with high levels of cytokines, including tumor necrosis factor-alpha, IL-1β, IL-6, IL-12, and interferon-gamma, in previous studies, a phenomenon known as the "cytokine storm". Cytokine storms can damage an intact BBB and disrupt normal functioning in the CNS without the virus crossing the BBB from the systemic circulation [12]. Also, SARS-CoV-2 infects leukocytes and infected leukocytes cross the BBB causing the secretion of proinflammatory cytokines that damage oligodendrocytes and neurons [6]. IL-6 is an important proinflammatory mediator potentially responsible for the activation of immune cells in the brain and injury to brain tissue [14]. This information may explain the reason for the high IL-6 levels in patients with neurologic disorders in our study. In one study, IL-6 levels were found to be high in patients with headache [15]. Changes in consciousness were found to be higher in the group with cytokine storm (69.4%) than in the group without (25.3%) [16].

D-dimer levels have also been investigated by researchers in various neurologic disorders, especially stroke. Hypercoagulation, evidenced by elevated D-dimer levels, may play a role in the pathophysiology of stroke in patients with COVID-19 [17]. One study found only elevated D-dimer levels to be an independently associated biomarker for acute ischemic stroke in COVID-19 patients [18]. In other studies, D-dimer levels were found to be high in patients with headache [15,19]. In another study, D-dimer blood levels were found to be significantly higher in patients with at least one neurologic symptom compared with patients without neurologic symptoms [20]. In our study, D-dimer levels were found to be significantly higher in the presence of neurologic disorders, similar to the literature.

In previous studies, increased neutrophil counts; decreased lymphocyte counts and hemoglobin levels; and increased D-dimer, CRP, LDH, and IL-6 levels have been associated with severe COVID-19 [1-5]. In addition, lymphocyte levels were found to be lower in patients with severe disease and CNS symptoms compared with those without [21]. Similarly, neutrophil counts and CRP, LDH, D-dimer, and IL-6 levels were found to be higher and lymphocyte counts and hemoglobin levels were found lower in patients with neurologic disorders. The similar results among the aforementioned studies brought to mind the question of whether patients with neurologic disorders have severe disease.

There are a limited number of studies in the literature on the lung involvement of patients with neurologic findings. In the study of Karadaş et al. [19], pulmonary involvement was found to be high in patients with headache. In our study, as the lung CT score increased, the presence and the severity of the neurologic disorders increased. In the study of Yazdi et al. [22], lung CT scores were found to be positively correlated with inflammatory biomarkers and disease severity. In addition, in the present study, as the severity of neurologic disorders of the patients increased, the O_2 need rate increased and the discharge rate decreased. In the correlation analysis performed in our study, a positive correlation was found between lung CT score, O_2 treatment, disease severity, poor prognosis of the patients, and the presence of neurologic disorders. In light of the literature, these results suggest that those with

neurologic disorders and those with more severe neurologic disorders have more severe disease. Our results support the study of Mao et al. [21], they have been showing that the prevalence of neurologic symptoms increases in patients with severe COVID-19.

Our study was limited by the fact that it was a single-center study and the neurologic disorders related to COVID-19 could not be determined adequately. Especially in ICUs with severe disease and sedation, the incomplete reflection of neurologic symptoms makes it difficult to perform comprehensive neurologic clinical examinations. The other limitation of this study is that neurological disorders were not handled and evaluated separately.

Conclusion

These results showed that in the presence of neurologic disorders and as the severity of the neurologic disorders increased, the disease was more severe. Also, increased CRP, neutrophil counts, D-dimer, LDH, and IL-6 levels, and decreased lymphocyte counts and hemoglobin levels, which were associated with severe COVID-19 in previous studies, were similarly seen in the presence of neurological disorders. To define the presence of an independent biomarker in the development and evaluation of neurologic symptoms and complications, there is a need for multicenter studies with larger patient populations in which neurologic disorders are handled separately.

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