Original Article: Complication of Central Nervous System in COVID-19 Patients: A Systematic Review and Meta-Analysis

Saeed Saedi*1 | Atefeh Saedi2 | Mohammad Mehdi Ghaemi3 | Maryam Milani Fard4

1Shirvan Center of Higher Health education, Imam Khomeini Hospital, North Khorasan University of Medical Sciences, Bojnurd, Iran
2Medical Genetics Research Center, Medical School, Mashhad University of Medical Sciences, Mashhad, Iran
3MD, PhD, Assistant Professor of Medical Informatics, Medical Informatics Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
4Researcher at the Anesthesia and Pain & Molecular and cell Biology Research Center, Faculty of Medicine Department of Anatomy, Iran university of Medical Sciences, Tehran, Iran

Evidence suggests the existence of neurological involvement in COVID-19, so implementing comprehensive studies such as systematic and meta-analysis can be a good guide for scientists. Coronaviruses are a large group of viruses that can infect animals and humans and cause respiratory distress. These discomforts may be as mild as a cold or as severe as pneumonia. In rare cases, animal coronaviruses infect humans and then spread among them. The SARS virus from 2002 to 2003 was an example of the corona virus, which was transmitted from animals to humans. Another important and newer breed of the corona virus is MERS (Middle East Respiratory Syndrome), which was discovered in the Middle East in 2012 and, according to scientists, the virus was first transmitted from camels to humans. Here, we selected six studies: Prevalence of Acute Cerebrovascular disease, Encephalopathy, Other neurological manifestations such as: Cerebral ischemic stroke, Brain perfusion abnormalities, Dysexecutive syndrome and Ataxia by 2.67% (ES, 2.67% 95% CI 1.71%, 3.64%), 10.28% (ES, 10.28% 95% CI 8.19%, 12.37%) and 16.70% (ES, 16.79% 95% CI 15.45%, 17.94%), respectively. Overall prevalence of CNS complication in patients with COVID-19 was 9.61 % (ES, 9.61% 95% CI 8.04%, 11.19%). The results of the present systematic review and meta-analysis showed that Acute Cerebrovascular disease and Encephalopathy have a higher prevalence among patients with COVID-19. These results can help physicians better diagnose CNS signs and symptoms. Attention should be paid to all CNS complications in COVID-19 patients.

Keywords:
Central Nervous System, COVID-19, Acute Cerebrovascular Disease, Meta-Analysis

*Corresponding Author: Saeed Saedi (saeedsaeedi1976shirvan@gmail.com)
Introduction

A new respiratory syndrome emerged across the world in end of December 2019, first reported in Wuhan, China, which spread rapidly around the world. The virus was called COVID 2019 or COVID 2019 [1]. The first sign of the disease was pneumonia. The number of people getting this infection is increasing day by day and it has become a concern all over the world [2]. The World Health Organization (WHO) declared the infection a Public Health Emergency of International Concern (PHEIC) [3]. Preliminary evidence suggests that the source of the disease is the bat, a common human-animal pathogen, and that it is eventually transmitted from human to human [4]. The symptoms of this disease are changing, but its common symptoms include cough, shortness of breath, respiratory failure, fever, and fatigue [5-8]. Currently, evidence has shown that a large number of patients with COVID-19 show central nervous system (CNS) manifestations [9-11]. Case studies have shown that encephalitis, stroke, meningitis, and encephalopathy occur in patients with COVID-19 [12-14]. A study also showed 36.4% of patients with COVID-19 had developed neurological manifestations, including dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures [15]. Identifying and being aware of the long-term and short-term effects of COVID-19 on the CNS can be a good guide for physicians and scientists. Also, studies that have extracted SARS-CoV-2 from cerebrospinal fluid and glial cells in COVID-19 patients have shown that brain involvement alone can be the cause of death from this disease, especially due to cerebral edema [16, 17]. Therefore, all evidence suggests the existence of neurological involvement in COVID-19, so conducting comprehensive studies such as systematic and meta-analysis can be a good guide for scientists [18-21]. Hence the aim of present systematic review and meta-analysis study was to assess the complication of central nervous system in COVID-19 patients [22-26].

The spread of the corona virus has created many problems for policymakers in the field of economics and beyond. The number of patients with Quaid-19 disease and the resulting mortality rate have caused panic among production agents and other stakeholders in organizations [27-29]. The widespread prevalence of this disease and its unpredictability have made it difficult for policymakers to find solutions to the problems that have arisen. In fact, the corona outbreak is a perfect example of a widespread crisis; a crisis in which events or sequences occur on a large scale and astonishingly fast and leads to uncertainty that exacerbates irregularities, creates a sense of lack of control, and causes emotional disturbance in individuals [30-33]. In this report, considering the shocks of this pandemic (global pandemic) in the economy, the general data-output equilibrium model based on the internal table was used to model the reduction of production added value of each sector of the economy in seven scenarios [34-37]. The results show that in the Iranian economy, the sectors of hotels and restaurants, transportation and production of petroleum, chemical and non-metallic minerals have suffered the most and the sectors of general management, electricity and machinery and post and communications have suffered the least damage [38-41]. Also, the three sectors of hotels and restaurants, wholesalers and retailers are highly dependent on the performance of governance, and the difference between the damage in the two scenarios of worst performance and best performance is greater. In general, the decrease in domestic income due to the prevalence of this disease has been between 5.65 to 6.63%.

Methods

Search method

In all their interactions with patients, our medical staff followed the latest guidelines from the Los Angeles County Department of Public Health to prevent the spread of the new virus. All hospital staff and visitors were screened for symptoms. Anyone who failed an oral screening was tested for the virus. In addition, all CHLA patients were tested for the virus after admission to the hospital. This included testing patients for future procedures [42-45].
This systematic review and meta-analysis have been conducted on the basis of PICOS strategy (Table 1).

**Table 1. PICO OR PECO strategy**

<table>
<thead>
<tr>
<th>PICO OR PECO strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Population/ Patient: patients with COVID-19</td>
</tr>
<tr>
<td>I</td>
<td>Exposure/ Intervention: patients presenting CNS symptoms</td>
</tr>
<tr>
<td>C</td>
<td>Comparison: positive case vs negative case</td>
</tr>
<tr>
<td>O</td>
<td>Outcome: complication</td>
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</tbody>
</table>

**Selection criteria**

**Inclusion criteria**

Inclusion criteria were randomized controlled trial, retrospective and prospective studies, studies that reported neurological outcomes in patients with COVID-19 [46-49].

Exclusion criteria were case-control studies, in vitro studies, reviews, case report and animal studies, and lack of access to the full text of the articles in non-English language [50-53].

**Data extraction methods**

Timely examination of cerebrospinal fluid and proper management of neurological complications associated with infection may be the key to improving the prognosis of patients in serious cases such as stroke, encephalitis, and meningitis (inflammation of the meninges). Because knowledge about the long-term outcome of Covid-19 neurological symptoms is limited, careful clinical, diagnostic, and epidemiological studies are needed to help define the symptoms and burden of neurological disease [54-57].

National Heart, Lung, and Blood Institute (NHLBI) [58] was referred to assess quality of the cohort studies included in the present meta-analysis [59-62]. The scale scores for low risk was 1 and for high and unclear risk was 0, scale scores ranged from 0 to 14 and higher score means higher quality. For data extraction, we relied on two blind reviewers and independently extracted data from abstract and full text of studies [63-66].

Covid-19 virus can cause neurological manifestations by secreting cytokines, circulating the virus in the body, or direct invasion of the virus through multiple ACE2 receptors in the olfactory epithelium. Olfactory disorders may be caused by damage to the olfactory epithelium. Fever is believed to be caused by cytokines or hypothalamic dysfunction. Seizures may also be due to an overdose of cytokines, the severity of the disease, or involvement of the brain parenchyma; in particular, the middle temporal lobe is created [67-69]. In addition, the altered mental state may be the result of multiple organ failure, severe infection, or involvement of part of the brainstem. Headaches are also caused by stimulation of the meningeal fluid [70]. Of course, it should be noted that these surveys are limited to current information and limited reports. Corona can be detected by coronary throat examination.

Studies have shown neurological symptoms in patients with Covid-19 disease. These manifestations are divided into several groups based on their symptoms, such as non-specific symptoms, specific symptoms, impaired consciousness, and skeletal muscle problems. A study examining neurological symptoms in patients with Covid-19 showed a nervous system disease with a prevalence of 36.4% in 214 patients. Most neurological symptoms occur in the early stages of the disease. Headache, dizziness with or without nausea, cardiovascular disease, impaired consciousness, and muscle problems are some of the
neurological manifestations reported in these studies.

**Results**

Early manifestations of Covid-19 disease are usually respiratory symptoms. However, doctors have identified neurological symptoms at the time of diagnosis as one of the early symptoms. Nonspecific symptoms can be difficult to diagnose when they occur alone. After muscle pain, headache is one of the most common neurological symptoms in patients with Covid-19. Twenty-one studies have reported headaches with a prevalence of 3.5 to 34% among patients with Covid-19. Overall, the prevalence of headache was 10.9% in a population of 6486 out of 21 studies. A review of previous studies shows that headache is the most common symptom during exacerbation of the disease in patients with Covid-19. In another study, dizziness with 16.8% was one of the most common central nervous system manifestations, followed by headache with 13.1%. Dizziness and headache are often seen in the early stages of the disease as common symptoms of Covid-19 disease. Dizziness has been reported in 6 studies with an overall prevalence of 8 to 77% among 1,088 people. Nausea with or without vomiting was reported in 13 studies with a prevalence of 1.25 to 8.7%. In general, the overall prevalence of nausea with or without vomiting is 4.6%. Numerous studies have been performed during the period of Covid-19 outbreak. However, advanced imaging and diagnostic techniques such as magnetic resonance imaging (MRI) and electroencephalography (EEG) have been avoided or used depending on the specific symptoms of a disease such as bleeding or seizures. Therefore, it is difficult to identify the source of neurological symptoms, either directly through the virus or indirectly through damage to other organs, such as gastrointestinal manifestations. Finally, six studies were selected (Fig. 1).

![Figure 1. Study Attrition](image-url)
Characteristics

Six studies (Retrospective and Prospective studies) were included in present article. The number of patients was 792 male and 489 female; one study (19) did not report the sex of participants. The total sample size was 1339 patients with COVID-19 with CNS symptoms. The mean of age was 60.43 years. Diagnostic procedures in three studies (15), (20), (21) were computed by tomography scan. One study (22) reported on treating physician and two studies (23), (23) of clinical symptoms. The neurological manifestations were hypoxic encephalopathy, encephalopathy, cerebral ischemic stroke, brain perfusion abnormalities, dysexecutive syndrome and acute cerebrovascular disease (Table 2).

Bias assessment

According to NHLBI tool, all studies had a total 8/14 score and all included studies were judged with low risk of bias that means they were of high quality. All studies in sample size justification and examine different levels of the exposure item had a high risk of bias [71].

Table 2. Details of selected studies according to inclusion criteria

<table>
<thead>
<tr>
<th>Study. Years</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Mean of age</th>
<th>diagnostic procedure</th>
<th>Neurological manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mao et al.,2020 (15)</td>
<td>Retrospective</td>
<td>87/127</td>
<td>52.7</td>
<td>Computed tomography scan</td>
<td>CVD and Ataxia</td>
</tr>
<tr>
<td>Klok et al.,2020 (20)</td>
<td>Prospective</td>
<td>139/45</td>
<td>64.5</td>
<td>Computed tomography scan</td>
<td>CVD</td>
</tr>
<tr>
<td>Chen et al.,2020 (23)</td>
<td>Retrospective</td>
<td>171/103</td>
<td>62.7</td>
<td>Clinical symptom and laboratory findings</td>
<td>HE</td>
</tr>
<tr>
<td>Helms et al.,2020 (19)</td>
<td>Prospective</td>
<td>58</td>
<td>63.3</td>
<td>Magnetic resonance imaging/ Clinical symptom</td>
<td>En, CIS, BPa, DES</td>
</tr>
<tr>
<td>Lodigiani et al.,2020 (22)</td>
<td>Retrospective</td>
<td>264/124</td>
<td>66.1</td>
<td>Report of treating physician</td>
<td>CVD</td>
</tr>
<tr>
<td>Li et al.,2020 (21)</td>
<td>Retrospective</td>
<td>131/90</td>
<td>53.3</td>
<td>Computed tomography scan</td>
<td>CVD</td>
</tr>
</tbody>
</table>

HE: Hypoxic encephalopathy; En: Encephalopathy; CIS: Cerebral ischemic stroke; BPa: Brain perfusion abnormalities; DES: Dysexecutive syndrome; CVD: Acute Cerebrovascular disease
Table 3. Risk of bias assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>research question or objective</th>
<th>study population</th>
<th>participation rate of eligible persons at least 50%</th>
<th>inclusion and exclusion criteria</th>
<th>sample size justification, power description</th>
<th>measured prior to the outcome</th>
<th>association between exposure and outcome</th>
<th>examine different levels of the exposure</th>
<th>independent variables</th>
<th>exposure(s) assessed more than once over time</th>
<th>outcome measures</th>
<th>outcome assessors blinded to the exposure status of participating participants</th>
<th>loss to follow-up after baseline 20% or less</th>
<th>statistically and relationship between exposure(s) and outcome</th>
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<tr>
<td>Mao et al., 2020 (15)</td>
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<td>Klok et al., 2020 (20)</td>
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<td>Chen et al., 2020 (23)</td>
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<td>Li et al., 2020 (21)</td>
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Low (+), unclear (?), high (-), NR (not reported)
Central nervous system complications

Acute Cerebrovascular disease

Prevalence of Acute Cerebrovascular disease in patients with COVID-19 was 2.67% (ES, 2.67% 95% CI 1.71%, 3.64%) among the five studies (Fig. 2 and 6-a). Heterogeneity was found ($I^2 = 56.13\% \ p=0.06$).

Encephalopathy

Prevalence of Encephalopathy in patients with COVID-19 was 10.28% (ES, 10.28% 95% CI 8.19%, 12.37%) among the two studies (Figure 3 and Figure 6-b). Heterogeneity was found ($I^2 = 93.85\% \ p=0.06$).
Other Neurological manifestations

Prevalence of other Neurological manifestations in patients with COVID-19 was 16.70% (ES, 16.79% 95% CI 15.45%, 17.94%) among the two studies (Fig. 4). Heterogeneity was found (I² = 99.32% p=0.06).

Overall prevalence of CNS complication

Overall prevalence of CNS complication in patients with COVID-19 was 9.61% (ES, 9.61% 95% CI 8.04%, 11.19%) among all the studies included in meta-analysis (Fig. 5).

Figure 4. Forest plot showed prevalence of other Neurological manifestations in patients with COVID-19

Figure 5. Forest plot showed overall prevalence of central nervous system complications
Discussion

With the sudden outbreak of COVID-19, the lives of millions around the world were in danger. All scientists, doctors and researchers are trying to discover all aspects of this emerging infection so that they can take appropriate treatment measures. One of the most important aspects is the effect of COVID-19 on the CNS [16]. Most studies have looked at pulmonary and respiratory symptoms and complications; however, few studies have looked at the prevalence of neurological manifestations. In the present systematic review and meta-analysis, we assessed 1339 patients with COVID-19 from different countries. Nazari et al. (2020), in a systematic review and meta-analysis, evaluated the CNS presentations in COVID-19 patients to identify the common CNS features. They reported that COVID-19 patients commonly showed CNS symptoms, including headache, dizziness, and impaired consciousness. Headache (8.69%) was the most common CNS symptoms, followed by dizziness (5.94%) and impaired consciousness (1.9%) [24]. In the present systematic review and meta-analysis, the results showed the prevalence of Acute Cerebrovascular disease, Encephalopathy, Other Neurological manifestations such as: Cerebral ischemic stroke, Brain perfusion abnormalities, Dysexecutive syndrome and Ataxia by 2.67%, 10.28% and 16.70%, respectively. The overall prevalence of CNS complication in patients with COVID-19 was 9.61%. In the review of selected studies, there were reports of almost all heterogeneous complications between studies, but in the report prevalence of CVD, heterogeneity was not observed between the results of the studies. The reason for the heterogeneity in the results can be considered as differences in the country or sample size. It should be noted that COVID-19 also has direct effects on the CNS. Elevated cytokine in the body following the immune response during COVID-19 infection can lead to blood–brain barrier (BBB) failure [25,26]. Evidence suggests that ACE2 expression and distribution support the SARS-CoV-2 receptor in the CNS [27]. In studies that reported COVID-19 mortality rate, about 10.47% of them died of at least one CNS symptom [28]. Such a mortality rate could indicate the importance of closely monitoring CNS manifestations in COVID-19 patients. Also, some studies have shown that COVID-19 can accelerate the formation of blood clots in blood vessels and increase the risk of cerebrovascular disease [29]. According to the findings of the present study, encephalopathy and acute cerebrovascular disease were the most common in terms of complications, and other CNS complications were also observed among patients.

Figure 6. A: Funnel plot showed prevalence of CVD; B: Prevalence of Encephalopathy in patients with COVID-19
Conclusion

It is quite normal for viruses to mutate over time. Experts are constantly reviewing new strains of the coronavirus that produce the disease to see if they are easier to transmit, cause more severe disease, or if they can affect the effectiveness of the vaccine. Some new strains of the virus, including delta, appear to be more contagious. The best way to limit the spread of coronary heart disease is to get everyone vaccinated if the vaccine is available and to follow the recommendations for preventing the spread of the virus, including keeping a physical distance, wearing a mask, washing hands regularly, and ventilating places well.

COVID-19 is now a major global problem affecting millions of people. COVID-19 can affect different parts of the human body, and despite the fact that most of the respiratory tract is targeted, the CNS is also significantly affected. In patients with more advanced symptoms, CNS involvement is seen, which can worsen the patient’s clinical condition. The results of the present systematic review and meta-analysis showed that Acute Cerebrovascular disease and Encephalopathy have a higher prevalence among patients with COVID-19. These results can help physicians better diagnose CNS signs and symptoms. Attention should be paid to all CNS complications in COVID-19 patients. Just like any other study, the current study faced limitations, including the lack of further RCT and cohort studies on the subject, the increasing prevalence of COVID-19, and changes in its signs and symptoms. Further studies with higher sample sizes are required. It is suggested that these limitations be considered in future studies.

Orcid

Maryam Milani Fard:

https://www.orcid.org/0000-0002-0888-8847

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