

Neurological Manifestation of COVID-19: An Updated Literature Review

Sohaib Eltayeb, and Nathalia Peixoto, PhD
Bioengineering Department
George Mason University
Fairfax, Virginia

ORCID: <https://orcid.org/0000-0003-2282-4599>

ABSTRACT

SARS-CoV-2, which causes the disease known as Coronavirus Disease 2019 (COVID-19), is a novel coronavirus that arose in Wuhan, China in 2019. Within a short time, it rapidly spread across the world and has been declared a global pandemic by the World Health Organization (WHO) due to its severe morbidity and mortality rate. This virus left many scientists and biomedical engineers perplexed due to the various uncertainties about its infection rate as new COVID-19 variants arise. However, attempts to contain the virus are ongoing all over the world. Some of the most common symptoms of COVID-19 include fever, dry cough, and fatigue. However, some physicians in affected areas have discovered that some patients that were diagnosed with COVID-19 did not exhibit these expected respiratory symptoms at the time of diagnosis, but rather these patients displayed only neurological symptoms as their initial symptoms. For instance, the symptoms range from non-specific to more particular, such as headaches or dizziness which were one of the more common symptoms, to more complicated symptom onset such as convulsions, cerebrovascular and peripheral diseases.

Keywords: COVID-19, Pandemic, Neurological Manifestations, Neurological Complications Central Nervous System

INTRODUCTION

In December 2019, the Novel Coronavirus disease 2019 (COVID-19) epidemic began in Wuhan [1],[2]. Initially, all of the cases were linked to the Huanan wholesale seafood market. On March 11, 2020, the World Health Organization (WHO) designated it a worldwide pandemic [3],[4]. As of March 25, 2022, there have been more than 478.8 million confirmed cases of COVID-19 worldwide, where over 6.1 million deaths have been recorded with the United States seeming to be the leading country with over 43 million cases reported [5]. COVID-19 is one of the most common viruses that predominantly affects the respiratory system, but it also has neuroinvasive capabilities and may spread from the respiratory system to the central nervous system (CNS) [6].

In most cases, the symptoms of COVID-19 generally manifest after a five-day incubation period. For instance, fever, cough, and exhaustion are the most prevalent symptoms of COVID-19; additional common symptoms that were reported include headache, hemoptysis, and

dyspnea, among others. Patients may develop pneumonia, acute respiratory distress syndrome, abrupt heart difficulties, and multi - organ failure in the most severe situations [6][7]. Only a few cases of cranial neuropathies have been linked to COVID-19 pneumonia. A case of acute oculomotor nerve palsy in a 62-year-old severely ill patient was first described by Wei et al. [51]. In SARS-CoV-2-infected patients with ophthalmoparesis, only a few cases of abducens nerve palsy have been reported [52]. Even though COVID-19 is noted to primarily affect the respiratory and cardiovascular systems, other neurological symptoms such as headache, hypogeusia, stroke, seizure, and neuralgia have been observed as well as other manifestations such as encephalopathy, acute cerebrovascular diseases, impaired consciousness, and skeletal muscular injury are common observed in COVID-19 patients [1],[8],[9]. The way COVID-19 can enter the brain can be directly or indirectly through different pathways. For instance, the virus can directly infect the nervous system via the olfactory nerve, blood circulation, ACE2 in the brainstem, immunological damage, and neuronal pathways, causing neurological problems. The enteric nervous system (ENS) and sympathetic afferent neurons can also be used by COVID-19 infection in the gastrointestinal tract to reach the Central Nervous System (CNS) as seen in the figure below [10],[11].

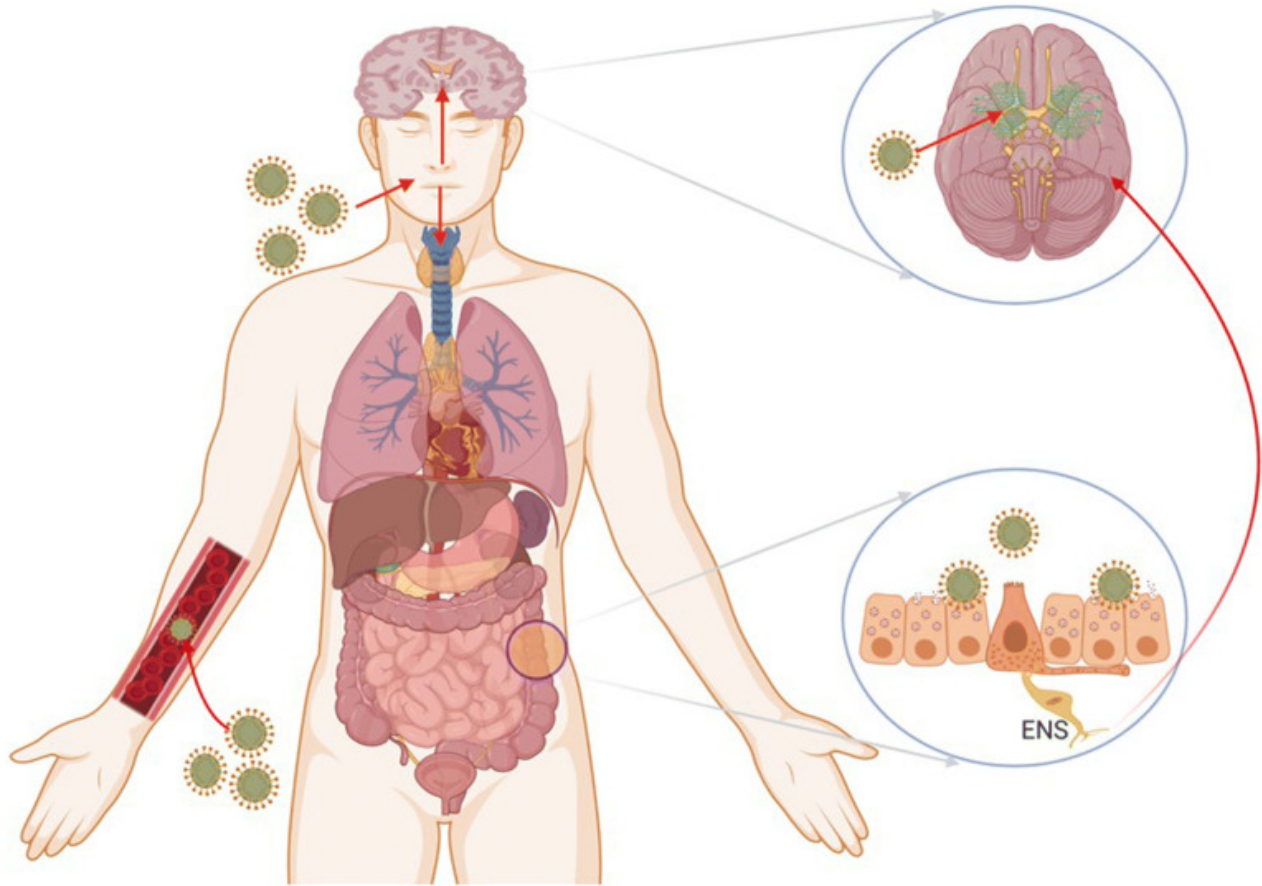


Figure 1. Illustrations of the direct and indirect pathways that SARS-CoV-2 enter the nervous system. (P.G) [10]

The most common reported symptoms in patients with CNS manifestations were dizziness and headache, whereas the most common reported symptoms in patients with Peripheral Nervous System (PNS) symptoms were taste impairment and smell impairment [11]. After the virus infects the nasal cells, it can directly invade the brain, presumably via the olfactory bulbs, and quickly spread to specific brain locations such as the thalamus and brainstem, producing inflammation and demyelinating reactions. It was mentioned that a viral infection might invade the nasal passage, disrupting smell and taste sensations. According to increasing data, COVID-19 may also infiltrate the CNS via a synapse-connected pathway after infiltrating the respiratory network's peripheral nerve terminals [10, 46].

METHODS

This review was conducted through online relevant studies and reviews that were mostly found on PubMed, Google Scholar, GMU library as well as medRxiv and bioRxiv. In order to find possibly related papers, different search strategies were taken to search the bibliographies of the obtained references below. For instance, articles that were published within one year of April 2020 were examined and other articles that were before 2018 were filtered out. Also, different keywords such as SARS-CoV-2, Covid-19, Neurological manifestations or complication, and other relevant words were used to maximize the finding output of literature review.

In general only a few articles regarding COVID-19's neurological involvement using the search method were found. Some of these articles were solely a narrative review, while the others were literature reviews. Moreover, on the relevant articles that were collected and had useful information, a thorough search on the reference lists of these papers was done and other relevant references were found and collected for further review. For instance, one interesting study that was looked at was the neurological signs of COVID-19 and on that paper it was mentioned that about 25 percent of the individuals had CNS abnormalities that were said to be related to COVID-19 [6,18]. However, the majority of other papers that were looked into mentioned only COVID-19's symptoms and general common neurological manifestations.

After reading the abstract and scanning through the articles found, specific studies were chosen according to some criterias. Editorials, commentary, and narrative reviews with no reports on case outcomes or proposed treatments methods were excluded from the review, but if they had reported any neurological manifestation in relation to COVID-19, then they would be chosen. Also if a paper is reporting on many aspects of COVID-19 and neural aspects, then the results have been shared and saved for different parts of the review.

RESULTS

The most common symptom observed in COVID-19 patients is respiratory distress which was reported by Huang et al. About 55% of patients had respiratory disturbance [19]. In additions, are three types of neurological findings: central nervous system manifestations (headaches dizziness, impaired consciousness, acute cerebrovascular illness, and seizures),

peripheral nervous system manifestation (hypogeusia, hyposmia), and skeletal muscle manifestations (hypogeusia, hyposmia) [21, 22].

CNS MANIFESTATIONS

SARS-CoV-2 is primarily a respiratory virus that mostly spreads through the air and affects the respiratory system as a result, however it was discovered that it can potentially infect the brain in many ways. Numerous studies show that SARS-CoV-2 has been reported to localize in the brain and Cerebrospinal fluid (CSF) of infected individuals [23, 25], signifying a pathogenic impact on the CNS. It can also have an indirect effect on the CNS through immunological and inflammatory pathways. Headache, dizziness, encephalopathy, acute myelitis, cerebrovascular accident, and encephalitis are all other major CNS symptoms [24, 25]. As there is no specific treatment for headaches caused by SARS-CoV-2 infection, pain management is essential. Pain is also linked to myalgia and peripheral neuropathies in COVID-19 patients. COVID-19 patients are resuscitated using high-dose intravenous opioid infusions for an extended period due to a lack of nursing and physiotherapy [50]. In COVID-19 patients with peripheral neuropathies, gabapentinoids like gabapentin and pregabalin may be required for pain management [50]. The most frequent CNS signs in COVID-19 patients are dizziness and headache, followed by encephalopathy [24, 25]. In adult and senior COVID-19 patients, encephalopathy has been identified as the leading cause of morbidity and death, regardless of the degree of respiratory problems [25, 26].

In COVID-19 patients, altered sensorium has been linked to an increased risk of death [25, 27]. COVID-19 has been shown to promote the inflammatory response, which leads to hypoxic and metabolic alterations [25, 59]. The hypoxic and metabolic insult causes a cytokine storm, which is thought to be the primary cause of encephalopathy in COVID-19 patients [25, 27]. According to a study done by Umapathi, et al. demonstrated three COVID-19 patients who acquired acute encephalopathy during the disease phase, and one patient died after three months [28]. Encephalopathy is one of the most prevalent CNS signs in COVID-19 patients, according to several other studies as well [29]. It was also stated in a new study done by Delamarre et al. which shows that SARS-CoV-2 can also cause acute hemorrhagic necrotizing encephalopathy [25, 30].

COVID-19-associated encephalopathy, on the other hand, is not limited to just the elderly. A study that was done by Kinikar et al. described a case of COVID-19-provoked acute encephalopathy in an 11-year-old boy who had abnormal sensorium and seizures in a case report [31]. A severe encephalopathy was also reported in COVID-19-positive children in other studies that are attached to this report [32, 33]. Clinical characteristics of COVID-19-manifested encephalopathy include altered awareness, anxiety, delirium, and profound coma were also noted [34, 25]. Another study that was done by Kihira et al. discussed different imaging results of COVID-19 patients such as leukoencephalopathy, reduced diffusion of both gray and white matter, microhemorrhages, and leptomeningitis [35,44]. Encephalitis is another CNS manifestation in COVID-19 patients of various ages, according to new findings [36]. The presence of SARS-CoV-2-specific RNA in the CSF of a patient with COVID-19-associated encephalitis confirmed the virus's direct pathogenic role in the development of encephalitis.

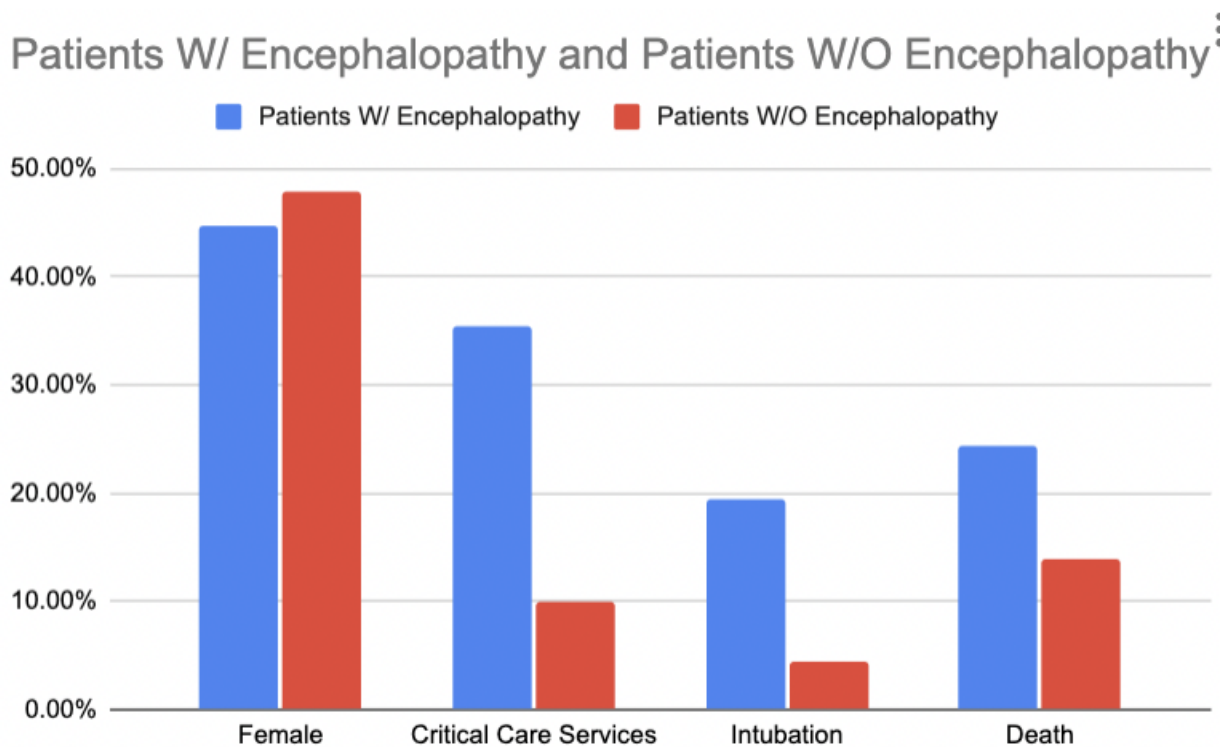


Figure 2. A Histogram illustrating the Percentage of Patients with and without Encephalopathy in a Study Done by Vishank et al. [44]

PNS MANIFESTATIONS

COVID-19 also causes PNS symptoms that are however less severe in comparison to CNS, such as chemosensory dysfunctions, muscular pain, and Guillain-Barré syndrome (GBS) [37]. The most common chemosensory dysfunctions found in SARS-CoV-2-infected individuals are hyposmia, anosmia and hypogeusia and ageusia, which account for 5–98 percents of cases, depending on the country the research, and methods involved [34]. These olfactory and gustatory abnormalities were usually observed in asymptomatic people or as the first stage of SARS-CoV-2 infection [25, 38]. Hyposmia and anosmia as well as hypogeusia and ageusia on the other hand are both common symptoms of SARS-CoV-2 infection in mild-moderate cases; however, hyposmia and anosmia is more severe than hypogeusia and ageusia [25, 34]. According to statistics from Iran, Europe, and the United States, 64.5 percent and 54.0 percent of COVID-19 patients, respectively, had smell and taste disruptions before the onset of the other common disease symptoms [25, 39].

A study by Moein et al. demonstrated 60 COVID-19 positive patients at Masih Daneshvari Hospital in Iran were given a smell identification test by the University of Pennsylvania, and 98 percent of them had smell loss that was said linked to the complication of COVID-19. On that study these patient were said to be diagnosed as anosmic which was about 25% of the patients, severely microsmic about 33% of patients, moderately microsmic 27% of patients, light microsmic 13% of patients, and lastly normosmic was 2 % of patients [40] and this data is better seen in figure 3. A different investigation that was done by Yan et al. included 262 ambulatory patients with influenza-like symptoms, with 59 of them being diagnosed with COVID-19 [25, 41]. In comparison to COVID-19-negative patients, SARS-CoV-2-infected individuals are more prone to hyposmia and anosmia which was said to be roughly about 68 percent vs. 16 percent and hypogeusia and ageusia around 71 percent vs. 17 percent [25, 41].

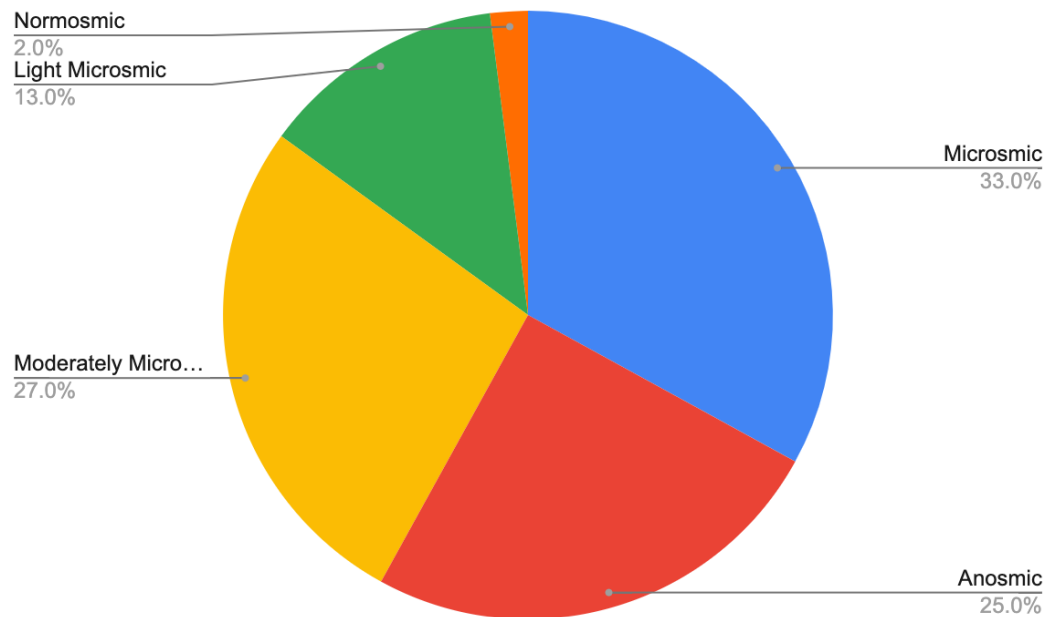


Figure 3. A graph illustrating the results of the smell identification test done by University of Pennsylvania.

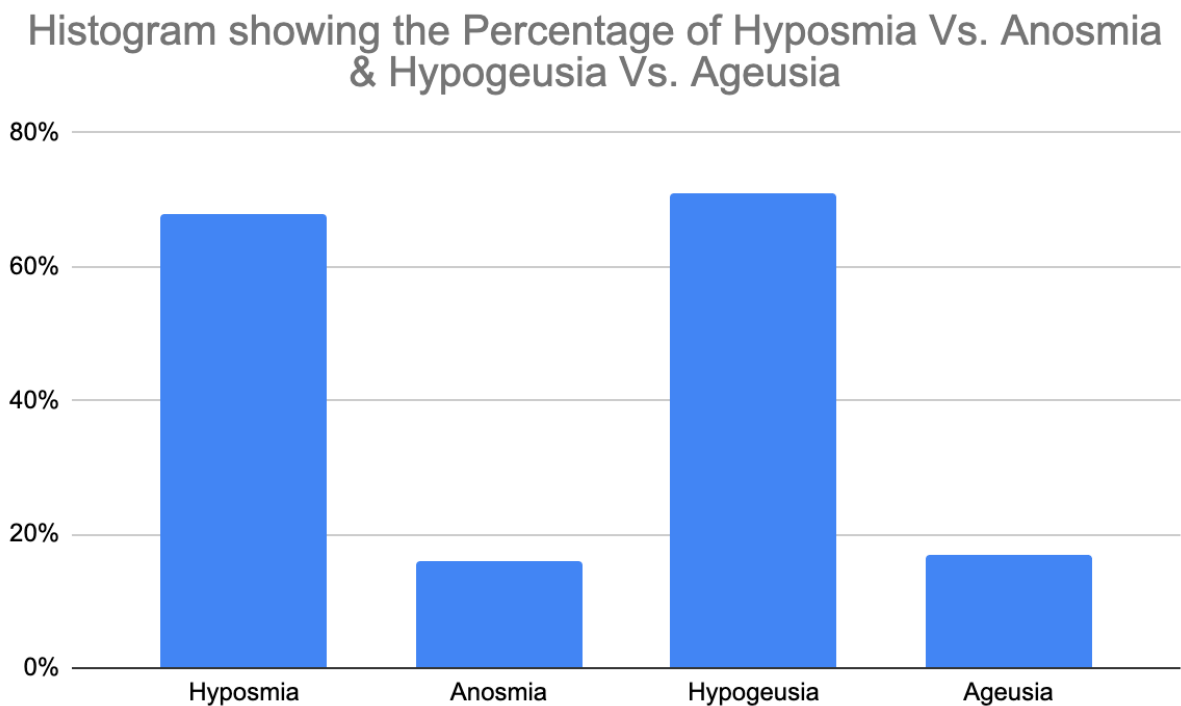


Figure 4. A Histogram illustrating the Percentage of Hyposmia vs. Anosmia and Hypogeusia vs. Ageusia obtained from the study done by Yan et al.

SKELETAL MUSCLE MANIFESTATIONS

According to Mao et al. when a patient had skeletal muscular pain and a blood creatine kinase level more than 200 u/L, it was considered skeletal muscle damage. According to a study they conducted their findings showed that muscular ache also known as myalgia, muscle soreness, and fatigue are all common symptoms among COVID-19 patients, where they stated that the frequencies of muscular damage in severely and moderately sick COVID-19 patients, respectively, were 19.3 percent and 4.8 percent [48]. In the same review Mao et al. stated that in an experiment that had a total of 214 hospitalized patients with proven SARS-CoV-2 infection were included in the study, with roughly 23 individuals suffering from skeletal muscle injuries (10.7 percent). [8, 25]. Myalgia might be the first symptom in 36% of COVID-19 patients, according to a different study that was done by Lippi et al. [49, 42]. Zhu et al. discovered that 33 percent of COVID-19 patients had muscular pain in a meta-analysis encompassing 38 studies that covered 3062 COVID-19 patients [2, 25]. Cao et al found that 35.5 percent of 46,959 COVID-19 patients (in 31 trials) had muscular pain and fatigue in another meta-analysis [25, 44]. In addition to CNS, PNS, and skeletal muscle Manifestations discussed above, and other major manifestations were also noted in other studies.

A study that was done in *Harvard Medical School* shows that among patients who visit their cognitive clinic, an estimate of about 22 percent to 32 percent of COVID-19 patients who completely recovered still seem to suffer from brain fog as a result of their extended COVID, or post-acute sequelae of SARS CoV-2 infection (PASC), as specialists refer to it. Fong et al. also described brain fog in this study as a slow or sluggish thinking that can occur in a variety of situations, such as when someone is sleep deprived or sick, or as a side effect of drowsiness-caused by medications. Or in many cases following chemotherapy or a concussion, brain fog can also be developed [18]. In addition, a study that was published on PubMed Central had a study on the COVID-19 proportion which included 22,063 women (55 percent) and 18,364 men (45 percent). A large majority of these patients, 19,709 (48.7%), were between the ages of 18 and 50, while a small but significant group of patients, 3830 (9.5%), were over the age of 80.

The racial breakdown was 15,113 Caucasians (37%), 8,350 African Americans (21%), 797 Asians (2%), and 16,000 people of unknown race (40%). Overall, 30,589 people (76%) lived in the United States (US), while 9,880 people (24%) did not. Within the United States, the Northeast had 8,951 (22 percent), the Midwest had 7,375 (18 percent), the South had 7,228 (18 percent), and the West had 7,035 (17 percent) (figure 5). Patients from both outpatient (73.7%) and inpatient (10.63%) settings were included in the COVID-19 population study [47].

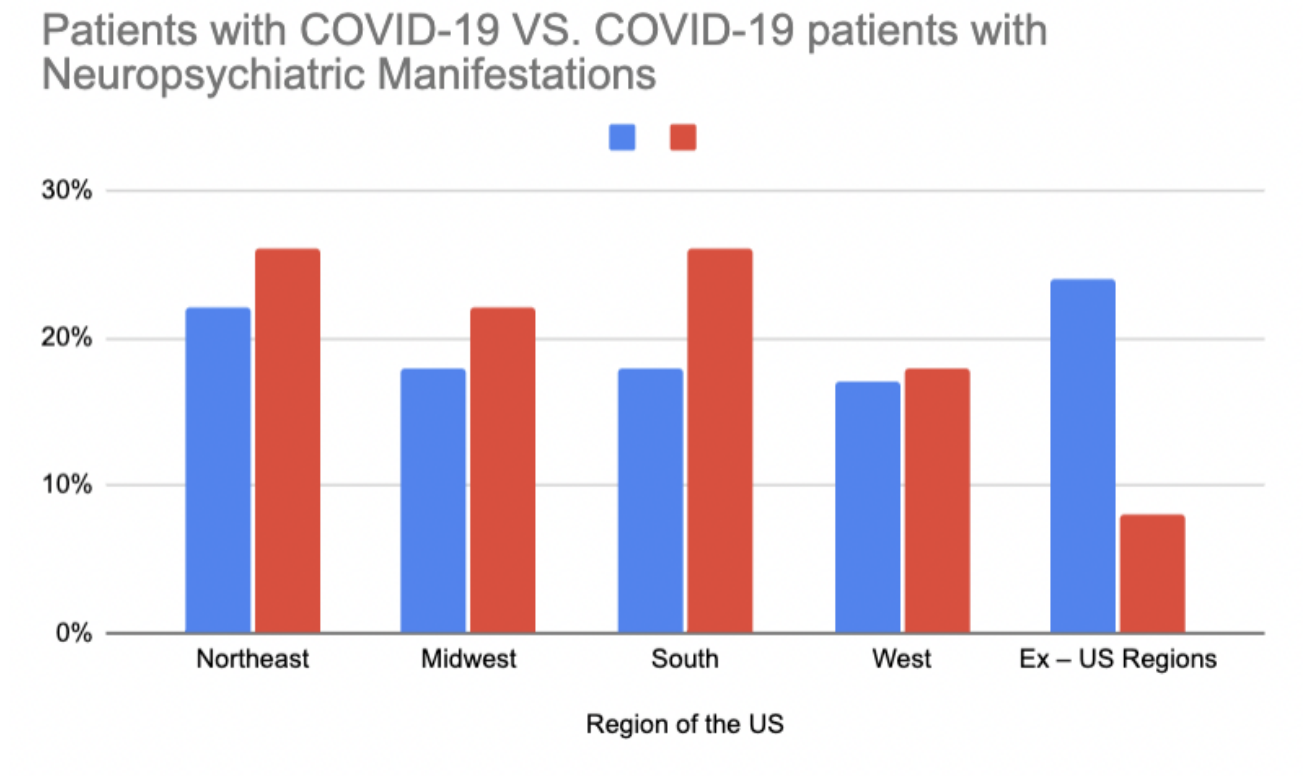


Figure 5. A Histogram illustrating the Percentage of COVID-19 Patients vs. COVID-19 patients with Neuropsychiatric Manifestations.

CONCLUSION

SARS-CoV-2 can infect the brain system, skeletal muscle system, and respiratory tract. Neurologic involvement is more common in patients with a severe infection, including acute cerebrovascular disorders, reduced consciousness, and skeletal muscle damage. Patients' clinical conditions may deteriorate, and they may die sooner. This research might provide critical new clinical information on COVID-19, allowing doctors to better understand its role in neurologic symptoms. It's especially interesting to note that quick clinical deterioration or worsening in people with severe COVID-19 might be linked to a neurologic catastrophe like stroke, which would add to the pandemic's high death rate [17].

COVID-19's specific neurotoxic mechanism is yet to be discovered, although a significant body of clinical and experimental evidence suggests that neuroinvasion, endothelial dysfunction, neuroinflammation, immune-pathogenicity, and hypoxemia may all play a role in the development of these CNS symptoms. Existing neurodegenerative or inflammation-mediated neurological conditions may enhance the likelihood of neurologic symptoms in COVID-19 patients, although the exact link and post-infective impact have yet to be discovered. COVID-19 patients' neurological complications are not limited to acute consequences; they can also have a long-term influence on the nervous system. Despite the fact that neurologic manifestation is linked to the severity of the disease and the existence of comorbidities, it may also emerge in individuals before COVID-19 pneumonic and respiratory symptoms. As a result, neurologic patients, as well as COVID-19 individuals without neurologic symptoms, require specific monitoring. COVID-19 patients may also be given preventive treatment to prevent or postpone neurologic symptoms. Ultimately, COVID-19-related neurological manifestations are a major problem that requires immediate attention until a remedy is developed [25].

REFERENCE

- [1] Imran Ahmad, Farooq Azam Rathore, Neurological manifestations and complications of COVID-19: A literature review, *Journal of Clinical Neuroscience*, Volume 77, 2020, Pages 8-12, ISSN 0967-5868, <https://doi.org/10.1016/j.jocn.2020.05.017>.
- [2] Zhu N, Zhang D, Wang W et al (2020) A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 382:727–733

- [3] WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. 11 March 2020. Available at <https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>
- [4] World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 92 <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
- [5] <https://www.worldometers.info/coronavirus/>
- [6] Ali A. Asadi-Pooya, Leila Simani, Central nervous system manifestations of COVID-19: A systematic review, *Journal of the Neurological Sciences*, Volume 413, 2020, 116832, ISSN 0022-510X, <https://doi.org/10.1016/j.jns.2020.116832>.
- [7] H.A. Rothan, S.N. Byrareddy The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak *J. Autoimmun.*, 102433 (2020)
- [8] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China *JAMA Neurol* (2020), 10.1001/jamaneurol.2020.1127
- [9] J. Helms, S. Kremer, H. Merdji, R. Clere-Jehl, M. Schenck, C. Kummerlen, *et al.* Neurologic Features in Severe SARS-CoV-2 Infection *N Engl J Med* (2020), 10.1056/NEJMc2008597
- [10] Khatoun, F., Prasad, K., & Kumar, V. (2020, October). *Neurological manifestations of COVID-19: Available evidence and a new paradigm*. *Journal of neurovirology*. Retrieved February 26, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7444681/>
- [11] Helms J, Kremer S, Meziani F (2020a) More on neurologic features in severe SARS-CoV-2 infection. Reply *N Engl J Med* <https://pubmed.ncbi.nlm.nih.gov/32453517/>
- [13] Gklinos, P. (2020, September). *Neurological manifestations of covid-19: A review of what we know so far*. *Journal of neurology*. Retrieved February 26, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250266/>
- [14] *Melatonin: Roles in influenza, Covid-19, and other viral ...* (n.d.). Retrieved February 26, 2022, from https://onlinelibrary.wiley.com/doi/full/10.1002/rmv.2109?casa_token=EgS0dSuCuNwAAAAA%3AAbieaTNbY-6T3WvogLD0SJm4d3cv2_jH6k-3TFd0eyiOzKU33d6l1KU5dWam5QluiPTzDgDL2BBVCNGSd
- [15] *Neurological complications associated with Covid-19 ...* (n.d.). Retrieved February 26, 2022, from <https://onlinelibrary.wiley.com/doi/full/10.1002/rmv.2334>
- [16] *Potential neurological symptoms of COVID-19 - Sage Journals*. (n.d.). Retrieved February 26, 2022, from <https://journals.sagepub.com/doi/full/10.1177/1756286420917830>
- [17] Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a Retrospective Case Series Study. <https://www.medrxiv.org/content/10.1101/2020.02.22.20026500v1/>
- [18] Tamara Fong, M. D. (2022, March 17). *Brain fog: Memory and attention after COVID-19*. Harvard Health. Retrieved April 29, 2022, from <https://www.health.harvard.edu/blog/brain-fog-memory-and-attention-after-covid-19-202203172707#:~:text=Among%20people%20who%20were%20hospitalized,simultaneously%20ignoring%20other%20details>.
- [19] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi: 10.1016/S0140-6736(20)30183-5.
- [20] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. doi: 10.1001/jama.2020.1585.
- [21] Richman DD, Whitley RJ, Hayden FG. 4th edn. ASM Press; Washington: 2016. *Clinical virology*. [Google Scholar]
- [22] Ksiazek TG, Erdman D, Goldsmith CS. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*. 2003;348:1953–1966. [PubMed] [Google Scholar]

- [23] Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, Laue M, Schneider J, Brünink S, Greuel S, Lehmann M, Hassan O, Aschman T, Schumann E, Chua RL, Conrad C, Eils R, Stenzel W, Windgassen M, Rößler L, Goebel HH, Gelderblom HR, Martin H, Nitsche A, Schulz-Schaeffer WJ, Hakroush S, Winkler MS, Tampe B, Scheibe F, Körtvélyessy P, Reinhold D, Siegmund B, Kühl AA, Elezkurtaj S, Horst D, Oesterhelweg L, Tsokos M, Ingold-Heppner B, Stadelmann C, Drosten C, Corman VM, Radbruch H, Heppner FL. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci.* 2021;24(2):168–175. doi: 10.1038/s41593-020-00758-5.
- [24] Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia.* 2020;77:8–12. doi: 10.1016/j.jocn.2020.05.017.
- [25] Dewanjee, S., Vallamkondu, J., Kalra, R. S., Puvvada, N., Kandimalla, R., & Reddy, P. H. (2021). Emerging COVID-19 Neurological Manifestations: Present Outlook and Potential Neurological Challenges in COVID-19 Pandemic. *Molecular neurobiology*, 58(9), 4694–4715. <https://doi.org/10.1007/s12035-021-02450-6>
- [26] Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, Korálnik IJ. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Annals of Clinical and Translational Neurology.* 2020;7(11):2221–2230. doi: 10.1002/acn3.51210.
- [27] Garg RK. Spectrum of neurological manifestations in Covid-19: a review. *Neurol India.* 2020;68(3):560–572. doi: 10.4103/0028-3886.289000.
- [28] Umaphathi T, Quek WMJ, Yen JM, Khin HSW, Mah YY, Chan CYJ, Ling LM, Yu WY (2020) Encephalopathy in COVID-19 patients; viral, parainfectious, or both? *eNeurologicalSci* 21:100275. doi:10.1016/j.ensci.2020.100275
- [29] Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, Viganò M, Giovannelli G, Pirro F, Montisano DA, Appollonio I, Ferrarese C. Guillain-Barré syndrome related to COVID-19 infection. *Neurology - Neuroimmunology Neuroinflammation.* 2020;7(4):e741. doi: 10.1212/nxi.0000000000000741.
- [30] Delamarre L, Gollion C, Grouteau G, Rousset D, Jimena G, Roustan J, Gaussiat F, Aldigé E, Gaffard C, Duplantier J, Martin C, Fourcade O, Bost C, Fortenfant F, Delobel P, Martin-Blondel G, Pariente J, Bonneville F, Geeraerts T. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *J Neurol Neurosurg Psychiatry.* 2020;91(9):1004–1006. doi: 10.1136/jnnp-2020-323678.
- [31] Kinikar A, Kulkarni R, Rajput U, Karyakarte R. Acute encephalopathy in a child with coronavirus disease-2019 infection. *Pediatr Infect Dis.* 2020;2:62–63. doi: 10.5005/jp-journals-10081-1244.
- [32] Chen TH. Neurological involvement associated with COVID-19 infection in children. *J Neurol Sci.* 2020;418:117096. doi: 10.1016/j.jns.2020.117096.
- [33] McAbee GN, Brosgol Y, Pavlakis S, Agha R, Gaffoor M. Encephalitis associated with COVID-19 infection in an 11-year-old child. *Pediatr Neurol.* 2020;109:94. doi: 10.1016/j.pediatrneurol.2020.04.013.
- [34] Garg RK. Spectrum of neurological manifestations in Covid-19: a review. *Neurol India.* 2020;68(3):560–572. doi: 10.4103/0028-3886.289000.
- [35] Kihira S, Delman BN, Belani P, Stein L, Aggarwal A, Rigney B, Schefflein J, Doshi AH, Pawha PS. Imaging features of acute encephalopathy in patients with COVID-19: a case series. *AJNR Am J Neuroradiol.* 2020;41(10):1804–1808. doi: 10.3174/ajnr.A6715.
- [36] Bhavsar SM, Agarwal S, Lewis R, Ganta A, Roshchina YS, Clouser KN, Baer AZ, Gliksman F, Piwoz JA. COVID-19 infection associated with encephalitis in an adolescent. *Neurol Clin Prac.* 2021;11(2):e189-e192. doi: 10.1212/cpj.0000000000000911.
- [37] Niazkar HR, Zibae B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2020;41(7):1667–1671. doi: 10.1007/s10072-020-04486-3.
- [38] Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology.* 2020;58(3):299–301. doi: 10.4193/Rhin20.114.

- [39] Sainz-Amo R, Baena-Álvarez B, Pareés I, Sánchez-Díez G, Pérez-Torre P, López-Sendón JL, Fanjul-Arbo S, Monreal E, Corral-Corral I, García-Barragán N, Martínez-Castrillo JC, Fasano A, Alonso-Cánovas A (2020) COVID-19 in Parkinson's disease: what holds the key? *Journal of Neurology*:1–5. doi:10.1007/s00415-020-10272-0
- [40] Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *International Forum of Allergy & Rhinology*. 2020;10(8):944–950. doi: 10.1002/alr.22587.
- [41] Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *International Forum of Allergy & Rhinology*. 2020;10(7):806–813. doi: 10.1002/alr.22579.
- [42] Lippi G, Wong J, Henry BM. Myalgia may not be associated with severity of coronavirus disease 2019 (COVID-19) *World J Emerg Med*. 2020;11(3):193–194. doi: 10.5847/wjem.j.1920-8642.2020.03.013.
- [43] Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. *J Med Virol*. 2020;92(9):1449–1459. doi: 10.1002/jmv.25822.
- [44] Shah, V. A., Nalleballe, K., Zaghloleh, M. E., & Onteddu, S. (2020, October). *Acute encephalopathy is associated with worse outcomes in COVID-19 patients*. Brain, behavior, & immunity - health. Retrieved May 13, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7462562/#:~:text=Among%20hospitalized%20COVID%2D19%20patients,and%20underlying%20medical%20co%2Dmorbidity>.
- [45] Helms J., Kremer S., Merdji H. Neurologic features in severe SARS-CoV-2 infection. *N. Engl. J. Med*. 2020;382(23):2268–2270. doi: 10.1056/NEJMc2008597.
- [46] Varatharaj, A., Thomas N., Ellul M., Davies N.W.S., Pollak T., Tenorio E.L., Sultan M., Easton A., Breen G., Zandi M., Coles J.P., Manji H., al-Shahi Salman R., Menon D., Nicholson T., Benjamin L., Carson A., Smith C., Turner M.R., Solomon T., Kneen R., Pett S., Galea I., Thomas R.H., Michael B., UK-wide surveillance of neurological and neuropsychiatric complications of COVID-19: the first 153 patients. Available at SSRN 2020. 10.2139/ssrn.3601761
- [47] Nalleballe K., Reddy Onteddu S., Sharma R. Spectrum of neuropsychiatric manifestations in COVID-19. *Brain Behav. Immun*. 2020 doi: S0889-1591(20)31008-4.
- [48] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China *JAMA Neurology* 77(6):683–690.
- [49] Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ (Clinical Research ed)* 368:m1091
- [50] Devlin JW, O'Neal HR Jr, Thomas C, Barnes Daly MA, Stollings JL, Janz DR, Ely EW, Lin JC (2020) Strategies to Optimize ICU Liberation (A to F) Bundle performance in critically ill adults with coronavirus disease 2019. *Critical Care Explorations* 2(6):e0139.
- [51] Wei H, Yin H, Huang M, Guo Z (2020) The 2019 novel coronavirus pneumonia with onset of oculomotor nerve palsy: a case study. *J Neurol* 267(5):1550–1553.
- [52] Dinkin M, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, Harpe J, Greer C, Mints G, Salama G, Tsiouris AJ, Leifer D (2020) COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology* 95(5):221–223.