

Evaluate Post-Covid-19 Syndrome from A Biological Perspective: A Review

Neha V

Assistant Professor, Lingayas Institute of Health Sciences Nursing
Faridabad, Haryana

ABSTRACT - Post-coronavirus illness 2019 (post-COVID-19) syndrome has been identified in a number of patients who initially experienced symptoms during the initial stages of the 2019 coronavirus disease pandemic. Since SARS-CoV-2 is a respiratory coronavirus that induces COVID-19, lung damage is a common complication; however, many other cells & organs are typically harmed as well, resulting in a wide range of symptoms. Patients with mild to severe COVID-19 experience these long-lasting symptoms, however there is little published research on the possible pathophysiological reasons behind this disease. This comprehensive study aims to sum up & assess the biological evidence surrounding post-COVID-19 syndrome. The research reviewed up to August 30, 2021 was included in an integrated review using the methods developed by Whittemore & Knafl.

KEYWORDS- COVID-19, SARS-CoV-2, Symptoms, Post-COVID-19, Pathophysiology

INTRODUCTION

COVID-19 has been identified in around 117 million people across the globe as of March 2021, resulting in over 2.6 million deaths. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for COVID-19, is a heterogeneous virus whose symptoms range from asymptomatic

to lethal (2–7). One of the most prevalent manifestations of SARS-CoV-2 is interstitial pneumonia, which can progress to acute respiratory distress syndrome (ARDS), a condition related with a high fatality rate, especially in the elderly with numerous comorbidities [Mao R 2020]. As the COVID-19 pandemic continues, many other symptoms have been reported [Levi M 2020].

These include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhea, headache, weakness, rhinorrhea, anosmia/ageusia, & numerous laboratory abnormalities, including lymphopenia & high inflammatory markers. Impaired heart, brain, lung, liver, kidney, & coagulation system function are other essential and severe consequences of COVID-19 [Long B 2020; Chen YT 2020].

Most people who contracted COVID-19 had full recoveries. Some people infected with SARS-CoV-2 do not fully recover from the earliest stages of COVID-19 disease, even years after the initial infection. Long-Haul COVID-19 or Long-term COVID-19 were the terms used by clinicians around the world to describe these complications caused by COVID-19 over the long term [COVID Symptom Study 2020]. Specifically, "long-term COVID-19" describes people who have been infected with SARS-CoV-2 but have not fully recovered within a short length of time (about 2-3 weeks) [Hui DS 2020]. According to the COVID-19 Symptom Analysis, an analysis of more than 4 million people in the United States, the United Kingdom, & Sweden in which people enter their ongoing symptoms on a smartphone app, around 10% of patients who have tested positive for SARS-CoV-2 virus persist

unwell beyond 3 weeks, & small proportion for months [Correia AO 2020]. That some persons with SARS-CoV-2 infections, even those considered "moderate," continue to experience persistent or cyclical symptoms is becoming increasingly apparent.

METHODS

To better comprehend the meaning, categorization, & pathophysiology of post-COVID-19 syndrome, an integrated evaluation of the published empirical & theoretical studies was performed. The integrative review followed the requirements established by PRISMA (Moher et al., 2009) & integrative evaluation approach established by Whittemore (2005). The issues of rigor, accuracy, & bias were addressed through the following methods.

Examination Strategy & Result

The search phrases used in this study were generated from the main ideas & review questions created to better comprehend post-COVID-19 syndrome. Post-COVID-19 syndrome, post-SARS-CoV-2, long COVID-19, long COVID-19 syndrome, & pathophysiology of post-COVID-19 were used to search PubMed, CINAHL, & Web of Science for publications released as of August 30, 2021. There was a total of 27,929 items found (Table 1). Search approach

flowchart depicted in Figure 1. The 324 most promising paper titles were identified through a process of screening and evaluation. The authors of this study only examined the abstracts for the other 324 papers and only reviewed 51 of them in detail. The pathophysiology of post-COVID-19 syndrome was the criteria for selecting the 51 papers. Articles focusing on people under the age of 18 or animals were disqualified. During a full-text review, we manually searched for cited works; three additional articles were sourced from government & academic health organizations like the Advisory Council to the National Institute of Health task force on post-COVID-19 sequelae & Centres for Disease Control & Prevention. In the Final, 54 papers were chosen for the examination since they were deemed relevant

Data Evaluation

Due to the heterogeneity of the investigated papers & lack of uniform criteria for quality assessment, conducting an integrated analysis' data and quality evaluation is a challenging task (Whittemore, 2005). Hawker et al(2002) .'s critical evaluation methodology was used to analyze each publication & assign a reliability grade to the data presented in both empirical and

theoretical studies. Very poor, poor, fair, & good are the levels of assessment provided by the instrument. Articles rated "poor" or "very poor" more than thrice did not make the cut. Articles having a large rating gap were reviewed between the two researchers in order to obtain a consensus.

Data Analysis

The data was analyzed utilizing a constant comparison method, which allowed for the data to be systematically reviewed in categories to reveal trends, differences, & connections. Data from each article was collected, coded, and then organized into one of three categories: classification of post-COVID-19 syndrome; long-term manifestations of post-COVID-19 syndrome; & post-COVID-19 pathophysiological variants. All team used an iterative comparison & contrast strategy to combine findings from several papers into a single body of research.

RESULTS

Until 2020, the long-term effects of recovering from COVID-19 syndrome were not a primary focus of research. However, the pathophysiology of the illness was often overlooked in favor of discussions of its nomenclature and epidemiology. For this reason, we made sure to define post-COVID-

19 syndrome, categorize its symptoms, or describe its current signs and symptoms. When we looked at the post-COVID-19 syndrome's pathophysiology, we observed four main groups:

Virus-specific pathophysiological alterations;
oxidative stress; immunologic abnormalities;
& inflammatory damage

Classifications of Post-COVID-19 Syndrome

A consensus on how to define post-COVID-19 syndrome has yet to form as of the middle of 2021. Post-COVID-19 was first defined by Greenhalgh et al. (2020) as a prolonged sickness lasting more than 3 weeks following the acute start of symptoms. Long-term sickness affects more than 10% of people infected with COVID-19. However, it has been established that symptoms that last for more than 12 weeks after initial start are considered chronic COVID-19. For this reason, several researchers and physicians have modified Greenhalgh's criteria to begin the post-acute COVID-19 period following hospital discharge (Amenta et al., 2020). Type 1 is the least severe kind of post-COVID-19 syndrome, while Type 5 is the most severe. These classifications are based on criteria like the severity of early symptoms, the length of time symptoms persist, the

timing of their development, and periods of remission (Table 2). The start of symptoms in those with Type 1 is sudden, the severity of symptoms is mild to severe, and there is no remission phase or delayed onset of symptoms. Due to differences in sickness and complication severity, these people require various amounts of time to recover. Initial symptoms in people with Type 2 are modest, and they persist for more than six weeks. There is no lag time between the start of symptoms & diagnosis, and there is no remission. Type 3 patients experience modest initial symptoms that persist for more than 3 months; they do not experience a delayed onset of symptoms, nor do they experience a remission phase. Persons With Type 4 SARS-CoV-2 test: and then develop symptoms hours to days later. There is no remission phase. Type) patients have a positive SARS-CoV-2 test but no initial morns; later on, they develop symptoms but there is no intercurrent asymptomatic phase (Table 2; Pavli et al., 2021). Some medical professionals divide post-COVID-19 into three stages: (a) post-infection symptoms that persist, (b) post-recovery symptoms that persist, and (c) new symptoms in previously asymptomatic patients (Amenta et al., 2020).

Table 1. Numerical Results/Articles from Search Terms and Sea

Search terms	PubMed	CINAHL Complete	Web of Science
Post-COVID-19 syndrome	298	17	1,444
Post-SARS-CoV-2	64	541	137
Long COVID-19	9250	129	11,556
Long COVID-19 syndrome	2097	1	2,210
Pathophysiology of post-COVID-19	82	1	102
	Total = 11,791	Total = 689	Total = 15,449

Table 2. Five categories of post-covid-19 syndrome based on four criteria

Categories by type	Initial symptoms	Duration of symptoms	Delayed onset of symptoms	Period of quiescence
Type 1	Variable	Variable	No	No
Type 2	Mild	>6 weeks	No	No
Type 3	Mild	3 to >6 months	No	Yes
Type 4	None	Variable	Yes	No
Type 5	None	None	≥3-6 months	No

Note: Post-COVID-19 syndrome: incidence, clinical spectrum, and challenges for primary healthcare professionals (Pavli et al., 2021). Archives of Medical Research.

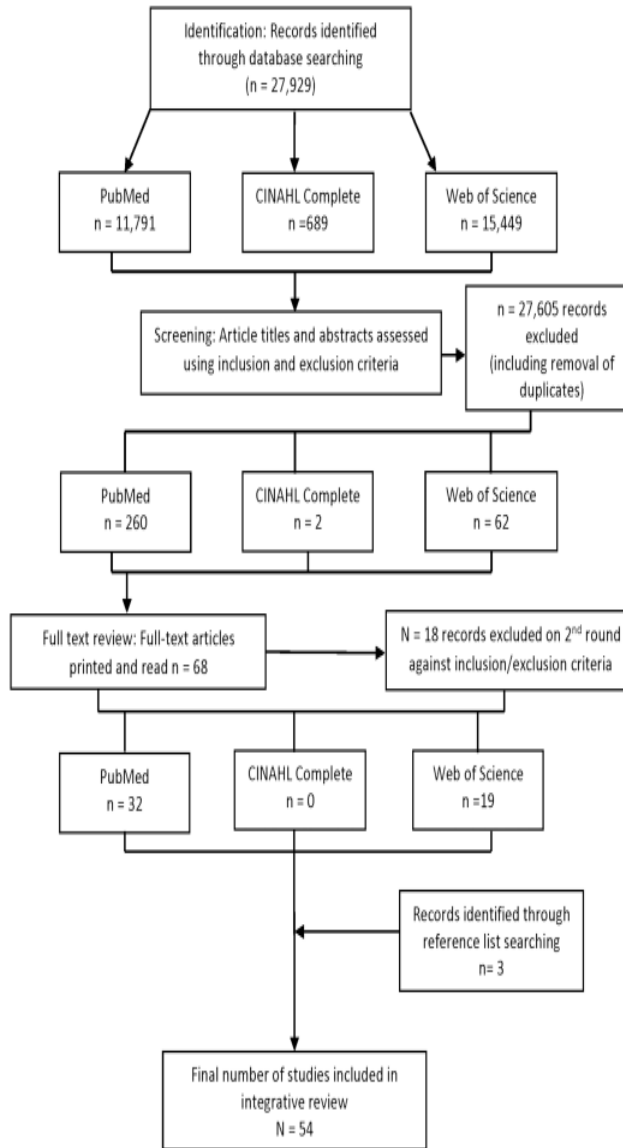


Figure 1. PRISMA flow chart of search strategy

Long-Term Manifestations of Post-COVID-19 Syndrome

Those with post-COVID-19 syndrome often exhibit a wide range of anomalies, some of which may interfere with the body's natural ability to heal. It is not uncommon for people hospitalized with adult respiratory distress syndrome (ARDS) to experience problems as a result of the therapeutic measures, prolonging already difficult recoveries (Matsuishi et al., 2021). According to research by Miwa et al. (2021), after 100 days, in contrast to the 90% of patients with invasive mechanical ventilation who still had pulmonary difficulties, only 47% of those who were not getting mechanical ventilation show severe persistent decreased pulmonary function. In fact, many people who were treated successfully for acute COVID-19 in a hospital setting are now dealing with post-acute infections. Following 60 days of treatment, 1,250 individuals diagnosed with

COVID-19 were analyzed by Chopra et al. (2021). Within 60 days, 6.7% of patients had died, & 15.1% had been readmitted due to problems following COVID-19. In addition, these researchers used telephone interviews with post-COVID19 patients (n = 488) & discovered that 32 percent still experienced COVID-19-related symptoms, with 18 percent experiencing either new or worsening symptoms. Most people complained of having trouble breathing when climbing stairs, coughing, & losing their sense of smell or taste. Seventy percent or more of people with these symptoms used to be physically active before they got sick, but now they rarely leave the house because of how bad the symptoms make them feel (Carfi et al., 2020). The most commonly seen post-COVID-19 syndrome symptoms are included in Table 3. Nearly 70% of these people also suffer from dyspnea, and 60% report feeling fatigued or extremely exhausted (Levison, 2020).

Epidemiology & Clinical Spectrum of Post-COVID Syndrome

Individuals who have tested positive for SARS-CoV-2 infection & handled in an outpatient environment or at home have a post-COVID sequelae incidence between 10% & 35% [Greenhalgh 2020], while the incidence of post-COVID syndrome in those who have been hospitalized may be as high as 80%. Patients who were hospitalized may experience symptoms for up to eight weeks

after being released, whereas those who were not admitted may experience them for longer than four weeks. The post-COVID syndrome is not unique to people with severe acute COVID-19. Patients who go on to develop post-COVID syndrome typically experience modest symptoms during the acute COVID-19 disease that gradually subside with time and for which no risk factors have been found [Moreno-Pérez 2021]. Asymptomatic SARS-CoV-2 infections have been linked to cases of olfactory and gustatory impairment [Le Bon SD 2020]. Additional Table 3 summarizes, as of March 15, 2021, the features & symptoms of individuals with post-COVID syndrome as reported in the literature. The following sections contain issued data on the epidemiology & clinical spectrum of cases following COVID:

Table 3. COVID-19 sequelae subtype criteria *, COVID-19 Clinic of the University of Cincinnati Medical Center

	Type 1	Type 2	Type 3		Type 4		Type 5
Initial symptoms	Variable ^a	Mild	A	B	A	B	None
Duration of symptoms	Variable ^a	>6weeks	Mild	Mild	None	None	N/A
Period of quiescence	No	No	3-6 months	>6 months	Variable	Variable	N/A
Delayed onset of symptoms	No	No	Yes	Yes	No	No	N/A
					Yes	Yes	Yes
					≥3 months	≥6 months	

Fatigue

Chronic fatigue syndrome/myalgic encephalomyelitis is associated with COVID-19 and manifests in patients with

persistent fatigue, cognitive impairment, depression, and other symptoms following even mild exertion [Moldofsky 2011]. According to Supplemental Table 3, For COVID-19 patients admitted to hospital wards or intensive care units, fatigue is the most common symptom of post-COVID syndrome, causing between 17.5% and significantly higher rates (Garrigues 2020). Patients with COVID-19 have reported considerable disability in the form of fatigue for up to seven months following the commencement of the virus & patients continue to have fatigue beyond 7 months, necessitating further examination [Davis HE, 2021]. Chronic exhaustion has been linked to being male and having co-occurring conditions including high blood pressure and diabetes [Simani L 2021]. Since there is no agreed-upon way to diagnose at the moment, it is vital to rule out other conditions that present similarly. Hormonal abnormalities, immune system malfunction, infections, and anomalies in the neurological system are all possible contributors to the pathophysiology of the condition.

Dyspnea & Chest Pain

Patients hospitalized with COVID-19 may be more likely to experience respiratory & physical complications [Bellan 2021]. Up to four months after being released from the

hospital, a sizable percentage of patients with COVID-19 may still report experiencing symptoms like dyspnea & impaired exercise tolerance. Ten % of COVID-19 survivors reported experiencing dyspnea for 2 months [Bellan 2021], whereas forty percent reported it lasting 4 months. Up to 42.6% of patients admitted & 65.6% of critical care unit patients reported new or worse breathlessness weeks after being discharged from the hospital. After 2 months, up to 22 percent of survivors still experienced chest pain [Carvalho-Schneider 2021]. Respiratory & physical functional impairment after COVID-19 are linked to long-term lung injury and may have an effect on mental health & quality of life in COVID-19 survivors. Long-term observation is necessary to determine whether patients with post-COVID syndrome are at an improved risk for liberal lung fibrosis due to the presence of chronic obstructive pulmonary disease.

Psychiatric Symptoms & Post-traumatic stress disorder

Persistent psychiatric symptoms (such as PTSD, depression, anxiety, & cognitive impairment) between patients with COVID-19 are likely to have a complex etiology that includes not only the effects of the virus itself but also the immune response, corticosteroid

treatment, serious care unit stay, social isolation, & stigma. Even six months after COVID-19 [Huang C 2021], as many as 26 and 23% of patients, correspondingly, may experience sleep difficulties, anxiety, or sadness. The development of obsessions & compulsions, lack of trust in others, withdrawal from social activities, inability to focus, anger, irritability, substance abuse, & cognitive impairment are all symptoms associated with stress disorders. Recovery from a potentially fatal condition like COVID-19 is associated with an increased risk of developing post-traumatic stress disorder (PTSD), [Soloveva 2020] A classification of mental health problems that have been linked to exposure to traumatic or otherwise emotionally taxing experiences. The psychological, neurologic, or somatic symptoms or the inflammatory consequences on the brain may increase the risk of suicidal ideation and

behavior not only in patients with post-COVID syndrome but also in Covid-19 survivors without post-Covid syndrome. Some people infected with COVID-19 experience neurological symptoms and mild-to-moderate cognitive impairment, and this may be the result of several of factors, such as indirect effects from things like systemic damage outside the CNS and psychological

trauma [Ritchie K, 2020]. Female gender is associated with increased risk for the development and maintenance of psychological disorders including anxiety and sadness. But there hasn't been any evidence linking long-lasting mental health issues to a more serious condition. Neurological consequences of post-COVID syndrome, such as Guillain-Barré syndrome, have been more common in males than females, a difference not evident in the classic form [Raahimi MM 2021].

Rare Neurologic Clinical Syndromes

Although reports of post-COVID neurological problems are scarce, the complexity of this issue is gradually being revealed [Emamikhah 2021]. Novel neurological symptoms are being revealed in those with COVID-19, which is a neuro-inflammatory disorder. These include cerebrovascular disorders, altered mental status involvement of the peripheral nervous system & neuropsychiatric involvement infection is associated with a small risk of developing Guillain-Barré syndrome months or years later. Guillain-Barré syndrome has a complicated etiology, but it is thought to be the result of an immunological reaction to an infection [Scoppettuolo 2020]. This would lead to larger series, which in turn would provide light on the whole range of this

neurological disorder [Camdessanche 2020]. Post-infectious neurologic complications of COVID-19 have been documented, specifically opsoclonus-myoclonus syndrome [Emamikhah 2021], which may be associated to an immune-mediated mechanism. Knowing the signs & symptoms of this condition can help doctors make a correct diagnosis & select the best treatment for their patient [Emamikhah 2021]. There is evidence that acute transverse myelitis can develop after COVID infection. Acute spinal cord inflammation (ASC) can be further subdivided into discrete etiological subgroups. The most frequent form of myelitis has an autoimmune basis. Neuronal loss or spinal tract lesions may ensue from the viral inflammatory process that follows myelitis, which typically develops as a post- or para-infectious illness due to an immunologic process targeting the exterior nervous system [Kilbertus S. 2021].

Olfactory & Gustatory Dysfunction

Patients may still be affected by olfactory & gustatory impairment up to 11% & 9%, respectively, six months following hospital release [Chopra V, 2020]. There has been no correlation between age or gender and olfactory results. Mechanisms by which SARS-CoV-2 causes olfactory dysfunction are not fully understood, but may involve the

loss of peripheral olfactory receptor neurons or cells that express two proteins recognized to be utilized by SARS-CoV-2 to infect human cells (ACE2 and TPMRSS2). The exact mechanism by which SARS-CoV-2 induces a loss of taste is still unknown. As ACE2 receptors have been located in the oral cavity & tongue, it's possible that this is caused by direct injury to the gustatory organ. Up to one third of patients may still be experiencing gastrointestinal symptoms 2 months following discharge [Liang L, 2020], including diarrhea & vomiting.

CONCLUSION

Patients with severe acute COVID-19 are not the only ones at risk for developing post-COVID syndrome, affect around 10% of COVID-19 patients. Clinical indications of COVID-19 affecting several organ systems, including as the cardiovascular, pulmonary, renal, & neuropsychiatric, have been reported, however it is unknown how long these effects will last. Hospitalization and the "effects of COVID-19 treatment" have the same long-term consequences as other serious infections. Post-intensive care syndrome (PICS), which causes profound fatigue, & post-traumatic stress disorder (PTSD) are two examples. It appears that time is helping many people recover from these COVID-19 problems. The symptoms of post-COVID syndrome are often modest, get better with time, and have no known causes.

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Correspondence Author

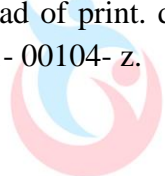
Neha V

Assistant Professor, Lingayas Institute of Health Sciences Nursing, Faridabad, Haryana

Email Id: vneha1083@gmail.com



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