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Neurological Manifestations and Comorbidities in Coronavirus Disease 2019 (COVID-19) Patients: Multicenter Study

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ABSTRACT

Objective: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, responsible for the Coronavirus Disease 2019 (COVID-19) pandemic, originated in China and swiftly spread globally, resulting in significant mortality worldwide. We aimed to create an overview of the significant symptoms, clinical indicators, and concurrent comorbidities observed in COVID-19 patients that require hospitalization and neurology consultation, adversely affecting the severe course of the disease and leading to mortality.

Materials and Methods: We designed our study as a multicenter and cross-sectional survey, which was conducted with patients hospitalized in seven medical centers in Türkiye over six months.

Results: A cohort of 504 patients diagnosed with COVID-19 were included in the study. In terms of the complaints at the time of admission, high fever (48%), cough (45%), sore throat (23%), and diarrhea (9%) were the most common symptoms expressed by the patients. The most commonly observed symptoms included myalgia (55%), headache (46%), loss of taste (46%), and loss of smell (39%). Furthermore, 68 patients (13.5%) within the cohort had a history of neurological diseases, distributed as follows: cerebrovascular attack (4%), migraine (2.8%), extrapyramidal disease (1.8%), dementia (1%), polyneuropathy (1%), epilepsy (0.6%), and demyelinating disease (0.6%). In the logistic regression analysis, key factors affecting mortality were identified as body mass index and age.

Conclusion: The most common complaints in COVID-19 patients were high fever and sore throat. Fatigue, myalgia, headache, loss of smell, and taste were the most common symptoms. Accompanying comorbid diseases increased the severity of COVID-19 disease. Advanced age and body mass index were effective factors on mortality.

Keywords: Coronavirus Disease 2019 (COVID-19), neurological symptoms, mortality, prognosis, comorbidity.

INTRODUCTION

In 2020, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a global pandemic, leading to impactful socioeconomic, cultural, and economic changes in Türkiye and worldwide.[1,2] The medical information amassed during the pandemic has revealed that the disease induces clinical manifestations across multiple systems, including respiratory and organ failure.[2] Neurological symptoms may be considered initial indicators of COVID-19 or emerge during the disease's progression.[3] Predominant nonspecific symptoms such as headache, dizziness, and confusion have been reported, yet various other neurological complications were also found to arise throughout the course of the disease.[4–6] Coronaviruses may cause neurological symptoms due to endothelial injury, inflammatory mediators, macrophages, or direct infection of the nervous system.[5] The aim of our study is to examine the accompanying neurological symptoms and comorbid diseases that have the most impact on the severe course of the disease and mortality and to discuss them in light of the literature. Based on the current literature, this multicenter, cross-sectional study aims to discuss the distribution of clinical findings and comorbidities in patients diagnosed with COVID-19 and evaluated with neurology consultation during the pandemic.

MATERIALS AND METHODS

This study encompassed 504 patients with a confirmed diagnosis of COVID-19 in seven medical centers across Türkiye subsequent to the declaration of the pandemic in 2020. The survey was conducted cross-sectionally with patients diagnosed with COVID-19, who were evaluated with neurology consultation while they were hospitalized and followed up in the outpatient clinics from March 2020 to September 2020.

Patients below the age of eighteen were excluded from the study, as they were under the care of the Pediatric Neurology clinic. Recorded data included demographic information, body mass index (BMI), complaints on admission, neurological findings, comorbidities, and the clinical severity classification of disease considered in the study.

Comorbidities addressed in this study included hypertension (HT), diabetes mellitus (DM), congestive heart failure (CHF), coronary heart disease (CHD), chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), polyneuropathy, dementia, headache, multiple sclerosis (MS), Parkinson's disease, and malignancy.

Disease severity classification in this study adhered to the criteria outlined by the World Health Organization as of November 23, 2021, specifying four categories: mild, moderate, severe, and critical. Accordingly, the mild category encompasses patients exhibiting various symptoms without the presence of pneumonia. The moderate category includes patients with an oxygen saturation (SpO_2) ≥90% at ambient temperature, fever, cough, dyspnea, and hyperpnea. Patients in the severe category exhibit SpO_2 <90% at ambient temperature along with fever, cough, dyspnea, a respiratory rate of >30/min, and pronounced respiratory distress.[7] Those with a body mass index <25 were considered normal, those between 25–29.9 overweight, and those ≥30 obese.[8]

KEY MESSAGES

- The most commonly observed symptoms included myalgia (55%), headache (46%), loss of taste (46%), and loss of smell (39%).
- Accompanying comorbid diseases increased the severity of COVID-19 disease.
- Advanced age and body mass index were effective factors on mortality.

Ethics Committee Approval: Approval for our study was obtained from the Ethics Committee of the Faculty of Medicine at Erciyes University (20/05/2020 - decision no 2020/229).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, Chicago, IL, USA). The distribution of data was assessed using the Shapiro-Wilk test. Descriptive statistics for demographic data were calculated. The results were explained as the mean±standard deviation (SD) for quantitative data and as a percentage for categorical data. A one-way Analysis of Variance (ANOVA) test was used for multiple group analyses. Logistic regression analysis was used to predict the factors affecting mortality. Statistical significance was determined at a level of $p<0.05$ in both directions.

RESULTS

A cohort of 504 patients (220 females, 284 males; mean age: 44±17 years), diagnosed with COVID-19 and consulted by Neurology Clinics, were included in this study.

The cohort consisted of 333 patients aged ≤50 years (66%), 141 patients aged >50 years (28%), and 30 patients aged >75 years (6%) (p=0.001). The body mass index of 164 patients (32.5%) was normal, 218 (43.3%) were overweight, and 119 (23.6%) were within the obesity range.

The predominant comorbidities were hypertension (22%), diabetes mellitus (13.5%), coronary heart disease (5.5%), chronic obstructive pulmonary disease (5%), congestive heart failure (3%), chronic renal failure (3%), and malignancy (3%).

Table 1. Distribution of comorbidities by clinical severity of Coronavirus Disease 2019 (COVID-19)

	Clinical severity			F	p
Comorbidities	**Mild (n=217)**	**Moderate (n=238)**	**Severe (n=20)**		
Age	**36.5±14**[a]	**48.3±17**[b]	**65.9±15**[c]	40.225	<**0.001**
≤50, n (%)	189 (87)[a]	133 (56)[b]	1 (5)[c]	34.560	<**0.001**
>51	22 (10)	89 (37)	16 (80)		
>75	6 (3)	16 (7)	3 (15)		
Gender, n (%)				0.990	0.397
Female	**88 (41)**	**111 (47)**	**7 (35)**		
Male	**129 (59)**	**127 (53)**	**13 (65)**		
BMI	**25±3**[a]	**28±4**[b]	**27±5**[b]	13.45	<**0.001**
Normal <25, n (%)	107 (49)[a]	47 (21)[b]	5 (25)[b]		
Overweight 25–29.9	81 (37)	114 (48)	8 (40)	17.306	<**0.001**
Obese ≥30	29 (13)	74 (31)	7 (35)		
CVD, n (%)	3 (1.4)[a]	9 (3.8)[a]	4 (20)[b]	10.631	<**0.001**
Dementia	2 (0.9)	2 (0.8)	1 (5)	1.070	0.361
CHF, n (%)	3 (1.4)[a]	4 (1.7)[a]	4 (20)[b]	11.781	<**0.001**
DM, n (%)	12 (5.5)[a]	40 (16.8)[b]	7 (35)[c]	11.430	<**0.001**
HT, n (%)	26 (12)[a]	64 (26.9)[b]	10 (50)[c]	9.306	<**0.001**
CHD, n (%)	4 (1.8)[a]	18 (7.6)[b]	2 (10)[b]	3.087	**0.027**
CRF, n (%)	4 (1.8)	7 (2.9)	2 (10)	1.616	0.185
COPD, n (%)	6 (2.8)	15 (6.3)	3 (15)	2.555	0.055
Malignancy, n (%)	3 (1.4)	9 (3.8)	1 (5)	1.007	0.390
Exitus, n (%)	0[a]	3 (1.3)[b]	5 (25)[c]	22.685	<**0.001**

CVD: Cerebrovascular disease; CHF: Congestive heart failure; HT: Hypertension; CHD: Coronary heart disease; CRF: Chronic renal failure; COPD: Chronic obstructive pulmonary disease; a–cX There is no difference between groups with the same letter for each measure.

Furthermore, 68 patients (13.5%) within the cohort had a history of neurological diseases, distributed as follows: cerebrovascular attack (4%), migraine (2.8%), extrapyramidal disease (1.8%), dementia (1%), polyneuropathy (1%), epilepsy (0.6%), and demyelinating disease (0.6%).

In terms of complaints at the time of admission, high fever (48%), cough (45%), sore throat (23%), and diarrhea (9%) were the most common symptoms expressed by the patients.

Fatigue (80%), myalgia (55%), headache (46%), loss of taste (46%), loss of smell (39%), sleep disorder (31%), difficulty in performing daily activities (26%), gait disturbance (23%), dizziness (18%), paresthesia (15%), and distraction (12%) were observed. Headache, predominantly frontal, regardless of side, and often nonspecific, constituted a prevalent symptom. Further characterization revealed that 26% of patients experienced throbbing headaches, 13% reported pressure and tension, 1% described neuralgic symptoms, and 46% presented with atypical characteristics.

Additionally, in conjunction with COVID-19 infection, three patients exhibited Guillain-Barre syndrome, 21 patients had epileptic seizures, and 17 patients had cerebrovascular disease.

According to classification by clinical severity, 217 patients were categorized as mild, 238 as moderate, and 20 as severe. Notably, among COVID-19 patients aged 18–50, there was a concentration of mild and moderate cases, whereas a significant increase in the percentage distribution of severe cases was observed in individuals over 50 years of age ($p<0.001$). No discernible gender-based differences were identified between the groups. The prevalence of obesity varied significantly among severity categories, with rates of 13% in the mild group, 31% in the moderate group, and 35% in the severe group. Furthermore, severe COVID-19 patients frequently presented with a combination of comorbidities such as CVD, CHF, DM, HT, and CHD (Table 1). The distribution of symptoms according to disease severity is shown in Figure 1.

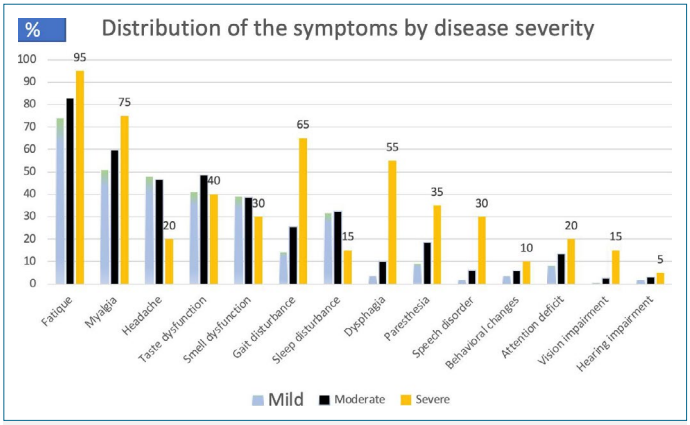

Figure 1. Distribution of symptoms by disease severity.

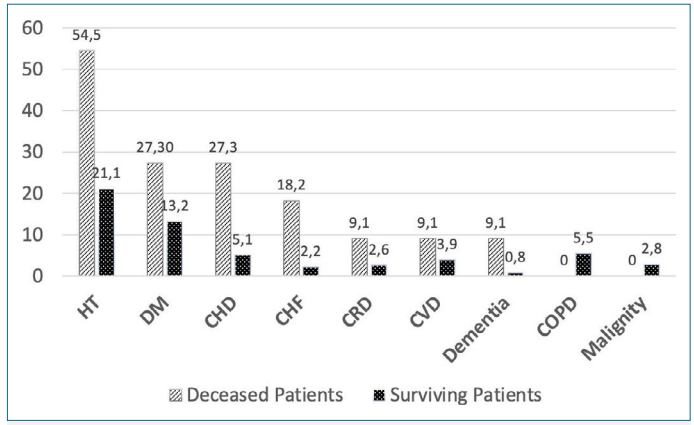

Figure 2. Distribution of symptoms by the disease course of Coronavirus Disease 2019 (COVID-19) in surviving and deceased patients.

CVD: Cerebrovascular disease; CHF: Congestive heart failure; HT: Hypertension; CHD: Coronary heart disease; CRF: Chronic renal failure; COPD: Chronic obstructive pulmonary disease.

At the time of discharge from the medical facility, 34% of the patients had recovered and 43% were released with isolation instructions. Furthermore, 10% were observed in the COVID-19 clinics and 9% were observed in outpatient clinics. Five patients were followed in the intensive care unit in critical condition on mechanical ventilation. The average age of these patients was 69.4±15, the female-to-male ratio was 3:2, the average BMI was 28.2, and three of them died. In the entire cohort, 11 patients died due to COVID-19. The death rate was 1.3% in moderate cases and 25% in severe cases (p<0.001). In patients who died, HT (54.5%), DM (27%), CHD (27%), CHF (18%), and chronic renal disease (CRD) (9%) were detected. Of the patients who died, five had a new cerebrovascular attack and one had an epileptic seizure. The distribution of comorbidities in deceased and surviving patients is shown in Figure 2. When the factors affecting mortality were evaluated one by one in the logistic regression analysis, only advanced age and BMI were found to be determining factors on mortality (Table 2).

DISCUSSION

In our study, we found that the most common complaints in COVID-19 patients were high fever and sore throat. Fatigue, myalgia, headache, loss of smell, and taste were the most common symptoms. Accompanying comorbid diseases increased the severity of COVID-19 disease. Advanced age and body mass index were effective factors in mortality.

COVID-19, which affects multiple systems, has been associated with neurological symptoms in approximately 30% of cases.[9] The neurological manifestations of the disease are intricately linked to the neurotrophic impact of the virus.[9] In 15% of cases, neurological symptoms developed within two days following the onset of viral symptoms.[10] Neurological syndromes

Table 2. Summary of regression analysis for variables predicting mortality

	B	SD	β	p	95% CI
Mortality	5.838	3.622	343.181		
BMI	0.207	0.095	**1.231***	**0.029***	**1.022–1.482**
Age	-0.122	0.033	**0.885***	**0.0001***	**0.830–0.944**
Dementia	-0.945	1.543	0.388	0.540	0.019–7.993
CHF	10065	0.948	2.941	0.261	0.452–18.600
CHD	0.513	0.835	1.670	0.539	0.325–8.586
DM	-0.350	0.958	0.705	0.715	0.108–4.611
HT	-0.261	0.844	-0.770	0.770	0.147–4.024

Summary of logistic regression analysis for variables predicting mortality. Dependent variable: Mortality Nagelkerke R^2=0.442. SD: Standard deviation; CI: Confidence interval; CHF: Congestive heart failure; HT: Hypertension; CHD Coronary heart disease; DM: Diabetes mellitus; BMI : Body mass index; *: P<0.05.

associated with COVID-19 are divided into two categories: parainfectious (occurring during the course of the disease) and postinfectious (emerging after the disease is controlled). Parainfectious conditions encompass disorders such as taste and smell dysfunctions, encephalopathy, and myositis, whereas postinfectious conditions include acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome, myelitis, and cognitive impairment.[11] Another classification categorizes neurological findings due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) into three groups: central nervous system (CNS) findings (headache, dizziness, stroke, epileptic seizures, changes in consciousness), peripheral nervous system (PNS) findings (smell and taste disorders, visual impairments, Guillain-Barre syndrome and its variants), and skeletal muscle system (SMS) findings.[2]

In our study, the most commonly observed symptoms included myalgia (55%), headache (46%), loss of taste (46%), and loss of smell (39%). During the course of the disease, Guillain-Barre syndrome developed in three patients, epileptic seizures in 21 patients, and cerebrovascular disease in 17 patients. Studies conducted in Wuhan reported a prevalence of neurological complications at 36.4%.[2] In our study, the rates determined in terms of neurological symptoms were in alignment with the literature.

In studies conducted in Wuhan, prevalent symptoms included dizziness (16.8%) and headache (13.1%).[2] Headache, reported in 39–55% of cases during the early symptomatic phase of the disease and presenting as the first symptom in 25% of cases,[12] was identified at a rate of 46% in our study, indicating higher prevalence in cases with moderate and severe disease severity. In our study, dizziness was recorded as an initial symptom in 18% of cases.

As per the International Classification of Headache Disorders (ICHD-3) definition, the headache accompanying COVID-19 aligns with headaches associated with systemic infection.[13] These headaches are generally described as having a gradual onset, being bilateral, moderate to severe, and of a tension and compressive nature.[14] Various types such as flu-like headache, migraine, and tension-type headache are reported in the early phase, while late-phase headaches are typically attributed to cytokine storms and hypoxia.[15] Different studies have reported varying prevalence of migraine phenotype and tension-type headache in COVID-19 patients.[12,16]

In our study, throbbing pain (26%), tension-type headache 13%, neuralgic headache 1%, and atypical headache 4% were recorded. Possible mechanisms suggested for headache include direct virus damage, inflammatory events, hypoxemia, coagulopathy, and endothelial effects.[17]

Fatigue is another prevalent and commonly reported accompanying symptom, occurring at an average rate of 39.8%.[18] However, in our study, fatigue emerged as the most prevalent symptom, with an incidence of 80%. Furthermore, its prevalence varied across the spectrum of disease severity, identified in 57% of mild cases, 69% of moderate cases, and 75% of severe cases.

Taste and smell dysfunctions are among the most common clinical symptoms associated with COVID-19. The pathogenesis is attributed to hypersensitivity to the virus in supporting cells and basal cells, the consequent destruction of the nasal epithelium, invasion of the central nervous system through the olfactory bulb, and the secretion of angiotensin-converting enzyme 2 (ACE2).[19] A meta-analysis by Favas et al.[20] reported taste disorders in 38.5% and olfactory disorders in 35.8% of cases. In alignment with this meta-analysis, our study identified taste disorders in 46% and olfactory disorders in 39% of cases.

Myalgia, reported at rates varying from 3.3% to 64%, is often associated with generalized inflammation and a cytokine storm. In our study, its prevalence was observed to be 55%. Despite this notable occurrence, myalgia is not recognized as a prognostic factor for severe cases.[21]

Among the neurological conditions accompanying COVID-19 infection, stroke has been reported with a prevalence ranging from 0.5% to 5.9%, while epileptic seizures occur at a rate of approximately 0.5%.[2, 22] The pathogenesis of cerebrovascular events is attributed to an increase in thrombin production resulting from endothelial dysfunction, the inhibition of the fibrinolytic system, elevated levels of inflammatory markers, and increased blood viscosity.[3,23] Additionally, studies suggest that the release of inflammatory cytokines and activation of glutamate receptors lead to increased neuronal hyperexcitability, potentially causing epileptic seizures.[19] In our study, stroke was identified at a rate of 3.4%, and epileptic seizures were observed in 4% of COVID-19 cases. Out of all the patients who had a stroke during COVID-19 infection, 45.5% died.

Advanced age stands out as a critical determinant of the adverse course of COVID-19 infection, with reports indicating more severe symptoms and increased mortality among older individuals. The susceptibility to severe outcomes in the elderly population is attributed not only to a compromised immune system but also to a higher prevalence of comorbidities.[24] In our study, patients aged 50 and above comprised the group exhibiting the highest disease severity. Furthermore, among fatal cases, older patients constituted the majority.

Reports indicate that the clinical course of the disease tends to be more severe in men, possibly due to the immunosuppressive effect of testosterone and an increase in ACE-2 receptor activity.[24] However, our study did not reveal a significant difference between genders with respect to disease severity.

Studies have suggested that obesity is associated with higher severity in COVID-19. Pathogenesis is attributed to ACE-2 secretion from adipose tissue resulting from obesity, along with the release of adipokines contributing to inflammation and a decrease in lung capacity.[25] In our study, regarding disease severity, obesity was observed in 13% of the mild group, 31% of the moderate group, and 35% of the severe group, indicating an association with disease severity.

It has been reported that 75% of patients hospitalized due to COVID-19 exhibit at least one comorbidity, with the most prevalent conditions being HT, DM, cardiovascular diseases, neurodegenerative diseases, cancer, kidney diseases, and obesity.[26] Statsenko et al.[27] reported rates of 12% for DM, 40.4% for CVD, 11% for digestive system diseases, and 0.01% for cancer in their study. Other studies indicate DM prevalence ranging from 11% to 58% among COVID-19 patients, with 8% experiencing a severe course.[28] Within our cohort, DM was detected in 13.5%, and it was present in 35% of cases with a severe course.

Hypertension, a prevalent comorbidity, has been linked to disease severity and mortality,[29] with disruption of the Renin-Angiotensin-Aldosterone System in COVID-19 patients implicated in its pathogenesis.[30]

In our cohort, the severe disease group also demonstrated elevated rates of HT (50%), DM (35%), COPD (15%), and congestive heart failure (20%). The high affinity of the virus for ACE-2 receptors, abundant in endothelial cells of the lungs, kidneys, blood vessels, and the gastrointestinal system, may contribute to these outcomes.[31] In the case of cancer, a comorbidity and an immune-compromised condition, older patients are more susceptible compared to the general population. In cancer patients, COVID-19 frequency was reported as 2–3% and mortality rate as 22%, with a tendency toward a severe course.[32] In our study, the cancer rate was found to be 2.8%, and this was one of the factors that increased mortality.

Chronic renal failure is identified as a risk factor for COVID-19, with reported mortality rates reaching 50%.[33] However, in our study group, chronic renal failure was observed at a rate of 2.8% and not found to be associated with increased mortality.

Hypoxemia has been reported to develop in 15–20% of COVID-19 cases during the disease course, necessitating support from the intensive care unit (ICU).[34] Previous COPD has been identified in 50–52% of COVID-19 patients requiring ICU admission.[35] In our cohort, COPD exhibited a prevalence of 5%, with rates of 3% in mild cases, 6% in moderate cases, and 15% in severe cases.

The design in a survey format, lack of information about the applied treatments and their effects, and the low number of patients in intensive care were the limitations of our study.

CONCLUSION

In conclusion, central and peripheral nervous system and musculoskeletal symptoms are prevalent in hospitalized COVID-19 patients. Common manifestations include fatigue, headache, and muscle pain as well as smell and taste disorders. Comorbidities such as advanced age, obesity, hypertension, diabetes, heart diseases, and cerebrovascular diseases adversely affect the severe course of the disease.

In particular, advanced age and obesity stand out as independent influential factors on mortality.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 20.05.2020, number: 2020/229).

Author Contributions: Concept – NGB, MMA, SK, FFE; Design – NGB, FFE, MMA; Supervision – FFE, SK; Data Collection and/or Processing – NGB, MMA, FFA, MFA, BS, FE, SG, UBŞ, KG, MFY, ÇE, ŞT, ZTY, MA, MAT, NT, EÖB, SK, ST, ŞB, ZK, KK, UY, AY, BBK, AUK, MAH; Analysis and/or Interpretation – AÖ; Literature Search – NGB; Writing – NGB; Critical Reviews – NGB, FFE, SK.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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