

SYSTEMIC REVIEW ARTICLE

Long-COVID and its Physical and Neurological Symptoms in Adults: A Systematic ReviewABDUL MANNAN BAIG¹, SAMEERA RIZVI², SHAHLA PARDHAN³, JOACHIM GERLACH⁴, TAZEEN SAEED ALI⁵¹Mentor and Supervisor, Assistant Professor Department of Biological and Biomedical Sciences, Aga Khan University²Assistant Professor, Department of Public Health, Faculty of Life Sciences SZABIST Karachi³MSN, Aga Khan University School of Nursing and Midwifery Karachi.⁴Health-Shield, Vedicinals-9 40764 Langenfeld, Germany⁵Associate Dean Aga Khan University School of Nursing and Midwifery Aga Khan University Karachi.Correspondence to Dr. Tazeen Saeed Ali, Email: tazeen.ali@aku.edu, Cell: 03318365669**ABSTRACT**

This review was carried out with the objective to study patterns of neurological, psychological and other physical consequences of COVID-19 in the long term. The guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) had been followed; 22 articles, published during January 2020 to September 2021, were selected. Original research, review articles, editorial and viewpoints were included. Google Scholar, Medline, and PubMed were searched through 2020 till 2021. Data collection in selected studies was performed mainly through the online survey, telephone survey, use of medical records, and patient interviews. This systematic review contains the studies conducted in the American, Asian and European countries. The major outcomes identified were the neurological, psychological, and other long-term chronic manifestations of COVID-19. This review demonstrates that long-COVID has started to bring a huge wave of patients, the count of them being millions now, who can enter a phase of disability due to neurological damages if not treated during the early course of illness. Though more disabling than lethal, long-COVID patients with a neurological deficit is expected to overburden the healthcare system globally which is already been struggling to handle acute COVID-19 patients in this once-in-a-lifetime pandemic.

Keywords: COVID-19, Neurological and Psychological symptoms, Physical Symptoms, Long-COVID.

INTRODUCTION

COVID-19 virus (also known as SARS-CoV-2) was reported in December 2019, for the first time, in city of Wuhan, China where many people were complaining of asymptomatic or mild to moderate phase of acute covid-19 symptoms whereas 15% of infected individuals were progressing towards hospitalization and 5% of people were reported critically ill (*Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance*, 2020). Further, research studies have described that essentially 80% of patients who were discharged after hospitalization reported having at least one symptom that persisted 2 to 6 months after the onset of disease, including sleep disturbances, muscle weakness, and fatigue as well as affecting other systems of body spanning from cardiopulmonary system to neurological and psychiatric ones as a long-term sequelae among the survivors of the COVID-19 pandemic (Zhu N, 2023) It is also stated that the symptoms of the acute phase were diagnosed early, but the data is rare regarding the long-term symptoms of COVID-19 (McBride, Arden, Chater & Chilcot, 2021). Long COVID is considered to be a heterogeneous condition, the definition of which is still not clear; it doesn't affect the patients with acute symptoms however those patients who are managed at home, and whose symptoms remained for several weeks to six months or more are mostly affected. Therefore, caution should be taken when interpreting and generalizing such results (Lik-Yuen et al., 2005; Nabavi, 2020). Moreover, researchers have also stated in a systematic review that symptoms of SARS-CoV-1 on a prolonged period have affected one third of the patients who later suffered from post-traumatic disorders, depression, and anxiety for up to 6 months even after completely recovered from the acute illness (Ahmed et al., 2020). Authors also reported that 11-45% of patients suffered from pulmonary complication after one year of follow up (*Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance*, 2020; X. Wu, Dong, & Ma, 2016). Additionally, long COVID also targets the vital organs of the human body and leads to conditions such as hypotension (50.4%), tachycardia (71.9%), bradycardia (14.9%), and cardiomegaly (10.7%), as suggested by L. Wu et al. (2020).

Similarly, long COVID caused acute renal impairment (Chu et al., 2005), acute gastrointestinal effects (Callard & Perego, 2021), acute viral hepatitis (Chau et al., 2004) and acute diabetes mellitus from the binding of the virus to its receptors on pancreatic islets cells (Yang, Lin, Ji, & Guo, 2010). Furthermore, long term COVID led to several blood-related abnormalities which include leukopenia, lymphopenia, prolonged activated partial thromboplastin time, thrombocytopenia, coagulopathy (elevated D-dimer), and disseminated intravascular coagulation, and a pro-thrombotic state at micro and macro-vasculature involving arteries and veins along with thromboembolic complications (Higgins, Sohaei, Diamandis, & Prassas, 2021; Ngai et al., 2010). Besides, patients also suffered from psychosocial symptoms that include musculoskeletal pain, malaise, psychological stress, disturbed sleep, and impeding towards productive work for up to two years after recovering from an acute illness (Akbarialiabad et al., 2021; Moldofsky & Patcai, 2011). Moreover, research also revealed that prevalence of neurological manifestations due to long-COVID and its severity are still under debate and no proper assessment scale had been identified to assess the neurological symptoms amongst patients (Pilotto et al., 2021).

This systematic review was carried out with an objective to study the frequency and patterns of neurological, psychological, and other continuing consequences of COVID-19 infection in long term.

MATERIALS AND METHODS

This systematic review was conducted in order to provide frequently updated evidence regarding the symptoms and related complications of long-COVID. PRISMA reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were followed wherein 22 articles had been selected for a systematic review that was published within one and a half year, between January 2020 and December 2021. The articles focusing on neurological symptoms and sequelae of COVID-19 were included.

Original research, review articles, editorial and viewpoints were included in this systematic review. Medline, PUBMED, WHO Global Research on COVID-19 database, and Google Scholar were searched through 2020-2021. We manually searched the databases and also checked the reference list of the searched studies. There was no restriction on the country of research however articles only in English language were selected. Studies

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with confirmed clinical COVID-19 with long COVID symptoms were included. The study material was strategized to be searched through various combinations of keywords from the aforementioned databases, in the following orders:

- i. "Coronavirus" or "COVID-19" or "SARS-CoV-2" or "Novel Coronavirus" [Title/Abstract]
- ii. "Neurological characteristics" or "Neurological feature" or "Neurological symptoms" [Title/Abstract]
- iii. "Consequences" or "Chronic complications" or "Late complications" or "Long-term effects" or long haul COVID [Title/Abstract]

The relevant studies on the basis of abstracts and titles were fetched and retrieved by two study investigators. The complete content of these papers was thoroughly reviewed; the most relevant and relatable papers were selected and complied in compliance to the eligibility criteria. The pertinent data mining was done and the details were organized in a table that has been summarized as in table 1.

Those original papers that were published in English language, complied with the eligibility criteria, and peer-reviewed were incorporated in our final report. The studies selected that were selected for this review included randomized clinical trials, cohort studies (both prospective and retrospective), case-control studies and/or case-series with diagnosed patients. Studies were included if they carried information of subjects according to the criteria that all adult male and female participants, with a history of previous COVID-19 infection and presence of neurological symptoms at present and other complications after a diagnosed COVID-19 positive status. Research papers covering non-human studies including publications focusing on animal experiments and in-vitro investigations were not included.

RESULTS

Characteristics of included studies: For systematic review, original research articles, systematic review, viewpoints, review articles, and editorials were selected. We retrieved 931 studies on Long COVID Syndrome. Out of these 208 studies were on Long COVID Syndrome with Neurological symptoms while 70 studies were about Long COVID with Neurological symptoms among adults. Eventually, 22 studies were identified that had covered late complications of COVID-19 with neurological symptoms along with the involvement of other organs or systems such as liver, lung, heart and kidneys, encephalopathy, cardiac/brain stroke, thromboembolism, and psychological issues from PubMed (Figure 1).

Long term complications by organ systems: Further appraisal of studies focusing on neurological issues revealed depression as a common issue in nine studies. Progressive brain damage was reported in six studies along with impairment in cognition was reported by two studies. PET scan was conducted in one study. A case series and comprehensive review on post-COVID syndrome was reported in one study. Diabetes & Metabolic Syndrome were found in one study. Brainstem and thalamic mal functions were reported in 2 studies. Neuropsychiatric effects were seen in one study. Deleterious outcomes in long-hauler COVID-19 were also reported by one study. The other reported complications were lung involvement in seven studies and cardiac/heart issues in three studies. Gastrointestinal complication was reported by two studies.

Followed by respiratory and generalized symptoms, the most reported ones were neurological symptoms. Moreover, significant levels of insomnia ($p < 0.05$) and an overall reduced quality of life were observed in the subjects. Symptoms such as fatigue, cough, chest tightness, and breathlessness were found as common symptoms. Reproductive effects were not seen in this review.

Figure 1: Prisma Flow Chart

| Identification |
|---|
| Preliminary search articles focusing on complications of COVID19 PUBMED, MEDLINE, Cochrane, Google Scholar Long COVID Syndrome Total: 931 2020: 29 2021: 700 2022: 202 |
| Screening |
| Keywords searched: Long COVID Syndrome, Chronic complications, Late complications, Long Haul COVID "Neurological" Total: 208 2020: 06 2021: 148 2022: 54 |
| Eligibility |
| Long COVID Syndrome "Neurological" "Adult" Original Research, English Language, Peer Reviewed, Original research Total: 70 2020: 02 2021: 58 2022: 10 |
| Included |
| Long COVID Syndrome "Neurological" "Adult" Original Studies, Case Reports, Case Series, View Points, Editorials Review Studies between January 2020- December 2021 Total: 17 2020: 10 2021: 07 |

DISCUSSION

The infection of novel coronavirus 2019 (later named as SARS-CoV-2) that emerged in Wuhan, China for the first time and thought to be a respiratory illness has now been clearly established to be a multi organ diseases. The disease it causes has been termed as COVID-19 has shown to involve almost all end-organs of the human body like lungs, heart, blood vessels, nervous system, kidneys, gastrointestinal tract, eyes and endocrine glands to name a few of the organs and systems involved. In particular, the nervous system involvement has been the focus of attention for its prognostic value as the outcome of COVID-19 has been seen to be poor in subject exhibiting neurological features in COVID-19 (Meinhardt et al., 2021; Sisniega & Reynolds, 2021). A list of neurological deficits has emerged in acute phase COVID-19 which has shown to continue in a chronic protracted phase of COVID-19 called long-COVID (Baig, 2021). Many published reports started emerging in the year 2020 and now continue to surface in the current year that were included as a part of this review. We took into account of the methodologies, overall aims and objectives, the sample sizes, outcomes of the studies done with the trends that followed after published studies that help understand the neurological deficits of COVID-19 and long-COVID in particular. These deficits witnessed in COVID-19 illness and long-COVID syndrome have shown to depend upon several factors as seen in the published literature, factors like viral loads, ability of the body to eradicate the SARS-CoV-2, the immune escaping tactics of SARS-CoV-2 and antiviral drug treatment were seen to be the major factors determining the neurological damages resulting in COVID-19 and long-COVID syndrome. The shortcut routes of the SARS-CoV-2 to the brain through cribriform plate of the ethmoid bone also seemed to be causing the neurological involvement in COVID-19 and long-COVID syndrome (Meinhardt et al., 2021; Nalbandian et al., 2021). Persistence of viral niches in the body with periodic provocation of the immune system was seen to be a pivotal factor in neurological

involvement in COVID-19 disease and long-COVID syndrome (Baig, 2021). Access of the SARS-CoV-2 to the brain via retrograde axonal route has also been implicated to be causing damages seen in neuro-COVID (Sisniega & Reynolds, 2021). A significant contribution from cytokines and inflammatory mediators has been documented in studies published (Baig, 2022; Sisniega & Reynolds, 2021). The neurological features that are seen in long-COVID include continuations of features seen in acute-phase of COVID-19 along with appearance of new features like tinnitus, hearing impairments, cranial nerve palsies. It is worthy to mention here that feature related to loss of cognitive features referred to "brain-fog" are been reported in long-haulers with prior history of COVID-19. There is a wide array of features that have been reported in long-COVID many of which overlap with non-neurological origins of symptoms, like headaches, fatigue, skeletal muscle weakness, blurry vision, tinnitus, hearing loss, and convulsions that can have origins from organ systems other than the CNS. There is a need to have a definitive diagnosis of these complex symptoms by in-depth investigations to ascribe them to be of CNS in origin. Of the neurological features seen in long-COVID some features clearly can be allocated to lesions in CNS. Delirium, cranial nerve palsies, motor aphasia, limb paralysis and loss of muscle tone are few such examples which can be allocated to CNS with a rigorous clinical examination and imaging modalities like CT scan and MRI. The impression gathered from writing this review is that long-COVID has started to bring a huge wave of patients, the count of them been in millions now, who can enter a phase of disability due to neurological damages if not treated early in the course of the disease (Baig, 2022). Though more disabling than lethal, long-COVID patients with neurological deficit is expected to over burden the healthcare system globally which is already been struggling to handle acute COVID-19 patients in this once in a life time pandemic. There is a need to identify high-risk individuals who can proceed to long-COVID with neurological involvement and attempts should be made to adopt measures that can slow down the progression of neuronal damages that continue to occur in COVID-19 (Sisniega & Reynolds, 2021). From the knowledge presented in this review and emerging studies reporting neurological damages in COVID-19 and long-COVID, there is need to gather data from global resources and invest in research of the pathogenesis and treatment of the affected patients. With our knowledge in its infancy in the underlying mechanisms that result on neurological damages and the slow progression in acknowledging these groups of patients it appears that if we do not act quick enough, millions would be affected by the resultant disabilities caused by neurological damages caused in COVID-19 and long-COVID syndrome (Baig, 2021; Sisniega & Reynolds, 2021). The presented review implores the healthcare systems and healthcare policy makers to anticipate the enormity of the situation and act preemptively to tackle this huge population of affected individuals in long-COVID syndrome. There is a need for agencies like WHO and CDC to draw guidelines to follow to enroll, diagnose and offer treatment to patients who have developed neurological sequelae and deficits due to COVID-19 disease and long-COVID syndrome.

More than the healthcare systems and global health policy makers, the patient advocacy groups and charity foundations have been observed to raise awareness of the neuro-COVID as a disease and to fight for millions of the affected people who had no voice for their disabling conditions. Huge number of social media platforms is working round the clock to help raise money for funding research, forming clinician groups and alerting government to come forward to help their fight against neuro-COVID.

The recognition of the neuro-COVID as a disease entity should be the first step towards future management of the affected patient COVID-19 and long-COVID syndrome with neurological features. Many countries have been reluctant to even recognize these groups of patients which are alarming. The next step should be to attempt to reduce the risk of acquisition of viral access to the CNS in early stages of COVID-19. Speedy measures to reduce

nasal viral loads and limit the cytokine storm in the neurological tissue is expected to reduce the deficits caused by the disease process due to its effects on CNS either directly or indirectly. Neurological evaluation and use of imaging modalities cannot be over emphasized here, as they would prove to be playing a major part in the diagnosis of the areas and tissues involved in Neuro-COVID patients. Investing into the research of the pathogenesis and treatment of the neuro-COVID is needed now as the time is of essence to succeed while fighting against the damages caused by COVID-19 to the CNS. A global collaboration is needed indetermining and understanding the complex process of the causation of neuro-COVID and to discover treatment option in these group of patients in near future.

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Table 1: Methodological aspects of the Selected Studies from 2020-2021.

| Title, Study Type, Publication Year | Research Objectives | Research Setting | Sample and Sample Size | Results and Recommendations |
|--|--|--|---|--|
| Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. Prospective study 2021 | To determine the frequency, pattern and severity of cognitive impairments among COVID-19 affectees | Patients were recruited at the outpatient based respiratory clinic during their follow-up visit. | All previously admitted patients with a follow up visit 3 to 4 and 12 months post discharge from hospital. | Cognitive sequelae after COVID-19, lung infection and restricted cerebral oxygen delivery. |
| Post-COVID Syndrome-A case series and comprehensive review Review 2021 | To investigate the symptoms after being tested positive for SARS-CoV-2. | Case series: 100 patients in the Republic of Colombia | Comprehensive Review: patients were hospitalized due to acute COVID-19 | Respiratory symptoms. |
| Long COVID: An overview Review 2021 | To analyze various aspects of Long COVID | PubMed and Scopus databases were searched for original articles and reviews. | Patients with COVID, post COVID symptoms. Short COVID. Long COVID: old and new symptoms | Symptoms such as fatigue, cough, breathlessness, palpitations, chest tightness, myalgia and difficulty in maintaining focus. |
| Cognitive deficits in people who have recovered from COVID-19. Research Paper 2021 | To find out the severity of cognitive problems post-infection | Participants undertook clinically validated web-optimized assessment | Individuals who had recovered from COVID-19 disease | Significant deficits related to cognition, tiredness, depression, and anxiety. |
| How to detect and track chronic neurologic sequelae of COVID-19 Review 2020 | To provide an overview of the knowledge on neurological complications and sequelae of COVID-19 | Intensive care units | COVID-19 patients who were admitted to intensive care units (ICU) | Respiratory difficulties and neurological symptoms. |
| Long-Haul COVID. Special Editorial 2020 | To find the symptoms after being affected with COVID | Patients admitted to the hospital while majority were isolated at home. | Patients who have been affected with COVID | Neurological symptoms |
| Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers." Prospective study 2021 | To characterize the spectrum of neurological manifestations in non-hospitalized COVID-19 patients(long-haulers) | Neuro-COVID 19 clinic | COVID-19 patients | Frequent depression/anxiety, attention deficit |
| Neuropsychiatric complications of COVID-19. Editorial 2020 | Discussion about abnormalities related to CNS with potentially long term and serious consequences | Clinic Laboratory | Patients with severe COVID-19 disease and were treated in hospital setup | Stroke, other CNS abnormalities with long term consequence, and isolated psychiatric syndromes. |
| Long COVID—mechanisms, risk factors, and Management. Review 2021 | The review identifies and summarizes studies regarding long-term effects of COVID-19. | COVID affected who were admitted in a hospital setup and/or not hospitalized | Hospital Patients recorded results of Long COVID | Symptoms broadly involving neurological, gastrointestinal, cardiovascular, respiratory, and Musculoskeletal systems. |
| Characterization and Biomarker Analyses of Post-COVID-19 Complications and Neurological Manifestations. Article 2021 | To investigate neurological complications and sequelae following recovery from COVID-19. | Subjects' plasma was collected | Study participants were the volunteers from the San Francisco Bay area with a well-documented history of contracting SARS-CoV-2 infection, referrals and participant self-referrals. | Neuro inflammation, neurological symptoms |
| Neurological manifestations in COVID-19 caused by SARS-CoV-2. Editorial Commentary 2020 | To determine effects of COVID-19 in developing neurological manifestations | Laboratory and hospital | COVID-19 infected patients | Neurological deficits |
| Chronic COVID syndrome: Need for an appropriate medical terminology for long- COVID and COVID long- haulers Commentary 2020 | To illustrate the needed organ- based staging system of COVID- 19. | Laboratory and hospital | COVID-19 patients experiencing long COVID | Renal, cardiac, neural, gastrointestinal, and coagulative |
| Updates on What ACS Reported: Emerging Evidences of COVID-19 with Nervous System Involvement Editorial 2020 | To investigate the exclusive features of COVID-19 | Laboratory and hospital | COVID-19 patients | Systemic dysregulation including brainstem, neuronal damage |
| Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms Viewpoint 2020 | To find out the density of ACE2 expression levels ACE2 in the central nervous system | Laboratory and hospital | COVID-19 Patients | Cerebral involvement was noted as reported in the past among SARS-CoV-1 affected patients. |
| Post-COVID 19 neurological syndromes: Implications for sequelae's treatment Review 2021 | To study the implications of post-COVID syndrome secondary to neurological sequelae | Non -systematic review | Description of cases | Metabolic alterations and cardiovascular risk factors |
| Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID- 19. Clinical & Experimental Allergy. Clinical Trial 2021 | To assess persistent symptoms among patients who were previously hospitalized with COVID-19 potential risk factors. | Follow-up data from patients discharged from hospital | Adult patients | neurological and mood and behavioral changes and chronic pulmonary disease |
| Long-term brain disorders in post COVID-19 neurological syndrome (PCNS) patient. Case report 2021 | To describe the prolonged neurological consequences related to COVID-19. | PCR test, antibody tests, CT Lungs, and MRI brain | A 56-year-old patient admitted in hospital. | neurological disorders with depression. |
| Historical Insight into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID Review 2021 | To examine that cerebral hypoxia secondary to SARS-CoV-2 infection that possibly resulted from virus-induced dysfunction of mitochondria | Data obtained from past epidemics and pandemics | COVID-19 Patients | Reviewing the neurological and psychiatric complications of SARS-CoV-2 described the historical context of long outcomes of COVID infection |
| Long-Term Neurological Impact of COVID-19 Original Article 2021 | To describe the neurological sequelae in long-term among patients with COVID-19 disease. | A long-term study was conducted at a tertiary care hospital in Pakistan | 1,000 patients who were admitted in the hospital due to COVID-19 and later recovered. These participants were followed up at 30 and 90 days respectively, post discharge from hospital. | The most commonly reported neurological symptom was headache, followed by insomnia and altered sense of smell. |
| COVID-19 Symptoms Over Time: Comparing Long-Haulers to ME/CFS Article 2021 | To find out the symptoms among long-hauler COVID-19 patients changing over time. | Questionnaires were posted on social media sites, dedicated to the exchange of information among long-haulers. | Comparison groups of 502 patients diagnosed with myalgic-encephalomyelitis and chronic fatigue syndrome | Several neurocognitive symptoms kept on worsening over time among the COVID-19 long haulers. |
| COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review Review 2021 | Review of COVID-19 patients who experienced a prolonged convalescence phase. | Data from narrative patient experiences after COVID-19 infection | COVID-19 patients | Pivotal similarities were found between post-acute COVID-19 symptoms and ME/CFS, however, the evidence currently at hand is not sufficient enough to establish COVID-19 as an infectious trigger for chronic fatigue syndrome. |
| Chronic long-COVID syndrome: A protracted COVID-19 illness with neurological dysfunctions Editorial Commentary 2021 | To determine the resolution for the patients with long-COVID. | Patients with long-COVID present persistent neurological disabilities and deficits. | Patients having long-COVID symptoms | Neurological deficits in long-COVID are evidencing itself as a foremost cause of disability in the post-acute COVID patient group |