# Evaluation of the factors associated with neurological manifestations in COVID-19 patients

Mona Ramezani Ghamsari, Zahra Mirzaasgari, Mahsa Ziaee, Marjan Zeinali, Tara Khoeini, Mohammad Rezaei, Mohammad Mahdi Niksima, Ehsan Hajiramezanali, Hoda Derakhshani, Meysam Abolmaali

## Abstract

Background: The coronavirus disease 2019 (COVID-19) is the most terrible pandemic of a respiratory disease that we had in 100 years. The majority of existing researches explore different manifestations in COVID-19. Few recent works have been studied to describe neurological manifestations of patients with COVID-19 but their associations with age, laboratory findings, and mortality rates are not well explored.
Methods: This case-control study includes a total of 263 COVID-19 patients without neurological symptoms (control group) and all COVID-19 patients with the central nervous system symptoms (n=460, case group) hospitalized between February 2020 and April 2020. Data on demographic factors, medical history, symptoms, and laboratory tests, all are extracted from medical records.
Results: Out of 723 patients with confirmed SARS-CoV-2 infection, 460 (63.6%) patients are identified to have at least one of the neurological manifestations. The mean ages of patients with and without neurological manifestation are 60.6±18.0 and 60.8±15.7 years, respectively. The most common symptoms were myalgia (41%), headache (20.3%), and loss of consciousness (LOC) (16.5%). Women were perceived to be more likely to develop a neurological manifestation ($p = 0.001$). Moreover, smoking history was significantly more in patients with neurological manifestations ($p = 0.03$). We also compared two groups in terms of tracheal intubation. The need for tracheal intubation was 19% and 12% in patients with and without neurological manifestations, respectively. Furthermore, the prevalence of intensive care unit admission is 28% and 24% in COVID-19 patients with and without neurological manifestations, respectively. Some of the neurological manifestations such as LOC, limbs weakness, and seizure might need more intensive care unit admission and tracheal intubation. The frequency of comorbidities and the laboratory test results were almost similar between the two groups.

Conclusions: Our analysis results show that myalgia, headache, and LOC are the most common neurological manifestations and their distributions vary depending on age. The results also demonstrate only a few neurological manifestations are related to mortality and morbidity rates, while some of them occur in mild cases.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to be a serious public health challenge facing the world nowadays [1]. Although coronavirus infections mainly invade the respiratory tract, available evidence suggests that they may also target several non-respiratory organs, including the nervous system [2]. This neuroinvasive potential is supposed to be a feature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) such as headache and disturbed consciousness [3,4].

A few previous studies have described multiple neurological symptoms in patients with SARS- CoV-2 infection, including headache, dizziness, encephalitis, and loss of consciousness (LOC) [5]. One of these studies also revealed the potential role of the central nervous system (CNS) symptoms as a prognostic factor for the poor outcomes of COVID-19 [6]. However, not only the knowledge about the frequency of different neurological manifestations is still scant, but also their association with age, laboratory findings, prognosis, and mortality rates are not well explored. Here, we would like to first report the frequency of neurological manifestations of COVID-19. Then, we investigate the associated factors of neurological manifestations and show which neurological manifestations can be considered as a poor prognostic factor.

## Materials & Methods

Study design and participants
This retrospective observational study is done at two referral centers of designated COVID-19 Hospitals in Iran, i.e., Rajaei Hospital of Alborz University of Medical Sciences (ABZUMS) and Firoozgar Hospital of Iran University of Medical Sciences (IUMS). We collected data from February to April 2020 and only focused on the confirmed cases of COVID-19. During this study, we considered a confirmed COVID-19 patient if any of the following conditions exist: 1) a positive result on polymerase chain reaction (PCR) test of nasal and throat swab specimens; 2) recognize the chest computed tomography (CT) scan appearance of COVID-19 based on two radiology specialists reporting. Based on these two conditions, 723 admitted patients to the hospital are enrolled in the analysis. This study is performed in accordance with the Declaration of Helsinki. Research and Ethics Committees of both ABZUMS and IUMS approved the

study protocols. A unique identification number is assigned to each patient to protect the confidentiality of the participants.

Data collection

We explored both paper and electronic medical records, laboratory results, and radiological reports for all patients. The collected data include demographic characteristics, past medical history, clinical factors including neurological signs and symptoms, COVID-19 related symptoms, patients vital signs at first examination in triage emergency ward, the laboratory findings at the first day of the hospitalization, reverse-transcription polymerase chain reaction (RT-PCR) test and chest CT scan findings. Two assistant professors of neurology reviewed neurological manifestations. Please note that only hospitalized patients are included in this study. Therefore, it might not fully describe mild to moderate COVID-19 patients that are not admitted. We also would like to mention that neither neurological manifestations that were not reported due to a defect in completing the history nor the patient's unconsciousness are included in this study. We divided patients into two major groups: 1) COVID-19 patients with at least one neurological manifestation; 2) COVID-19 patients without any neurological manifestation.

Laboratory testing

The blood parameters listed below all are extracted from the blood tests performed on the first day of the hospitalization for each patient. The test results include the counts of white blood cells (WBC), lymphocyte count (LYM), absolute lymphocyte count, (ALC), serum hemoglobin level (Hb), platelet count (PLT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR), aspartate transaminase (AST), alanine transaminase (ALT), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), blood sugar (BS), potassium (K), and concentrations and serum level of vitamin D.

Medical history and Comorbidities

On admission, we have checked the patients' medical history, including seizure, cerebrovascular accident (CVA), diabetes mellitus (DM), hypertension (HTN), multiple sclerosis (MS), coronary artery disease (CAD), brain mass, cardiovascular disease (CVD), cancer, chronic renal failure (CRF), chronic liver diseases, psychological disorder, chronic respiratory disease, asthma, hypothyroidism, hyperthyroidism, immunodeficiency, autoimmune disease, hematologic disease,
and any other notable disorder.

Neurological symptoms

Two neurologists extracted neurological symptoms from the medical records. More specifically, myalgia, headache, dizziness/vertigo, disturbed consciousness,

encephalopathy, agitation, seizure, sleep disorder, disturbed taste, disturbed smell, blurred vision, diplopia, dysphagia, speech disorders, weakness of limbs (mono or hemiparesis and para or quadriparesis), urine incontinency, ataxia, and movement disorders are assessed.

Statistical analysis

Continues variables are described as means and standard deviations and compared by using Fisher's exact test. All statistical analysis is performed using R (version 3.3.0) software. The significant threshold is set at a p-value < 0:05.

## Results

Out of a total of 723 hospitalized patients with confirmed SARS-CoV-2 infection, 460 (63.6%) patients are identified to have at least one of the neurological manifestations.

The most common symptoms are myalgia (41%), followed by headache (20.3%) and loss of consciousness (16.5%). The frequency of the various type of neurological symptoms observed in COVID-19 patients is mentioned in (Table 1).

**Table 1. The frequencies of neurological symptoms observed in COVID-19 patients.**

| Symptoms | Frequency (%) |
|---|---|
| Myalgia | 41.03 |
| Headache | 20.35 |
| LOC | 16.57 |
| Dizziness Vertigo | 9.20 |
| Encephalopathy | 2.76 |
| Meningeal | 0.14 |
| Agitation | 2.22 |
| Seizure | 3.10 |
| sleep disorder | 4.28 |
| Taste disturbance | 6.99 |
| Smell disturbance | 7.14 |
| Visual disturbance | 0.45 |
| Diplopia | 0.60 |
| Dysphagia | 1.73 |
| Speech disorder | 3.35 |
| Hemiparesis | 3.04 |
| Quadriparesis | 3.46 |
| Hypoesthesia paresthesia | 4.74 |
| Sphincteric disturbance | 0.58 |
| Lumbar pain | 6.01 |

LOC, loss of consciousness.

Table 1: The frequencies of neurological symptoms observed in COVID-19 patients.

The average ages of patients with and without neurological manifestation are 60.6±18.0 and 60.8±15.7 years, respectively. (Table 2) shows the demographic factors and the early vital signs of the included patients by the study groups.

**Table 2. Demographic findings and early vital signs of the patients with and without neurologic manifestations.**

|  | Total | With | Without |
|---|---|---|---|
| Patient No. | 723 | 460 | 263 |
| Age (year±SD) | 60.7±17.2 | 60.6±18.0 | 60.8±15.7 |
| Sex (male/female) | 412/311 | 250/210 | 162/101 |
| Admission (ward/ICU) | 527/196 | 327/133 | 200/63 |
| SBP (mmHg) | 123.9 | 125 | 122.1 |
| DBP (mmHg) | 78.5 | 78.4 | 78.8 |
| HR (beat/min) | 85.1 | 85.7 | 84.2 |
| RR (breaths/min) | 19.5 | 19.1 | 20.1 |
| T (°C) | 37.2 | 37.4 | 36.8 |
| $SPO_2$ (%) | 91 | 91.1 | 91 |

ICU, intensive care unit; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; respiratory rate; T, temperature; $SPO_2$, blood oxygen saturation.

Table 2: Demographic findings and early vital signs of the patients with and without neurological manifestations.

We divided patients into three different groups based on their ages and compared different age groups based on each neurological manifestation prevalence. More precisely, we assumed three groups G1, G2, and G3 as younger than 40-year-old, between 40- to 60-year-old, and higher than 60-year-old, respectively. The prevalence of myalgia in G1, G2, and G3 is 54%, 45%, and 34%, respectively. While the prevalence of headache is around 32% in G1, it is less than 18% in the other two groups. The prevalence of decreased consciousness is less than 9% in G1 and G2, and around 25% in G3. Finally, the prevalence of seizure is around 9% in patients of G1 and less than 2% in the other two groups. It is interesting to note that 54% of patients with at least one neurological manifestation are male, while 62% of patients of the other group are male (p = 0.001). Also, smoking prevalence was 7.44% in patients with neurological manifestations and only 1.09% in another group (p = 0.03). We might need further studies with larger sample sizes to confirm the last two observations.

We also compared two groups in terms of tracheal intubation. While 19% of patients with neurological manifestations required tracheal intubation, only 12% required

intubation in the other group. More precisely, more than 56% of patients with a decreased level of consciousness, 57.89% of patients with encephalopathy, and 59.09% of patients with seizures are intubated. The prevalence of intensive care unit (ICU) admission is 28% and 24% in COVID-19 patients with and without neurological manifestations, respectively. The prevalence of ICU admission is 73.19% in patients with disturbed consciousness, 63.15% in patients with encephalopathy, and 54.5% in patients with weakness of limbs. As a result, we can conclude that COVID-19 patients with some of the neurological manifestations such as decreased level or impaired content of consciousness, weakness of limbs, and seizure might need ICU admission and tracheal intubation. They might also be considered to predict a poor prognosis.

The mortality rate is 25% and 21% in patients with and without neurological manifestations, respectively. The high mortality rate of the COVID-19 patients in our study should be mostly due to the way we enrolled the patients in the study. As we mentioned before, we did not investigate patients that are not admitted to the hospitals. We also note that patients admitting vital signs in two groups (with vs without neurological manifestations), including respiratory rate (19 vs 20), body temperature (37.36 vs 37.35), and o2 saturation (91.17 vs 91.02) are very close. (Table 3) shows that the frequency of comorbidities between the two groups is almost the same.

**Table 3. Comparison of the frequency of comorbidities between two groups with and without neurological symptoms.**

| Comorbidities (%) | With symptoms | Without symptoms | p-value < 0. |
|---|---|---|---|
| Seizure | 2.85 | 1.96 | NO |
| CVA | 8.85 | 7.48 | NO |
| DM | 39.66 | 32.03 | NO |
| HTN | 48.58 | 39.45 | NO |
| Brain mass | 0 | 0.39 | NO |
| MS | 0.28 | 0.78 | NO |
| CAD | 23.93 | 27.34 | 0.03 |
| Other | 43.88 | 39.16 | NO |

CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; MS, multiple sclerosis; CA coronary artery disease; NO, not observed.

Table 3: Comparison of the frequency of comorbidities between two groups with and without neurological symptoms.

In addition, the laboratory test results are almost similar between patients in the two groups, as all P values are greater than 0.05, except for ALT and CPK (Table 4).

**Table 4. Comparison of the laboratory test results between two groups, with and without neuro manifestations.**

| Lab findings | Total | With | Without | P va... |
|---|---|---|---|---|
| WBC ($\times 10^3/\mu L$) | 8139.6 | 8103.1 | 8203.8 | 0.83... |
| LYM ($\times 10^3/\mu L$), (%) | 1672.7 | 1645, (20.3) | 1714, (20.9) | 0.55 |
| ALC | 1432.8 | 1462.4 | 1378.7 | 0.57 |
| Hb (gr/dl) | 13.13 | 13.29 | 12.85 | 0.55 |
| PLT ($\times 10^3/\mu L$) | 205324 | 199919 | 214823 | 0.67 |
| PTT (seconds) | 34.5 | 34.4 | 34.5 | 0.76 |
| PT (seconds) | 15.1 | 14.9 | 15.39 | 0.37 |
| INR | 1.15 | 1.16 | 1.12 | 0.25 |
| BS (mg/dl) | 155.4 | 157.5 | 151.7 | 0.08 |
| K (mEq/L) | 4.1 | 4.06 | 4.2 | 0.62 |
| ESR (mm/h) | 41.3 | 41.02 | 41.7 | 0.2 |
| AST (U/L) | 70.5 | 63.8 | 81.6 | 0.08 |
| ALT (U/L) | 59.3 | 48.9 | 76.6 | 0.01... |
| LDH (U/L) | 659.9 | 652.4 | 672.5 | 0.25 |
| CPK (U/L) | 329.7 | 358.8 | 280.2 | 0.05 |
| Vit D (ng/ml) | 22.9 | 22.8 | 23.07 | 0.28 |

WBC, white blood cell; LYM, lymphocyte; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, plat...
PTT, partial Thromboplastin Time; PT, prothrombin time; INR, international randomized ratio; BS, bloo...
K, potassium; ESR, estimated sedimentation rate; AST, aspartate Aminotransferase; ALT, alanine
Aminotransferase; LDH, lactate Dehydrogenase; CPK, creatine phosphokinase.

**Table 4: Comparison of the laboratory test results between two groups, with and without neurological manifestations.**

## Discussion

Shortly after the declaration of the COVID-19 pandemic, studies demonstrated numerous non-respiratory features of COVID-19. Among them, neurological symptoms were the most important ones. In this regard, dozens of neurological signs and symptoms in COVID-19 patients were reported by clinicians from different countries. There are some mechanisms in the development of neurological symptoms among these patients. The most important theory is the direct invasion of SARS-CoV-2 through neurons by the ACE2 receptor [7]. In this study, we evaluated the frequency and characteristics of COVID-19 patients with neurological manifestations. Among 21 neurological manifestations in this study, myalgia, headache, and disturbed consciousness are the most prevalent ones, followed by dizziness/vertigo, smell disturbance, and taste disturbance.

Our study indicated a 63.6% prevalence of at least one neurological involvement among the COVID-19 patients who were assessed for the neurological symptoms. Prior studies have also presented a prevalence of 45.5 to 84 percent of neurological symptoms in

patients with COVID-19 [8]. Review studies about the neurological manifestations of COVID-19 patients usually divided these symptoms into the CNS and PNS symptoms. In that regard, headache and loss of smell/taste are considered to be the most common symptoms in the CNS and PNS, respectively [8, 9]. We noticed that in our study, smell and taste disturbances are less prevalent compare to other reports. Based on a recent systematic review conducted by Saniasiaya et al., consisting of 83 studies (n=27492) about the olfactory dysfunction in COVID-19 patients, the pooled prevalence of overall smell disturbance was assessed to be 47.85% [10]. This might be due to the collected data in which we exclude mild to moderate COVID-19 patients. Our results also show that the neurological symptoms are not distributed uniformly for patients with different age ranges. While headache, myalgia, and seizure are the most prevalent symptoms in young patients, disturbed consciousness is mostly presented in older patients. In our study, some neurological manifestations including blurred vision, diplopia, ataxia, movement disorders, obvious autonomic symptoms, and urine incontinency are not seen in any patients. Based on this study, there are certain neurological manifestations including disturbed consciousness, encephalopathy, and seizure that will predict poor prognosis. In addition, some neurological symptoms including myalgia, headache, taste, and smell disturbances are more common in young patients and mild cases infected with SARS-CoV-2. The absence of a significant difference in admitting vital signs, including respiration rate per minute, body temperature and oxygen saturation, intubation rate, ICU admission, and mortality rate indicates that neurological manifestations, in general, cannot predict the prognosis. We also notice that only disturbed consciousness, encephalopathy, weakness of limbs, and seizure can be considered as the neurological sign or symptoms with a meaningful relationship to increased tracheal intubation, ICU admission, and mortality rate. The smoking rate is significantly higher in COVID-19 patients with neurological manifestations. However, the number of smokers in our study is 48, and suggest further investigations with higher sample sizes in this regard to get a more concrete conclusion. In this study, the underlying diseases and comorbidities were not associated with a higher incidence of neurological manifestations. No laboratory findings have also shown a significant difference between the two groups. However, Ashrafi et al. showed a higher neutrophil to lymphocyte ratio (NLR) and C-reactive protein (CRP) in COVID-19 patients with neurological manifestations compared to those without any neurological signs [11].

## Conclusions

A substantial proportion of the admitted patients with COVID-19 are found to have at least one neurological manifestation which can be seen more frequently among

smokers. Based on our findings, myalgia, headache, and alteration in mental status are the most common symptoms that can be seen in patients with moderate to severe involvement. With respect to the large meta-analyses, it can be understood that patients with moderate to severe involvement have less manifestation in taste and smell disturbances compared to those with mild involvement.

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## Appendices

| Symptoms | Frequency (%) |
|---|---|
| Myalgia Headache LOC Dizziness Vertigo Encephalopathy Meningeal Agitation Seizure sleep disorder  Taste disturbance Smell disturbance Visual disturbance Diplopia Dysphagia Speech disorder Hemiparesis Quadriparesis Hypoesthesia paresthesia Sphincteric disturbance Lumbar pain | 41.03 20.35 16.57 9.20 0.14 2.22 3.10 4.28 6.9 0.45 0.60 1.73 3.35 3.0 4.74 0.58 6.01 |

**Table 5: Neurological symptoms frequency observed in COVID-19 patients.**

LOC, loss of consciousness.

|  | Total | With | Without |
|---|---|---|---|
| Patient No. | 723 | 460 | 263 |
| Age (year±SD) | 60.7±17.2 | 60.6±18.0 | 60.8±15.7 |
| Sex (male/female) | 412/311 | 250/210 | 162/101 |
| Admission (ward/ICU) | 527/196 | 327/133 | 200/63 |
| SBP (mmHg) | 123.9 | 125 | 122.1 |
| DBP (mmHg) | 78.5 | 78.4 | 78.8 |
| HR (beat/min) | 85.1 | 85.7 | 84.2 |
| RR (breaths/min) | 19.5 | 19.1 | 20.1 |
| T (°C) | 37.2 | 37.4 | 36.8 |
| $SPO_2$ (%) | 91 | 91.1 | 91 |

**Table 6: Demographic findings and early vital signs of the patients with and without neurological manifestations.**

ICU, intensive care unit; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; T, temperature; SPO2, blood oxygen saturation.

| Comorbidities (%) | With symptoms | Without symptoms | p-value < 0 |
|---|---|---|---|
| Seizure | 2.85 | 1.96 | NO |
| CVA | 8.85 | 7.48 | NO |
| DM | 39.66 | 32.03 | NO |
| HTN | 48.58 | 39.45 | NO |
| Brain mass | 0 | 0.39 | NO |
| MS | 0.28 | 0.78 | NO |
| CAD | 23.93 | 27.34 | 0.03 |
| Other | 43.88 | 39.16 | NO |

**Table 7: Comparison of the frequency of comorbidities between two groups with and without neurological symptoms.**

CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; MS, multiple sclerosis; CAD, coronary artery disease; NO, not observed.

| Lab findings | Total | With | Without | P va |
|---|---|---|---|---|
| WBC ($\times 10^3$/μL) | 8139.6 | 8103.1 | 8203.8 | 0.839 |
| LYM ($\times 10^3$/μL), (%) | 1672.7 | 1645, (20.3) | 1714, (20.9) | 0.55 |
| ALC | 1432.8 | 1462.4 | 1378.7 | 0.57 |
| Hb (gr/dl) | 13.13 | 13.29 | 12.85 | 0.55 |
| PLT ($\times 10^3$/μL) | 205324 | 199919 | 214823 | 0.67 |
| PTT (seconds) | 34.5 | 34.4 | 34.5 | 0.76 |

| | | | |
|---|---|---|---|
| PT (seconds) | 15.1 | 14.9 | 15.39 | 0.37 |
| INR | 1.15 | 1.16 | 1.12 | 0.25 |
| BS (mg/dl) | 155.4 | 157.5 | 151.7 | 0.08 |
| K (mEq/L) | 4.1 | 4.06 | 4.2 | 0.62 |
| ESR (mm/h) | 41.3 | 41.02 | 41.7 | 0.2 |
| AST (U/L) | 70.5 | 63.8 | 81.6 | 0.08 |
| ALT (U/L) | 59.3 | 48.9 | 76.6 | 0.01 |
| LDH (U/L) | 659.9 | 652.4 | 672.5 | 0.25 |
| CPK (U/L) | 329.7 | 358.8 | 280.2 | 0.05 |
| Vit D (ng/ml) | 22.9 | 22.8 | 23.07 | 0.28 |

**Table 8: Comparison of the laboratory test results between two groups, with and without neurological manifestations.**

WBC, white blood cell; LYM, lymphocyte; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelets; PTT, partial Thromboplastin Time; PT, prothrombin time; INR, international randomized ratio; BS, blood sugar; K, potassium; ESR, estimated sedimentation rate; AST, aspartate Aminotransferase; ALT, alanine Aminotransferase; LDH, lactate Dehydrogenase; CPK, creatine phosphokinase.

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# Article Information