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Neurological Symptoms, Comorbidities, and Complications of COVID-19: A Literature Review and Meta-Analysis of Observational Studies

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Keywords
Coronavirus disease 2019 · Neurological symptoms · Headache · Olfactory dysfunction · Gustatory dysfunction · Cerebrovascular disease

Abstract

\textbf{Background:} Recently, it has been shown that coronavirus disease 2019 (COVID-19), which has caused a pandemic since December 2019, can be accompanied by some neurological disorders. This study aimed to assess the prevalence of the most common neurological symptoms and comorbidities and systematically review the literature regarding the most prevalent neurological complications of COVID-19 infection.

\textbf{Methods:} All relevant studies had been collected from PubMed, Scopus, Embase, and Web of Science databases. All extracted data were analyzed using Stata version 11.2. The $I^2$ index was applied, and a random-effects model or a fixed-effects model was used for pooled estimation to assess the heterogeneity of studies. Furthermore, Egger and Beeg’s tests were used to evaluate the publication bias.

\textbf{Results:} Fifty-seven studies (26 observational and 31 case reports) were included (including 6,597 COVID-19 patients). The most prevalent general symptoms were fever, cough, and dyspnea with 84.6% (95% CI: 75.3–92.1; $I^2 = 98.7$%), 61.3% (95% CI: 55.3–67.0; $I^2 = 94.6$%), and 34.2% (95% CI: 25.6–43.4; $I^2 = 97.7$%), respectively. Neurological symptoms observed among COVID-19 patients were fatigue, gustatory dysfunction, anorexia, olfactory dysfunction, headache, dizziness, and nausea with 42.9% (95% CI: 36.7–49.3; $I^2 = 92.8$%), 35.4% (95% CI: 11.2–64.4; $I^2 = 99.2$%), 28.9% (95% CI: 19.9–38.8; $I^2 = 96.3$%), 25.3% (95% CI: 1.6–63.4; $I^2 = 99.6$%), 10.1% (95% CI: 2.7–21.0; $I^2 = 99.1$%), 6.7% (95% CI: 3.7–10.5; $I^2 = 87.5$%), and 5.9% (95% CI: 3.1–9.5; $I^2 = 94.5$%). The most prevalent neurological comorbidity in COVID-19 was cerebrovascular disease with 4.3% (95% CI: 2.7–6.3; $I^2 = 78.7$%).

\textbf{Conclusion:} The most prevalent neurological manifestations of COVID-19 include fatigue, gustatory dysfunction, anorexia, olfactory dysfunction, headache, dizziness, and nausea. Cerebrovascular disorders can either act as a risk factor for poorer prognosis in COVID-19 patients or occur as a critical complication in these patients. Guillain-Barre syndrome, encephalitis, and meningitis have also been reported as complications of COVID-19.

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Introduction

The novel coronavirus disease 2019 (COVID-19) outbreak had infected 6,663,304 cases and caused 392,802 deaths worldwide by June 6, 2020 [1]. As the responsible virus, coronavirus 2 (SARS-CoV-2) is a highly transmissible pathogen. The most prevalent symptoms of COVID-19 are respiratory failure, fever, and dry cough [2]. Although coronaviruses do not usually cause neurological diseases, several reports indicate that the new virus can cause direct or indirect central nervous system (CNS) infections [3–5]. Moreover, several reports have shown the possible involvements of the CNS [6–8] or peripheral nervous system (PNS) [9–11], and multiple studies have revealed the presence of some neurologic symptoms [12–14]. These symptoms can be categorized into several groups, including acute cerebrovascular disease, intracranial infection (such as headache, epilepsy, and consciousness impairment), PNS involvement (such as olfactory and gustatory impairment), and neuromuscular symptoms (fatigue, myalgia, muscle cramp, or increased muscle enzyme levels). Some patients may also experience sensory abnormalities, sphincter impairment, and neuralgia [15].

The structure of the viral capsid of SARS-CoV-2 involves a receptor-binding domain, which specifically recognizes the human angiotensin-converting enzyme-2 receptor [16]. ACE2, as an entrance key for SARS-COV-2, has an approximately ubiquitous expression in different human organs, including lung parenchyma, airway epithelia, nasal mucosa, gastrointestinal tract, urinary tract, reproductive organs, lymphoid tissues, vascular endothelia, and brain [17]. Under normal conditions, the ACE2 expression level in the brain is low; therefore, ACE2 alone does not seem enough to make brain cells susceptible to infection [18].

In a study conducted by Li et al. [19], potential neuroinvasion routes of SARS-CoV-2 were introduced based on data of previous respiratory viruses, with a neuroinvasive propensity and neurological symptoms of COVID-19. Two major anatomical infection routes are discovered through which SARS-CoV-2 can enter the CNS, a neural pathway through the PNS and a fluid body pathway through blood, lymph, and CSF.

1. Peripheral nerves route: contagion via droplets is almost the main transmission route of SARS-CoV-2 (close contact can also be considered an essential route of infection); therefore, the mechanism of olfactory loss and gustatory impairment may be clarified by investigating potential intranasal and oral routes of SARS-CoV-2 to enter the CNS. In this pathway, the virus enters a nerve terminal and replicates, and then finds its route back to the CNS retrogradely [19]. Besides, SARS-CoV-2 can adhere to the nasal mucosa and directly disturb olfactory sensory neurons and olfactory epithelium by pro-inflammatory cytokines [20].

2. Hematogenous route: in a hematogenous invasion, the viruses disturb the endothelial cells in the blood-brain barrier or the blood-cerebrospinal fluid barrier and then find their way toward the CNS. In a transgenic mouse model expressing human ACE2 infected by SARS-CoV, the olfactory nerve was the main neuroinvasion route for the virus; however, some infected sites were observed in their brain indirectly connected with the olfactory bulb. Consequently, non-neuronal routes of viral infection, such as the hematogenous route, were suggested [21].

3. Lymphatic drainage of the cerebrospinal fluid route: Pathological conditions, such as viral infections, can destroy the lymphatic drainage system of the brain [22], leading to brain edema and alterations in brain structure and function, and ultimately leading to viral overflow into the perivascular space and CSF. This phenomenon may result in CNS symptoms in critical COVID-19 patients [23].

Another relationship between neurologic diseases and COVID-19 is about neurologic diseases that can coexist with COVID-19 as an underlying condition. Initial reports have revealed that cerebrovascular disease might play a substantial role in infected patients. They proposed that comorbid cerebrovascular disease, as a clinical significance, can lead to a worse prognosis in COVID-19 patients [24]. The present study aimed to investigate the relationship between COVID-19 infection and neurologic diseases by reviewing the most recent articles conducted on neurologic manifestations in COVID-19 infection, neurologic comorbidities in COVID-19 patients, and neuroinvasion mechanisms of SARS-CoV-2. The related data are analyzed to get a more quantitative perspective on these topics.

Methods

Study Selection

A Web search was conducted in PubMed, Scopus, Embase, and Web of Science databases to find eligible studies (cross-sectional, case-control, and case report) published until 17 April 2020. Two of the authors conducted the search process independently to promote accuracy. Neurological symptoms, neurologic complications, and CNS-related comorbidities in COVID-19 patients were explored using search queries, including ([Neuro-) OR [brain]) AND (COVID-19), (Neurological symptoms)
AND (COVID-19), and (Neurological complications) AND (COVID-19). At first, eligible studies were selected based on article titles. Subsequently, the reference lists of all related reviews (narrative and systematic) were searched to find more related articles.

**Inclusion and Exclusion Criteria**

All relevant data about neurological symptoms, neurologic complications, and CNS-related comorbidities in COVID-19 were screened to include in the final analysis. Other exclusion criteria were non-human studies, systematic review and meta-analysis studies, non-English publications, and duplicate publications.

**Data Extraction**

All data, including general information about the study and research team (the name of the first author, date of publication, location of publication, sample size), demographic data about the subjects (age and gender), the prevalence of general symptoms (fever, cough, and dyspnea), neurological symptoms (headache, nausea, dizziness, fatigue, olfactory dysfunction, gustatory dysfunction, and anorexia), neurological complications (seizure, status epilepticus, Guillain-Barre syndrome [GBS], meningitis, and encephalitis), and CNS-related comorbidities (cerebrovascular disease and other nervous system diseases), were extracted from all included studies.

**Statistical Analysis**

The effect size was the prevalence of neurological symptoms and complications and CNS-related comorbidities; therefore, the variance was estimated using the binomial distribution. Furthermore, the average weight value was assigned to each study to combine the prevalence of various studies. The heterogeneity was assessed utilizing Q statistics and F index (α significance level was >10%). For heterogeneous studies, the random-effects model was applied when p was near 0 or meta prop command in STATA was used for the stability of variance and after the calculation of Freeman-Tukey Double Arcsine Transformation pool estimation for this proportion [25]. STATA version 11.2 was used for data analysis. Ethical approval was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics code: IR. SBMU.RETECH.REC.1399.082).

**Publication Bias**

Publication bias was graphically detected by the Funnel plot. This funnel plot is a scatter plot with 2 variates (x, y), evaluating the study effect size estimates against its sample size. A linear regression analysis, including both intercept and slope parameters, was conducted for publication bias. It was calculated based on the following equation:

\[ y_i = \alpha + \beta x_i + \varepsilon_i \]

\[ i = 1, \ldots, r \ (r = \text{the number of studies}), \ y_i = \text{standardized estimate}, \ x_i = \text{precision of studies}, \ \text{and} \ \varepsilon_i = \text{error terms}. \]

**Quality Assessment**

The Newcastle-Ottawa Scale was employed to evaluate the quality of each included study [26] utilizing 8 assessment items, including selection, comparability, and outcome, based on the Ottawa checklist for cross-sectional studies. Based on the Newcastle-Ottawa Scale score standards, studies can be divided into 3 groups, including high quality (scores ≥7), moderate quality (scores of 5–6), and low quality (scores of 0–4) the table is accessible in Appendix; see www.karger.com/doi/10.1159/000516258 for all online suppl. material).
Results

Study Selection
This study has been conducted based on the PRISMA checklist [27]. One hundred twenty-three studies were identified after the initial database exploration. Moreover, 26 more studies were obtained from other sources (mostly by investigating a reference list of identified studies). From these 149 studies, 18 studies were duplicated and were excluded. In the next step, 57 other articles were excluded after the abstract screening. Subsequently, the full-texts of 74 remaining articles were reviewed, in which 16 articles were excluded due to the lack of appropriate data. Finally, 58 articles published from February 2020 until April 2020, including 26 observational studies and 32 case reports, were included for final analysis (Fig. 1; Table 1).

Demographic Characteristics of Subjects
Pooled together, 6,597 COVID-19 confirmed patients were included in the present study. The mean age of patients was 54.2 (95% CI: 48.4–58.0; $I^2 = 99.7$%). Furthermore, 55% (95% CI: 50–60; $I^2 = 100.0$%) of the patients were male.

General Symptoms
The most prevalent general symptoms observed among COVID-19 patients were fever (4,093/5,991),
| Study [ref.] | Place | Patients, n | Mean age (SD) | General symptoms, % | Neurological symptoms, % | Comorbidities, % |
|---|---|---|---|---|---|---|
| | | All | male | female | fever | cough | dyspnea | fatigue | anorexia | olfactory | headache | dizziness | nausea | all nervous system diseases | cerebrovascular disease |
| Huang et al. [1] | China | 34 14 20 | 56.24 (17.14) | 94.1 50 | 14.7 | 64.7 | 5.9 |
| Yang et al. [2] | China | 52 35 17 | 59.7 (13.30) | 98 77 | 63.5 | 11.5 | 6 | 4 |
| Yang et al. [3] | China | 92 49 43 | 69.8 (14.50) | 92.6 26 | 2.4 | 73.2 | 31.7 | 9.8 | 2.4 | 3.7 | 4.5 |
| Wu et al. [4] | China | 201 128 73 | 93.5 81.1 | 39.8 | 32.3 |
| Mo et al. [5] | China | 155 86 69 | 81.3 | 62.6 | 2.4 | 73.2 | 31.7 | 9.8 | 2.4 | 3.7 | 4.5 |
| Mao et al. [6] | China | 214 87 127 | 52.7 (15.50) | 61.7 50 | 5.6 | 31.8 | 5.1 | 13.1 | 16.8 | 38.8 |
| Cao et al. [7] | China | 199 120 179 | 91.5 |
| Shi et al. [8] | China | 81 42 39 | 49.5 (11) | 73 59 | 42 |
| Wang et al. [9] | China | 18 | 10 | 8 | 94.4 | 55.6 | 22.2 |
| Liu et al. [10] | China | 109 | 59 | 50 | 82.6 | 61.5 |
| Du et al. [11] | China | 179 97 | 82 | 57.6 (13.70) | 98.9 | 81.6 | 49.7 | 39.7 |
| Du et al. [12] | China | 85 | 62 | 23 | 65.8 (14.20) | 91.8 | 22.4 | 70.6 |
| Guan et al. [13] | China | 1,099 | 637 | 459 | 43.8 | 67.8 |
| Wang et al. [14] | China | 138 | 75 | 63 | 98.6 | 59.4 |
| Giacomelli et al. [15] | Italy | 59 | 40 | 19 | 72.8 | 37.3 |
| Chen et al. [16] | China | 99 | 67 | 32 | 55.5 (13.10) | 83 | 82 |
| Lechien et al. [17] | Europe | 417 | 154 | 263 | 36.9 (11.40) | 45 | 79 |
| Yan et al. [18] | China | 193 | 114 | 79 | 89.6 | 69.9 |
| Qin et al. [19] | China | 452 | 235 | 217 | 92.6 | 33.3 |
| Sun et al. [20] | China | 55 | 31 | 24 | 81.8 | 47.3 |
| Beltrán-Corbellini et al. [21] | Spain | 79 | 48 | 31 | 61.6 (17.40) | 35.44 |
| Wang et al. [22] | China | 28 | 21 | 7 | 68.6 (9.00) | 92.9 | 82.1 |
| Chen et al. [23] | China | 274 | 171 | 103 | 91 | 68 |
| Lechien et al. [24] | Europe | 1,420 | 458 | 962 | 39.17 (12.09) | 45.4 | 63.2 |
| Huang et al. [25] | China | 202 | 116 | 86 | 77.2 | 59.4 |
| Zhang et al. [26] | China | 663 | 321 | 342 | 55.6 | 79.5 |

1 Huang Y, et al. Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: A retrospective single center analysis. Travel medicine and infectious disease. 2020. 2 Yang X, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020. 3 Yang F, et al. Analysis of 92 deceased patients with COVID-19. Journal of medical virology. 2020. 4 Shi H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine. 2020. 5 Mo P, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. JAMA internal medicine. 2020. 6 Mao L, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology. 2020. 7 Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. Clinical Microbiology and Infection. 2020. 8 Shi H, et al. Radiological findings of 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020. 9 Wang L, et al. The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. European Respiratory Journal. 2020. 10 Yang F, et al. Analysis of 92 deceased patients with COVID-19 pneumonia in Wuhan, China. Clinical Infectious Diseases. 2020. 11 Du Y, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. American journal of respiratory and critical care medicine. 2020. 12 Guan W-j, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020. 13 Lechien JR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. European Archives of Oto-Rhino-Laryngology. 2020. 14 Du R-H, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2, a prospective cohort study. European Respiratory Journal. 2020. 15 Lechien JR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a descriptive study. Lancet. 2020. 16 Du Y, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020. 17 Wu C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. Clinical Microbiology and Infection. 2020. 18 Yan Y, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Research and Care. 2020. 19 Qu C, et al. Disproportionate immune response in patients with COVID-19 in Wuhan, China. Clinical Infectious Diseases. 2020. 20 Sun L, et al. Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China. Journal of Medical Virology. 2020. 21 Beltrán-Corbellini Á, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre study. Journal of Medical Virology. 2020. 22 Wang F, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. Endocrine Practice. 2020. 23 Chen N, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020. 24 Du Y, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. American journal of respiratory and critical care medicine. 2020. 25 Guan W, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020. 26 Du Y, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020.
cough (3,582/5,792), and dyspnea (1,960/5,469) with 84.6% (95% CI: 75.3–92.1; $I^2 = 98.7$%), 61.3% (95% CI: 55.3–67.0; $I^2 = 94.6$%), and 34.2% (95% CI: 25.6–43.4; $I^2 = 97.7$%), respectively.

**Neurological Symptoms**

Neurological symptoms in COVID-19 patients were fatigue (1,583/3,919), gustatory dysfunction (1,158/2,189), anorexia (1,100/3,095), olfactory dysfunction (1,594/2,189), headache (1,379/5,482), dizziness (140/2,032), and nausea (467/4,941) with 42.9% (95% CI: 36.7–49.3; $I^2 = 94.6$%), and 34.2% (95% CI: 25.6–43.4; $I^2 = 97.7$%), respectively.

**Neurological Complications**

Neurological complications of COVID-19 have been mostly reported in the case report articles; therefore, the data were extracted from these articles and pooled together, as presented in Table 3.

**CNS-Related Comorbidities**

A great number of COVID-19 patients had comorbid conditions (1,070/2,913) 43.9% (95% CI: 35.1–53.1; $I^2 = 95.2$%). The prevalence of underlying nervous system disease among these patients was (21/1,720) 1.5% (95% CI: 0.3–3.6; $I^2 = 69.6$%), while the most prevalent neurolog-
cal comorbidity was cerebrovascular disease (101/3,107) 4.3% (95% CI: 2.7–6.3; $I^2 = 78.7\%$) (Fig. 9).

**Publication Bias**

Figure 10 demonstrates the Begg’s funnel plot for related studies. The plot interpretation revealed a sign of publication bias ($p = 0.03$), indicating that both negative and positive results have not been published (Fig. 10).

**Discussion**

COVID-19 has rapidly spread throughout the world [28]. A wide range of symptoms and signs of COVID-19, including fever, cough, dyspnea, fatigue, diarrhea, and vomiting, have been reported in previous studies. However, some COVID-19 patients are asymptomatic [29]. The incubation period of this disease is approximately between 2 and 11 days, and its mortality rate is about 2–4% [30, 31]. In this study, the calculated prevalence of the most common general symptoms of this disease, including fever, cough, and dyspnea, was 84.6% (95% CI: 75.3–92.1; $I^2 = 98.7\%$), 61.3% (95% CI: 55.3–67.0; $I^2 = 94.6\%$), and 34.2% (95% CI: 25.6–43.4; $I^2 = 97.7\%$), respectively, which is in good agreement with previous measures [32].

This disease can cause acute respiratory distress syndrome in severe cases, which can be a lethal condition. Other aspects of this disease, such as cardiovascular manifestations and renal complications, are being identified every day. Although most articles imply that COVID-19 mainly affects the respiratory and cardiovascular system, growing pieces of evidence are showing that neurological symptoms (such as fatigue, headache, dizziness,
hypogeusia/hyposmia, and impaired consciousness) and complications (such as [Meningo-]encephalopathy, cerebrovascular diseases, PNS disorders, and skeletal muscle injuries) [12, 33] are likely to occur in COVID-19 patients.

As mentioned before, coronaviruses are mostly known for upper respiratory tract infections; however, it has recently been observed that they can be correlated with inflammatory neurological diseases [34]. For this purpose, many animal studies have been conducted. Murray et al. [35] revealed that oligodendrocyte lysis and further demyelination in the CNS could occur during the acute phase in primate brains due to murine coronavirus replication. Besides, IL-1β, IL-6, and TNF-α levels increased in the spinal cord of infected subjects. Butler et al. [36] showed that intranasal infection with HCoV-OC43 could lead to retrograde dissemination of the virus and infect the brainstem and pyriform cortex. According to these findings, the risk of neural involvement by SARS-CoV-2 should not be overlooked.

Various neurotropic mechanisms, such as ACE2 receptor expression in neural tissue, are designated for COVID-19. Following previous reports, ACE2 receptors are expressed in both glial cells and neurons. On the other hand, SARS-CoV-2 has around 20-fold higher receptor affinity than ACE2 receptors than SARS-CoV [37], indi-

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**Fig. 5.** Forest plot of the prevalence of fatigue in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author’s names (based on a random-effects model). COVID-19, coronavirus disease 2019.
**Fig. 6.** Forest plot of the prevalence of gustatory dysfunction in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author’s names (based on a random-effects model). COVID-19, coronavirus disease 2019.

**Table 2.** Statistical analysis of reviewed studies

| Study                                      | Patients, n     | Prevalence, % (95% CI) | I², % | p value for heterogeneity |
|--------------------------------------------|-----------------|------------------------|------|--------------------------|
| Jerome R. Lechien (Europe)                 | 3,277/6,694     | 45 (40–50)             | 100  | 0.00                     |
| Ling Mao (China)                           | 3,417/6,694     | 55 (50–60)             | 100  | 0.00                     |
| Jerome R. Lechien (Europe)                 | 1,583/3,919     | 42.94 (36.70–49.29)    | 92.81| 0.00                     |
| A. Beltrán-Corbellini (Spain)              | 1,158/2,189     | 35.37 (11.22–67.04)    | 99.57| 0.00                     |
| Andrea Giacomelli (Italy)                  | 1,100/3,095     | 28.91 (19.92–38.79)    | 96.34| 0.00                     |
| Overall (I² = 99.22%, p = 0.00)            | 1,070/2,913     | 43.98 (35.06–53.11)    | 95.23| 0.00                     |

**Gender**

- Female: 26, 3,277/6,694, 45 (40–50), 100, 0.00
- Male: 26, 3,417/6,694, 55 (50–60), 100, 0.00

**General symptoms**

- Fever: 24, 4,093/5,991, 84.61 (75.31–92.07), 98.67, 0.00
- Cough: 23, 3,582/5,792, 61.26 (55.32–67.04), 94.57, 0.00
- Dyspnea: 20, 1,960/5,496, 34.18 (25.56–43.35), 97.70, 0.00

**Neurological symptoms**

- Fatigue: 16, 1,583/3,919, 42.94 (36.70–49.29), 92.81, 0.00
- Gustatory dysfunction: 5, 1,158/2,189, 35.37 (11.22–64.37), 99.22, 0.00
- Anorexia: 11, 1,100/3,095, 28.91 (19.92–38.79), 96.34, 0.00
- Olfactory dysfunction: 5, 1,594/2,189, 25.34 (15.8–63.41), 99.57, 0.00
- Headache: 19, 1,379/5,482, 10.07 (2.71–21.01), 99.14, 0.00
- Dizziness: 8, 140/2,032, 6.73 (3.72–10.50), 87.48, 0.00
- Nausea: 14, 467/4,941, 5.91 (3.12–9.45), 94.45, 0.00

**Comorbidities**

- Fatigue: 12, 1,070/2,913, 43.98 (35.06–53.11), 95.23, 0.00
- Nervous system diseases: 3, 21/1,720, 1.52 (0.25–3.62), 69.61, 0.00
- Cerebrovascular disease: 13, 101/3,107, 4.28 (2.65–6.25), 78.73, 0.00
cating a higher risk of neurologic infection in COVID-19 patients.

Mainly, SARS-COV-2 has 2 dissemination routes, through which it can infect the CNS: systemic circulation or ethmoid bone (i.e., olfactory nerve) [37]. When SARS-CoV-2 is present in general circulation, it can find its way through cerebral circulation, where slow blood flow through microcirculation can facilitate the interaction of its spike protein with ACE2 receptors on capillary endothelium. Subsequently, viral budding from the capillary endothelium and further endothelial disruption can support viral access to the brain [37]. This viral budding can also happen in neuronal tissues and cause neuronal damage without significant inflammation. It is also important to note that long before this neuronal damage occurs, the endothelial disruption in the capillaries of the brain can lead to bleeding within the cerebral tissue and cause critical consequences. Cribriform plate (near olfactory bulb) can be considered another entrance gate for SARS-CoV-2. Viral invasion through this pathway can be related to olfactory dysfunction observed among COVID-19 patients. As was evident, 25.3% (95% CI: 1.6–63.4; $I^2 = 99.6\%$) of patients represented different degrees of olfactory dysfunction from mild hyposmia to complete anosmia.

Gustatory dysfunction was also reported in 35.4% (95% CI: 11.2–63.4; $I^2 = 99.6\%$) of patients, which can be related to olfactory impairment or be directly related to the renin-angiotensin system (RAS). It has been revealed that RAS components (also ACE-2) are expressed in mouse taste organs [38]. In addition to the regulatory role of these components in the activity of taste organs, the presence of ACE-2 in these structures might explain gustatory dysfunction in COVID-19 patients [39].
Anorexia was also another symptom observed in 28.9% (95% CI: 19.9–38.8; \( I^2 = 96.3\% \)) of patients. This loss of appetite can have different reasons. As Kinnaird et al. [40] reported that altered taste sensitivity could disturb taste processing in anorexia nervosa, appetite loss can have different reasons, such as gustatory dysfunction. Alternatively, it can be a result of the immune responses of the patient. The role of a dysfunctional immune system has been proved in both COVID-19 and anorexia nervosa (AN) [41]. For example, patients with AN have significantly increased TNF-α, IL-1, IL-6, and TNF-receptor II levels, reducing the levels of C-reactive protein and IL-6 receptor. Increased levels of TNF-alpha and IL-6 have also been reported in COVID-19 [42]. Nevertheless, there is still more evidence needed to support this theory.

Moreover, headache was reported in 10.1% (95% CI: 2.7–21.0; \( I^2 = 99.1\% \)) of patients. According to initial reports, the intensity of headaches in the symptomatic COVID-19 patients was moderate to severe and new-onset (sudden to gradual). Their headache was bilateral with pulsating or pressing quality in the periorbital, forehead, or temporoparietal region [43]. The potential pathophysiological mechanisms that can lead to headache are direct activation of peripheral trigeminal nerve endings, increased pro-inflammatory cytokines in the cerebral circulation, vasculopathy, and hypoxia [43].

As one of the most common symptoms in many neurologic diseases [44], fatigue was reported in 42.9% (95% CI: 36.7–49.3; \( I^2 = 92.8\% \)) of COVID-19 patients. Fatigue can be considered a general symptom in most diseases; however, it must be taken more seriously in COVID-19 patients due to certain potential risks of neurologic involvement. Like many other respiratory infections, COVID-19 can lead to a state of malaise and severe acute fatigue [45]. Moreover, chronic fatigue can happen with a prevalence of about 10% (within 3 months) due to COVID-19 [46]. Studies on post-viral fatigue have revealed that the development of chronic fatigue can be predicted by blood levels of IL-6 and IL-10 in the acute phase of the disease [47]. These pro-inflammatory mediators (IL-6...
| Study [ref.] | Place | Patients, n | Gender (M/F) | Age, yr | General symptoms (yes/no) | Neurological symptoms (yes/no) | Neurological complications |
|--------------|-------|-------------|-------------|--------|----------------------------|------------------------------|---------------------------|
| Ye et al. [1] | China | 1           | M           | –      | Yes – Yes – Yes – Yes Yes Yes – – | Encephalitis |
| Duong et al. [2] | USA | 1           | F           | 41     | Yes – – – Yes – No – – | Meningoencephalitis without respiratory failure |
| Toscano et al. [3] | Italy | 5           | (1) – – Yes Yes – – – – – Yes | GBS |
|             |      |             | (2) – – Yes – – – – – – – | |
|             |      |             | (3) – – Yes Yes – – – – – – | |
|             |      |             | (4) – – – Yes – – – – Yes – Yes | |
|             |      |             | (5) – – – Yes Yes – – – – Yes Yes | |
| Gutiérrez-Ortiz et al. [4] | Spain | 2           | (1) M | 50     | Yes Yes – Yes Yes No – – – – | Miller Fisher syndrome and polyneuritis cranialis |
|             |      |             | (2) F | 39     | Yes No No No – – – – – | GBS |
| Zhao et al. [5] | China | 1           | F | 61     | No No – – Yes – – – | GBS |
| Sedaghat et al. [6] | Iran | 1           | M | 65     | Yes Yes Yes – – – – – | GBS |
| Poyiadji et al. [7] | USA | 1           | F | –     | Yes Yes – – – – Yes – – | ANE |
| Moriguchi et al. [8] | Japan | 1           | M | 24     | Yes – – Yes Yes – – – | Meningitis/encephalitis |
| Balloy et al. [9] | France | 1           | M | 59     | Yes Yes Yes Yes – – – – | Nonlesional status epilepticus |
| Coen et al. [10] | Switzerland | 1           | M | 70     | – Yes – – Yes – – – | GBS |
| Kaya et al. [11] | Turkey | 1           | M | 38     | Yes – Yes – – No – – | Transient cortical blindness (a PRES-like syndrome) |
| Viguier et al. [12] | France | 1           | M | 66     | Yes Yes Yes – – Yes – – | Acute ischemic stroke complicating common carotid artery thrombosis |
| Mermelstein [13] | Brazil | 1           | F | 27     | No Yes Yes Yes Yes Yes – | Acute anosmia |
| Sachs et al. [14] | USA | 1           | M | 59     | Yes – Yes – – – – – | Leukoencephalopathy |
| Padroni et al. [15] | Italy | 1           | F | 70     | Yes Yes – – – – – – | GBS |
### Table 3 (continued)

| Study [ref.]        | Place     | Patients, n (M/F) | Gender (M/F) | Age, yr | General symptoms (yes/no) | Neurological symptoms (yes/no) | Neurological complications                                      |
|---------------------|-----------|-------------------|--------------|---------|----------------------------|-------------------------------|------------------------------------------------------------------|
| Dinkin et al. [16]  | USA       | 2 (1) M           | Yes Yes      | 36      | No                         | Yes                          | Ophthalmoparesis                                                 |
|                     |           | (2) F             | Yes Yes      | 71      | Yes                        | No                           |                                                                  |
| Pfefferkorn et al.  | Germany   | 1 M              | Yes Yes      | 51      | No                         | Yes                          | Acute polyradiculoneuritis with locked-in syndrome               |
| Zanin et al. [18]   | Italy     | 1 F              | 54           | No Yes  | –                          | Yes                          | Demyelinating lesions in the brain and spine                   |
| Ottaviani et al.    | Italy     | 1 F              | 66           | Yes Yes | –                          | No                           | Early GBS                                                       |
| Kong et al. [20]    | China     | 1 F              | 53           | No No   | –                          | No                           | Dizziness                                                       |
| Wong et al. [21]    | UK        | 1 M              | Yes Yes Yes  | 40      | Yes Yes                    | Yes                          | Rhombencephalitis                                                |
| Filatov et al. [22] | USA       | 1 M              | Yes Yes      | 74      | Yes                        | Yes                          | Encephalopathy                                                   |
| Alberti et al. [23] | Italy     | 1 M              | Yes – – – –  | 71      | –                          | –                            | GBS                                                             |
| Bernard-Valnet et al.| Switzerland| 2 (1) F           | No Yes       | 64      | Yes                        | Yes                          | Acute meningoencephalitis                                       |
|                     |           | (2) F            | Yes Yes      | 67      | Yes Yes                    | Yes                          |                                                                  |
| Scheidl et al. [25] | Germany   | 1 F              | No No No    | 54      | Yes Yes Yes –              | Yes                          | GBS                                                             |
| Avula et al. [26]   | USA       | 4 (1) M           | Yes Yes      | 73      | Yes                        | Yes                          | Stroke                                                          |
|                     |           | (2) F            | Yes – – – – | 83      | Yes                        | Yes                          |                                                                  |
|                     |           | (3) F            | No No No    | 80      | –                          | –                            |                                                                  |
|                     |           | (4) F            | – – – –     | 88      | –                          | –                            |                                                                  |
| Goldberg et al. [27]| USA       | 1 M              | Yes Yes      | 64      | No                         | Yes                          | Cerebrovascular disease                                          |
| El Ottmani et al.   | Morocco   | 1 –              | No Yes No    | 70      | No                         | No                           | GBS                                                             |
| Huang et al. [29]   | USA       | 1 F              | Yes – – – – | 40      | –                          | –                            | Encephalitis                                                     |
| Sohal et al. [30]   | USA       | 1 M              | Yes – – Yes | 72      | –                          | Yes                          | Seizures                                                        |

*Note: The table continues with more entries.*
Table 3 (continued)

| Study [ref.] | Place | Patients, n Gender (M/F) | Age (yr) | General symptoms (yes/no) | Neurological symptoms (yes/no) | Neurological complications |
|--------------|-------|--------------------------|----------|---------------------------|-------------------------------|--------------------------|
| Muhammad et al. [31] | Germany | 1 F | 60 | – | – | – | – | Severe brain hemorrhage |
| Zoghi et al. [32] | Iran | 1 M | 21 | Yes | Yes | – | No | Demyelinating event of the CNS |

ANE, acute hemorrhagic necrotizing encephalopathy; CNS, central nervous system; GBS, Guillain-Barré syndrome; COVID-19, coronavirus disease 2019; ANE, acute hemorrhagic necrotizing encephalopathy; CT and MRI features. 1 Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain, behavior, and immunity*. 2020. 2 Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain, behavior, and immunity*. 2020. 3 Toscano G, et al. Guillain-Barré syndrome associated with SARS-CoV-2. *New England Journal of Medicine*. 2020. 4 Gutiérrez-Ortiz C, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020. 5 Zhao H, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *The Lancet Neurology*. 2020;19(5):383–384. 6 Sedaghat Z, Karimi N. Guillain Barré syndrome associated with COVID-19 infection: A case report. *Journal of Clinical Neuroscience*. 2020. 7 Poyiadji N, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy; CT and MRI features. *Radiology*. 2020;201187. 8 Moriguchi T, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*. 2020. 9 Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain, behavior, and immunity*. 2020. 10 Coen M, et al. Guillain-Barré syndrome as a complication of SARS-CoV-2 infection. *Brain, behavior, and immunity*. 2020. 11 Kaya Y, et al.Transient cortical blindness in COVID-19 pneumonia; a PRES-like syndrome: Case report. *Journal of the Neurological Sciences*. 2020;413:116858. 12 Viguier A, et al. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *Journal of neuroradiology*. 2020. 13 Mermelstein S. Acute anosmia from COVID-19 infection. *Clinical Neurophysiology*. 2020. 14 Dinkin M, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsies. *Neurology*. 2020. 15 Pfefferkorn T, et al. Acute polyradiculoneuritis with locked-in syndrome in a patient with Covid-19. *Journal of the Peripheral Nervous System*. 2020;1. 16 Dinkin M, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsies. *Neurology*. 2020. 17 Pfefferkorn T, et al. Acute polyradiculoneuritis with locked-in syndrome in a patient with Covid-19. *Journal of the Peripheral Nervous System*. 2020;1. 18 Zanin L, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochirurgica*. 2020;1–4. 19 Ottaviani D, et al. Early Guillain-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital. *Neurological Sciences*. 2020. 20 Kong Z, et al. 2019 novel coronavirus pneumonia with onset of dizziness: a case report. *Annals of Translational Medicine*. 2020;8(7). 21 Wong PF, et al. Lessons of the month 1: A case of rhombencephalitis as a rare complication of acute COVID-19 infection. *Clinical Medicine*. 2020;20(3):293–294. 22 Filatov A, et al. Neurological complications of coronavirus disease (COVID-19): encephalopathy. *Cureus*. 2020;12(3). 23 Alberti P, et al. Guillain-Barré syndrome related to COVID-19 infection. *Neurology-Neuromyelitis Neuromyelitis*. 2020;7(4). 24 Bernard-Valnet R, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. *European Journal of Neurology*. 2020. 25 Scheidt E, et al. Guillain-Barré syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. *Journal of the Peripheral Nervous System*. 2020. 26 Avula A, et al. COVID-19 presenting as stroke. *Brain, behavior, and immunity*. 2020. 27 Goldberg MF, et al. Cerebrovascular Disease in COVID-19. *American Journal of Neuroradiology*. 2020. 28 El Otmani H, et al. Covid-19 and Guillain-Barré syndrome: More than a coincidence! *Revue neurologique*. 2020. 29 Huang YH, Jiang D, Huang JT. SARS-CoV-2 Detected in Cerebrospinal Fluid by PCR in a Case of COVID-19 Encephalitis. *Brain Behav Immun*. 2020;87:149. 30 Sohal S, Mossammat M. COVID-19 Presenting with Seizures. *IDCases*. 2020;e00782. 31 Muhammad S, et al. Letter to editor: Severe brain haemorrhage and concomitant COVID-19 infection: A neurovascular complication of COVID-19. *Brain, Behavior, and Immunity*. 2020. 32 Zoghi A, et al. A case of possible atypical demyelinating event of the central nervous system following COVID-19. *Multiple sclerosis and related disorders*. 2020;102324.
and IL-10) are present in the cytokine that occurs in severe cases of COVID-19 and suggests an immunologic pattern for this chronic fatigue [48]. Dizziness 6.7% (95% CI: 3.7–10.5; $I^2 = 87.5\%$) and nausea 5.9% (95% CI: 3.1–9.5; $I^2 = 94.5\%$) have also been reported in COVID-19 patients. These symptoms can also predict neurological involvement in COVID-19 patients, as they are common symptoms of encephalitis [49].

As the most prevalent neurological comorbidity in COVID-19, the cerebrovascular disease with 4.3% (95% CI: 2.7–6.3; $I^2 = 78.7\%$) can put COVID-19 patients at significant risk. Cerebrovascular manifestations can also occur in patients as a result of COVID-19. This phenomenon can have different causes [24], including (1) ACE2 expression within venous and arterial tissues of the brain can make these structure susceptible for SARS-CoV-2 in-
vasion [50], (2) cardiac arrhythmia as a result of COVID-19 can lead to cardio-embolism formation [13], (3) coagulation impairments as a result of COVID-19 can predispose to thromboembolic events [51], (4) preexisting cerebrovascular disorder can lead to intracranial stenosis (and hypo-perfused brain areas), which can increase the risk of ischemic stroke after COVID-19 severe infection [51].

Based on the case reports, the most critical COVID-related neurological complications were cerebrovascular diseases, encephalopathy, GBS, and seizure. As observed, the critical patients had more propensity to develop cerebrovascular diseases; their D-dimer levels were also higher than nonsevere patients. This can somehow justify the higher rate of cerebrovascular diseases in these patients [52]. In addition to this elevated level of d-dimer, intracranial cytokine storm has been found guilty in the pathophysiology of stroke/cerebrovascular disease [53]. Seizures were also reported in some cases. It has been hypothesized that this epileptic event can happen due to decreased seizure threshold caused by cytokine storm [54]. It seems unlikely that this virus can cause seizures directly. Patients with prolonged presence in ICU had a higher rate of encephalopathic complications than usually expected. Previous studies stated that this issue could be caused by prolonged administration of high doses of sedatives and anesthetics (to manage severe respiratory disease) [52]. It has also been reported that viremia and hypoxia can exacerbate these encephalopathic situations in COVID-19 patients [31]. GBS (alongside another inflammatory demyelinating polyneuropathy, like Miller Fisher syndrome) has also been reported in multiple cases of COVID-19. The pathophysiology of this phenomenon might be secondary to the neuroinvasive nature of SARS-CoV-2 and its ability to precipitate the demyelination process [55]. This peripheral demyelination can also be triggered by aberrant immune responses caused by viral infection-related inflammatory environments [56]. Finally, it should be noted that all of the scenarios described lately are hypotheses and require further studies to be confirmed.

Conclusions

The neuroinvasive propensity of SARS-CoV-2 has been reported in previous studies. This neuroinvasion can be associated with different neurologic symptoms, directly or indirectly. The most prevalent neurologic manifestations of COVID-19 are fatigue, gustatory dysfunction, anorexia, olfactory dysfunction, headache, dizziness, and nausea. Cerebrovascular disorders can either be a risk factor for poorer prognosis in COVID-19 patients or occur as a critical complication in these patients. Although neurologic complications had not been reported in any observational study yet, GBS, encephalitis, and meningitis have been introduced as complications of COVID-19 in multiple case reports.

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Statement of Ethics

This study was conducted under the approval of Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics code: IR.SBMU.RETECH.REC.1399.082).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.V. and M.F. conceived of the presented idea, searched electronic databases, and collected the data. K.V. wrote the manuscript. F.S. performed the computation and analytical methods. M.H. and M.R supervised the findings of this work. A.T., M.S., M.H., and D.S. critically revised the manuscript. All authors discussed the results and contributed to the final manuscript.

Availability of Data and Material

All data analyzed or generated during this study are included in published articles available in Tables 1 and 3.
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