Neurological Symptoms and Diagnoses in Patients Hospitalized With COVID-19

Relationships With Mortality

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Background: Coronavirus disease 2019 (COVID-19) is a disease that affects many organs, especially the lung, and may lead to multiorgan failure. Studies describing neurological dysfunctions involving the central and peripheral nervous systems have emerged. In our study, we aimed to evaluate the neurological signs and symptoms in hospitalized patients with COVID-19.

Methods: The data of 290 patients admitted to our center (ward and intensive care unit) who received a diagnosis of COVID-19 were analyzed retrospectively. Patients' demographic, clinical and laboratory data, and their neurological diseases, symptoms, and complications were compared.

Results: Male sex, heart disease, chronic obstructive pulmonary disease and having a history of neurological disease were associated with increased mortality in patients with COVID-19. Seizures and altered consciousness were also found to be more common in patients who died. In addition, lower platelet counts ($P = 0.001$), higher C-reactive protein levels ($P < 0.001$) and higher D-dimer levels ($P = 0.003$) were associated with increased risk of mortality.

Conclusions: We believe that close monitoring of any possible neurological manifestations is mandatory in hospitalized patients at the onset of COVID-19 and during disease progression. Clinical findings such as neurological symptoms and acute phase reactants are important in the follow-up and treatment of the disease.

Key Words: COVID-19, mortality, neurological symptoms

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Coronavirus disease 2019 (COVID-19) cases were first reported in Wuhan, Hubei province, China, in December 2019. It was later confirmed that the disease was caused by a new strain of coronavirus, named as the severe acute respiratory syndrome-coronavirus-2, and the epidemic spread rapidly around the world.[1,2] The outbreak was declared as a pandemic by the World Health Organization on March 11, 2020.[3]

The most common clinical symptoms in COVID-19 patients have been described as fever and cough.[4–6] Gastrointestinal symptoms, such as anorexia, abdominal pain, nausea, vomiting, diarrhea, as well as dyspnea, hemoptysis, throat and chest pain and headache are also demonstrated to accompany the disease quite often. In severe cases, COVID-19 can cause death as a result of pneumonia, acute respiratory distress syndrome and multiple organ failure.[4,6–10]

Although coronaviruses mostly affect the respiratory system, they can cause neurological symptoms by affecting the central nervous system (CNS) and peripheral nervous system (PNS) due to properties enabling neuroinvasion and neurotropism.[11–13] The virus is thought to cause cerebrovascular disease or neurological symptoms through direct or indirect multiple mechanisms, including hematogenous and neuronal retrograde spread, hypoxia in the brain, cytokine storm, and changes in coagulation parameters.[14–18]

In various studies, COVID-19 has been associated with CNS, PNS, and musculoskeletal symptoms, with studies demonstrating neurological symptoms such as confusion, altered consciousness, ataxia, sleep disorders, vertigo, convulsion, headache, nausea, vomiting, myalgia, neuralgia, and impairments in smell, taste, and vision.[9,16,19–21] In addition, COVID-19-associated neurological problems can present as acute cerebrovascular disease, meningitis, viral encephalitis, acute necrotizing hemorrhagic encephalitis, Guillain Barré syndrome, Miller Fisher syndrome, multiple cranial neuropathy, postinfectious myelitis, and oculomotor nerve palsy.[22–31]

In our study, we aimed to share our data concerning neurological symptoms and accompanying comorbid neurological diseases of patients who were hospitalized in the wards or intensive care units (ICUs) of our center with a diagnosis of COVID-19.

METHODS

Patients

The study group was comprised of patients older than 18 years of age who were admitted to Bursa City Hospital from March 22 to May 22, 2020 and had been diagnosed with COVID-19 by reverse transcription polymerase chain reaction. Patients younger than 18 years, those that were asymptomatic or had mild disease individuals followed as outpatients and cases with incomplete data were excluded from the study.

Patients diagnosed with COVID-19 were divided into 3 groups: (i) patients who were hospitalized in wards and were discharged (ward group), (ii) patients who were admitted to the ICU and were discharged after treatment (ICU group), and (iii) patients who were admitted to the ICU and died (exitus group). Comparisons were based on demographic, clinical characteristics, laboratory data, accompanying neurological symptoms and complications, neurological comorbidities, discharge status, mortality, and length of stay. Data were obtained retrospectively from electronic hospital records.

Body temperature was defined as fever when in excess of 38°C. Patients' demographic characteristics (age, sex), symptoms, comorbid diseases (hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, kidney disease, malignancy, rheumatic disease), neurological

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TABLE 1. Characteristics of Patients

		Follow-up Status			
	Total (n = 290)	Inpatient Service (n = 240)	Discharged From ICU (n = 25)	Death (n = 25)	*P*
Age	50.97 ± 16.49	48.07 ± 15.61[a]	62.40 ± 13.54[b]	67.36 ± 12.82[b]	< 0.001
Sex					
Male	150 (51.72%)	121 (50.42%)[a]	10 (40.00%)[a]	19 (76.00%)[b]	0.024
Female	140 (48.28%)	119 (49.58%)	15 (60.00%)	6 (24.00%)	
Neurological disease history	10 (3.45%)	4 (1.67%)[a]	0 (0.00%)[a]	6 (24.00%)[b]	< 0.001
Emerging neurological disease	3 (1.03%)	0 (0.00%)[a]	1 (4.00%)[b]	2 (8.00%)[b]	< 0.001
Comorbidities	110 (37.93%)	76 (31.67%)[a]	16 (64.00%)[b]	18 (72.00%)[b]	< 0.001
Hypertension	76 (26.21%)	54 (22.50%)[a]	12 (48.00%)[b]	10 (40.00%)[ab]	0.006
Diabetes mellitus	47 (16.21%)	28 (11.67%)[a]	9 (36.00%)[b]	10 (40.00%)[b]	< 0.001
Heart disease	33 (11.38%)	17 (7.08%)[a]	6 (24.00%)[b]	10 (40.00%)[b]	< 0.001
Kidney disease	5 (1.72%)	2 (0.83%)[a]	1 (4.00%)[ab]	2 (8.00%)[b]	0.021
Malignancy	1 (0.34%)	1 (0.42%)	0 (0.00%)	0 (0.00%)	0.901
COPD	17 (5.86%)	5 (2.08%)[a]	5 (20.00%)[b]	7 (28.00%)[b]	< 0.001
Rheumatic disease	12 (4.14%)	10 (4.17%)	2 (8.00%)	0 (0.00%)	0.364
Length of stay in hospital (d)	11 (2-85)	11 (2-36)[a]	22 (9-85)[b]	12 (2-64)[a]	< 0.001
Length of stay in ICU (d)	11 (1-61)	—	14 (3-61)	8 (1-61)	0.029

The superscript letters in the tables represent the results of binary comparison. For example: the lettering a b b means that the first group is different from the other 2 groups, while the second and third groups are similar to each other. For example; aab b means that there is a difference between the first and third groups, and the second group is similar to the other groups.

COPD indicates chronic pulmonary obstructive disease; ICU, intensive care unit.

symptoms (myalgia, dizziness, headache, change in consciousness, ataxia, seizure, anosmia, ageusia, neuralgia, visual impairment), chronic neurological diseases (dementia, Parkinson disease, epilepsy, multiple sclerosis, motor neuron disease, cerebrovascular accident history), laboratory results (complete blood count, blood glucose, liver and kidney function tests, electrolytes, D-dimer, C-reactive protein), discharge status, mortality, and length of stay were analyzed.

The study was approved by the ethical committee of Bursa City Hospital (no: 2020-4/5). The study was designed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

All analyses were performed with SPSS v21 (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to determine whether variables were normally distributed. Data are given as mean ± SD or median (minimum to maximum) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the 1-way analysis of variances test. Pairwise comparisons of these variables were performed with the Tukey test. Non-normally distributed variables were analyzed with the Kruskal-Wallis test. Pairwise comparisons of these variables were performed with the Bonferroni correction method. Logistic regression analysis (forward conditional method) was performed to determine significant risk factors associated with mortality. Two-tailed *P* values <0.05 were considered statistically significant.

RESULTS

We evaluated 290 COVID-19-positive patients (150 males and 140 females) in our study; mean age was 50.97 ± 16.49 years. Fifty patients were followed in the ICU while 240 patients were followed in wards. All patients followed in wards were discharged after recovery, while 25 patients admitted to the ICU died.

Age was significantly lower in patients admitted to wards compared with patients in the ICU ($P < 0.001$). There was no significant difference in terms of age between ICU patients who were discharged and those that had died. The percentage of male patients in the exitus group was significantly higher than the other groups ($P = 0.024$). Ten (3.45%) patients had neurological disease history. Four of them were in the ward group (1 dementia, 2 epilepsy and 1 epilepsy+ischemic cerebrovascular accident) and 6 of them were in the exitus group (1 operated hypophysis adenoma, 3 dementia, 1 Parkinson disease and 1 dementia+Parkinson disease). Three (1.03%) patients had acute neurological disease. One of them was in the ICU group (stroke) and 2 of them were in the exitus group (1 seizure and 1 stroke).

The frequency of comorbidity was significantly lower in the ward group than in the exitus group ($P < 0.001$). Kidney diseases were more common in the exitus group ($P = 0.021$). Length of hospital stay was significantly longer in the ICU group ($P < 0.001$) (Table 1). Respiratory system symptoms were more common in the ICU and exitus groups ($P = 0.016$). Respiratory distress was more common in the ICU and exitus groups ($P < 0.001$).

Neurological symptoms were more common in the ward and discharged from ICU groups ($P < 0.001$). On the other hand, altered consciousness ($P = 0.001$) and seizure ($P = 0.005$) findings were more common in the exitus group. Myalgia ($P = 0.002$), dizziness ($P = 0.049$), headache ($P = 0.001$), anosmia ($P = 0.014$), and ageusia ($P = 0.002$) were more common in the ward and discharged from ICU groups (Table 2, Figs. 1, 2). Laboratory values of patients are shown in Table 3 and Figure 3.

We performed multiple logistic regression analysis to determine significant risk factors for mortality. Patients with neurological disease history had a 42.793-fold higher risk of death than the others [odds ratio (OR): 42.793, 95% confidence interval (CI): 5.679-322.455, $P < 0.001$]. Male patients had a 5.814-fold higher risk of death than female patients (OR: 5.814, 95% CI: 1.099-30.764, $P = 0.038$). Patients with heart disease had a 4.544-fold higher risk of death than others (OR: 4.544, 95% CI: 1.039-19.873, $P = 0.044$). Patients with chronic obstructive pulmonary disease had a 14.348-fold higher risk of death than those without (OR: 14.348, 95% CI: 2.030-101.423, $P = 0.008$). In addition, we detected that

TABLE 2. Clinical Features of Patients

		Follow-up Status			
	Total (n = 290)	**Inpatient Service (n = 240)**	**Discharged From ICU (n = 25)**	**Death (n = 25)**	***P***
General symptoms	237 (81.72%)	197 (82.08%)	21 (84.00%)	19 (76.00%)	0.720
Diarrhea	9 (3.10%)	5 (2.08%)[a]	1 (4.00%)[ab]	3 (12.00%)[b]	0.024
Shivering/chill	14 (4.83%)	13 (5.42%)	1 (4.00%)	0 (0.00%)	0.476
Fever	161 (55.52%)	131 (54.58%)	19 (76.00%)	11 (44.00%)	0.059
Weakness/fatigue	189 (65.17%)	162 (67.50%)	15 (60.00%)	12 (48.00%)	0.128
Back pain	10 (3.45%)	10 (4.17%)	0 (0.00%)	0 (0.00%)	0.340
Arthralgia	21 (7.24%)	21 (8.75%)	0 (0.00%)	0 (0.00%)	0.095
Respiratory system symptoms	200 (68.97%)	157 (65.42%)[a]	22 (88.00%)[b]	21 (84.00%)[b]	0.016
Cough	162 (55.86%)	136 (56.67%)[a]	18 (72.00%)[a]	8 (32.00%)[b]	0.014
Respiratory distress	117 (40.34%)	78 (32.50%)[a]	21 (84.00%)[b]	18 (72.00%)[b]	< 0.001
Sore throat	58 (20.00%)	53 (22.08%)	4 (16.00%)	1 (4.00%)	0.086
Neurological symptoms	209 (72.07%)	181 (75.42%)[a]	19 (76.00%)[a]	9 (36.00%)[b]	< 0.001
Myalgia	141 (48.62%)	126 (52.50%)[a]	11 (44.00%)[a]	4 (16.00%)[b]	0.002
Dizziness	51 (17.59%)	47 (19.58%)[a]	4 (16.00%)[a]	0 (0.00%)[b]	0.049
Headache	93 (32.07%)	87 (36.25%)[a]	6 (24.00%)[a]	0 (0.00%)[b]	0.001
Change in (loss of) consciousness	15 (5.17%)	10 (4.17%)[a]	0 (0.00%)[a]	5 (20.00%)[b]	0.001
Ataxia	26 (8.97%)	23 (9.58%)	3 (12.00%)	0 (0.00%)	0.240
Seizure	1 (0.34%)	0 (0.00%)[a]	0 (0.00%)[a]	1 (4.00%)[b]	0.005
Anosmia	69 (23.79%)	63 (26.25%)[a]	6 (24.00%)[a]	0 (0.00%)[b]	0.014
Ageusia	92 (31.72%)	84 (35.00%)[a]	8 (32.00%)[a]	0 (0.00%)[b]	0.002
Neuralgia	15 (5.17%)	15 (6.25%)	0 (0.00%)	0 (0.00%)	0.192
Visual impairment	8 (2.76%)	8 (3.33%)	0 (0.00%)	0 (0.00%)	0.424

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ICU indicates intensive care unit.

lower platelet count ($P = 0.001$) and higher C-reactive protein ($P < 0.001$) and D-dimer levels ($P = 0.003$) were associated with an increased risk of death (Table 4).

DISCUSSION

COVID-19 is a worldwide public health emergency. It affects many organs, especially the lungs, and may have a fatal course. As the number of patients with COVID-19 increases worldwide, neurological manifestations have been progressively described.[32] Neurologists need to pay close attention to the neurological manifestations of COVID-19, which may contribute to the patients' demise, especially among those with severe disease.[33]

Wang et al[9] found that patients diagnosed with COVID-19 treated in the ICU were older than those who were not treated in the ICU patients. In another study by Mao et al,[34] where 88 severe and 126 mild cases were examined clinically, severe COVID-19 cases were determined to be among older patients. Similarly, a study in which 274 patients were analyzed reported that mortality rate was higher in males and those with advanced age.[35] In our study, the age of the patients admitted to wards was significantly lower than patients followed in the ICU. We found no significant difference in

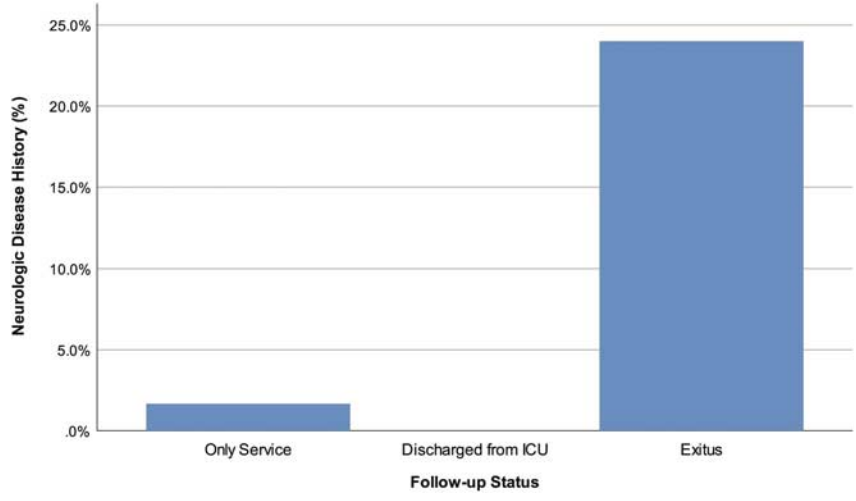

FIGURE 1. Neurological disease history of the groups. ICU indicates intensive care unit.

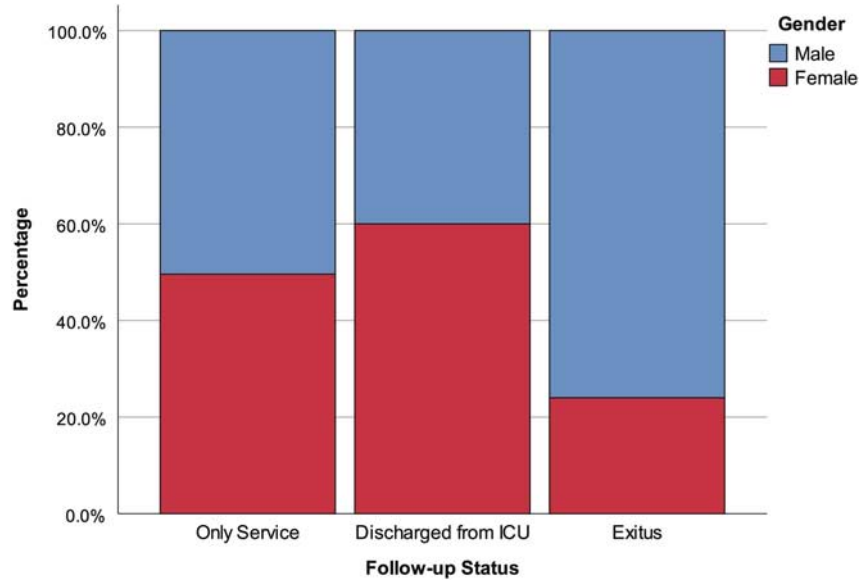

FIGURE 2. Sex distribution of the groups. ICU indicates intensive care unit.

terms of age between patients discharged from the ICU and those that died. Most of the patients who died were men (Table 1).

Fever and cough have been reported as the most frequent symptoms in COVID-19 patients.[4,34,36] In our study, weakness/fatigue (65.17%), cough (55.86%), and fever (55.52%) were the most common symptoms (Table 2).

In a study evaluating patients with COVID-19, comorbid diseases were detected in 46.4% of patients. They observed that comorbid diseases were more frequent in patients hospitalized in the ICU.[9] In another study evaluating patients with COVID-19, comorbid diseases were found in 38.8% of patients, and the number of comorbid diseases was higher among severe COVID-19 patients.[34] Chen et al[35] reported comorbid diseases more frequently among COVID-19 patients who died compared with patients who recovered. In our study, comorbid diseases were found in 37.9% of our patients. Similar to other studies,[9,34,35] we observed comorbid diseases more frequently in patients with severe disease and those followed in the ICU (Table 1).

In various studies, dyspnea was more common in patients followed up in the ICU or those that eventually died.[9,35] We found that respiratory system symptoms were more common in the ICU and exitus groups when compared with the ward group (Table 2).

Due to methodological differences, accompanying neurological symptoms in COVID-19 patients have been reported at different rates in various studies.[34,37–41] Mao and colleagues divided neurological symptoms into 3 categories: CNS findings, PNS findings and skeletal muscle involvement. In this study, neurological symptoms were described in 36.4% of patients with COVID-19. CNS-related symptoms were found in 24.8% of patients, while PNS-related symptoms were present in 8.9%, and skeletal muscle symptoms in 10.7%. It was reported that neurological symptoms (acute cerebrovascular diseases, impaired consciousness, skeletal muscle damage) were present at a greater frequency in patients with severe clinical state.[34] In our study, we found that 72.02% of our patients had at least 1 neurological symptom.

TABLE 3. Laboratory Values of Patients

		Follow-up Status			
	Total (n = 290)	**Inpatient Service (n = 240)**	**Discharged From ICU (n = 25)**	**Death (n = 25)**	***P***
White blood cell (×1000)/μL	6.01 (2.04-35.12)	5.79 (2.04-14.40)[a]	8.06 (3.86-17.60)[b]	8.73 (2.35-35.12)[b]	<0.001
Neutrophil (×1000)/μL	3.8 (0.20-33.28)	3.51 (0.20-11.16)[a]	6.30 (2.62-16.34)[b]	6.83 (1.56-33.28)[b]	<0.001
Lymphocyte (×1000)/μL	1.32 (0.16-3.79)	1.42 (0.33-3.77)[a]	1.07 (0.50-2.70)[b]	0.94 (0.16-3.79)[b]	<0.001
Monocyte (×1000)/μL	0.52 (0.09-1.91)	0.53 (0.09-1.91)	0.43 (0.10-1.22)	0.39 (0.10-1.47)	0.102
Hemoglobin (g/dL)	13.39 ± 1.93	13.61 ± 1.80[a]	12.24 ± 1.90[b]	12.39 ± 2.48[b]	<0.001
Platelet (×1000)/μL	212 (81-489)	214.5 (81-489)[a]	239 (133-429)[a]	155 (95-419)[b]	0.006
Serum urea (mg/dL)	26.1 (9.6-172)	24.8 (9.6-116)[a]	31.2 (13.2-105)[b]	52.6 (17.9-172)[b]	<0.001
Serum creatinine (mg/dL)	0.85 (0.42-4.96)	0.82 (0.42-2.67)[a]	0.92 (0.68-3.09)[b]	1.10 (0.61-4.96)[b]	<0.001
C-reactive protein (mg/L)	14.2 (0-388.8)	9.95 (0-250)[a]	75.6 (5.3-306.6)[b]	124.6 (2.9-388.8)[b]	<0.001
D-dimer (μg FEU/mL)	0.34 (0.02-8.98)	0.32 (0.02-5.90)[a]	0.55 (0.20-5.32)[b]	0.76 (0.24-8.98)[b]	<0.001

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ICU indicates intensive care unit.

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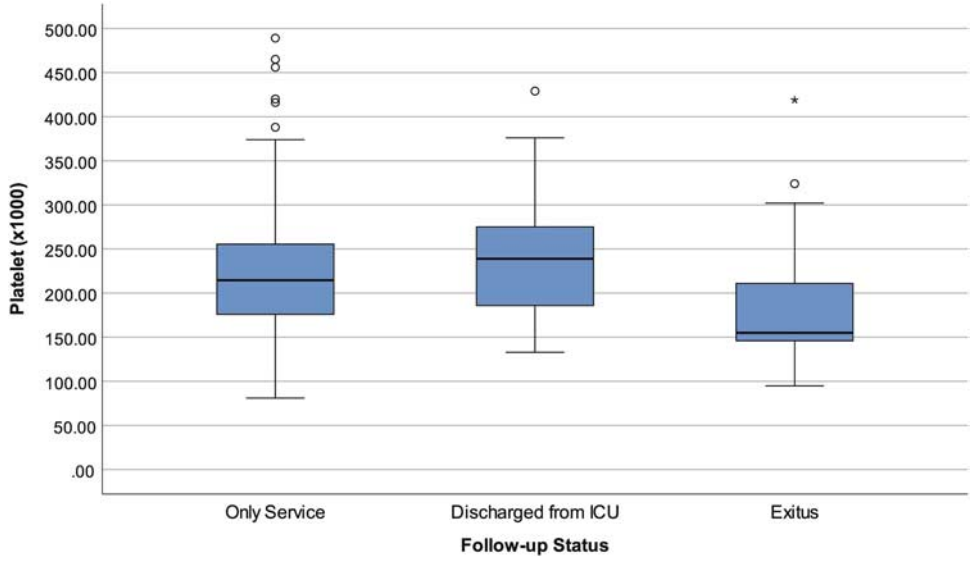

FIGURE 3. Platelets in the groups. ICU indicates intensive care unit. *$P = 0.006$.

In a meta-analysis of 78 studies and 104,751 COVID-19 cases, headache prevalence was shown to be 25.2%.[10] Studies have reported that headache may be one of the early or initial symptoms of COVID-19.[42,43] Headaches may be moderate, bilateral, pulsatile or compressive and localized in the temporoparietal, forehead or periorbital region in these patients[44] and it may be more common in patients with gastrointestinal symptoms such as nausea, vomiting or diarrhea.[45] In our study, the headache frequency was 32.07%, similar to other studies.[46,47]

Smell and taste impairment have been reported at different rates in COVID-19-positive cases. In studies conducted in China, taste impairment (dysgeusia and ageusia) frequency ranged between 5.6% and 6.7%, while smell impairment ranged from 5.1% to 7.5%.[34,41] In a study involving patients from 12 hospitals in Europe, smell and taste disturbances were detected in 85.6% and 88% of patients, respectively. There were significantly more smell and taste disorders in women.[48] We found anosmia in 23.79% and ageusia in 31.72% of our patients.

In the present study, neurological symptoms, such as myalgia, dizziness, headache, anosmia, and ageusia, were observed more frequently among patients who recovered after treatment in wards and ICUs compared with patients who died. We believe that this finding may be associated with the severity of disease in these patients, since these neurological symptoms may have been overlooked because of the presence of other, more severe symptoms, especially in patients admitted to the ICU who had fatal progression.

In a recently published systematic review and meta-analysis, it was reported that acute ischemic stroke was more common than hemorrhagic stroke in individuals with COVID-19, and the incidence of stroke was 1.4%. Stroke has been observed more frequently in elderly patients with COVID-19 who have severe disease and vascular risk factors.[22]

Ischemic infarction areas occurring during the course of COVID-19 have been mostly reported as cases of large vessel disease.[22,49] Mao et al[34] detected acute cerebrovascular disease (CVD) in 2.8% of COVID-19 patients. In another study that evaluated 219 COVID-19 patients, 4.6% of patients had acute ischemic stroke and 0.5% had hemorrhagic stroke.[50] In another multicentered study, in which 184 patients with COVID-19 infection had been included, ischemic CVD was described in 1.6% of patients admitted to the ICU.[51]

We found acute CVD in 0.7% of patients in our study. One of these patients was treated in the ICU and was discharged, while one was in the exitus group. Coagulation markers, such as D-dimer, increased in these patients and it was likely that comorbid diseases (hypertension and diabetes) and advanced age were the major factors that predisposed these patients to the development of stroke. The low frequency of CVD in our study may be due to the inability to perform a comprehensive

TABLE 4. Significant Risk Factors for Mortality

	β Coefficient	SE	Wald	*P*	Exp(β)	95.0% CI for Exp(β)	
Neurological disease	3.756	1.030	13.289	< 0.001	42.793	5.679	322.455
Male	1.760	0.850	4.287	0.038	5.814	1.099	30.764
Heart disease	1.514	0.753	4.043	0.044	4.544	1.039	19.873
COPD	2.664	0.998	7.126	0.008	14.348	2.030	101.423
Platelet	−0.021	0.006	10.566	0.001	0.979	0.967	0.992
C-reactive protein	0.019	0.004	20.993	< 0.001	1.020	1.011	1.028
D-dimer	0.789	0.266	8.828	0.003	2.201	1.308	3.705
Constant	−2.628	1.141	5.309	0.021	0.072		

Dependent variable: follow-up status (exitus); Nagelkerke $R^2 = 0.653$.
CI indicates confidence interval; COPD, chronic obstructive pulmonary disease.

neurological evaluation in patients with very severe disease, especially in the presence of serious respiratory symptoms.

In many studies, leukocyte and neutrophil counts, and D-dimer and C-reactive protein levels were higher in patients with fatal disease or severe infection.[34,35,52] In our study, we found leukocyte and neutrophil counts and the levels of serum urea, creatinine, C-reactive protein, and D-dimer to be higher in patients who were treated in the ICU.

The most important limitation of our study was that we could not access the data of some patients due to the lack of sufficient records. Neurological symptoms may have been overlooked or not questioned since other symptoms were more severe, especially in patients who were followed up in the ICU due to severe pulmonary disease. In addition, since there is a high risk of transmission and due to patient isolation measures, it may have been exceedingly difficult to question neurological symptoms and findings in these patients, as well as ordering and performing neurological examinations, cranial imaging (computerized tomography and magnetic resonance imaging), electroencephalography, electromyography, or cerebrospinal fluid analyses. Thus, it is possible that the neurological characteristics of patients with severe disease may have been overlooked to a greater degree when compared with the other groups.

Finally, although COVID-19 is undoubtedly a pulmonary disease with prominent effects on respiratory functions and inflammation, neurological involvement also appears to be frequent and may be critical or life-threatening in some patients. Our results demonstrated that altered consciousness and seizure were more common in patients who died. Therefore, neurological examination findings are important in the follow-up of these patients.

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