Post-COVID-19 Syndrome

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Background: Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, many individuals have reported persistent symptoms and/or complications lasting beyond 4 weeks, which is now called post-COVID-19 syndrome. SARS-CoV-2 is a respiratory coronavirus that causes COVID-19, and injury to the lungs is expected; however, there is often damage to numerous other cells and organs, leading to an array of symptoms. These long-term symptoms occur in patients with mild to severe COVID-19; currently, there is limited literature on the potential pathophysiological mechanisms of this syndrome.

Objectives: The purpose of this integrative review is to summarize and evaluate post-COVID-19 syndrome from a biological perspective.

Methods: An integrative review was conducted using Whittemore and Knafl's methodology for literature published through August 30, 2021. The PubMed, CINAHL, and Web of Science databases were searched for articles published as of August 30, 2021, using combinations of the following key words: post-COVID-19 syndrome, post-SARS-CoV-2, long COVID-19, long COVID-19 syndrome, and pathophysiology of post-COVID-19. Data were analyzed using the constant comparison method.

Results: The search generated 27,929 articles. After removing duplicates and screening abstracts and full-text reviews, we retained 68 articles and examined 54 specific articles related to the pathophysiology of post-COVID-19 syndrome. The findings from our review indicated that there were four pathophysiological categories involved: virus-specific pathophysiological variations, oxidative stress, immunologic abnormalities, and inflammatory damage.

Discussion: Although studies examining the pathophysiology of post-COVID-19 syndrome are still relatively few, there is growing evidence that this is a complex and multifactorial syndrome involving virus-specific pathophysiological variations that affect many mechanisms but specifically oxidative stress, immune function, and inflammation. Further research is needed to elucidate the pathophysiology, pathogenesis, and longer term consequences involved in post-COVID-19 syndrome.

Key Words: immunologic abnormalities • inflammatory damage • long-term symptoms of COVID-19 • oxidative stress • post-COVID-19 syndrome

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The first pandemic of the 21st century was in February 2003; it was a severe acute respiratory syndrome (SARS) caused by a coronavirus known as SARS-CoV. Then in December 2019, a deadly respiratory virus outbreak spread quickly in Wuhan, China, which became known as SARS-CoV-2, a new coronavirus named COVID-19 (coronavirus disease 2019; Chen et al., 2020). Both SARS and COVID-19 are respiratory illnesses caused by a specific human coronavirus, but there are differences between the two (Nalbandian et al., 2021). Coronaviruses are a family of viruses with a diverse range of hosts, particularly bats. Most often, the symptoms of a coronavirus are similar to the common cold with mild respiratory effects. These viruses have surface spikes that resemble crowns and are named for the Latin word for crown (corona).

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SARS-CoV-2 has caused terrible global morbidity and mortality rates because of severe damage to multiple organs. Even though many persons are surviving the acute phase of COVID-19, there is mounting evidence that the residual effects of SARS-CoV-2 infection can affect the person's quality of life and ability to return to work. There is often a constellation of persistent symptoms, including dyspnea, fatigue, loss of taste and smell, cognitive impairment, chest pain, and arthralgia (Nalbandian et al., 2021). The SARS-CoV-2 infection causes cellular damage by initiating the innate immune response with inflammatory cytokine production and a procoagulant state. These symptoms can be new, recurring, or ongoing—more than 4 weeks after the onset of infection. Persons with post-COVID-19 conditions may have these symptoms with varying degrees of illness during acute infection (Centers for Disease Control and Prevention, 2021).

A review of the literature reveals a wide range of terms for post-COVID-19 conditions: post-COVID-19 syndrome, post-acute COVID-19 syndrome, chronic COVID-19, long-term effects of COVID-19, long COVID-19, and post-acute sequelae of SARS-COV-2 infection. All these terms and others indicate that, following COVID-19 illness, the person lacks a return to a usual state of health. For the purpose of consistency and clarity,

the term *post-COVID-19 syndrome* is used in this article. Many scientists are investigating and searching for the causes of these symptoms, why and when they occur, and how to treat them (Oronsky et al., 2021). Researchers and clinicians have proposed numerous general pathophysiological mechanisms for post-COVID-19 syndrome based on the severity of the illness, the organs affected by the virus, immunologic abnormalities and inflammatory damage, virus-specific pathophysiological changes, and oxidative stress.

However, the exact pathophysiological mechanism of post-COVID-19 syndrome is still unclear, despite many hypotheses and studies suggesting mechanisms of action. As the COVID-19 pandemic continues, it is important to understand patient care needs beyond the acute phase, particularly the mechanisms causing persistent symptoms beyond 3 or 4 weeks from the onset of acute illness (Nalbandian et al., 2021). In this review, we describe the symptoms and various definitions and categories of post-COVID-19 syndrome. We also discuss the known pathophysiological changes that occur in post-COVID-19 syndrome and possible mechanisms for these symptoms. The objective of this integrative review is to summarize and evaluate post-COVID-19 syndrome from a biological perspective.

Background

Coronaviruses are positive-stranded RNA viruses that most often affect the respiratory tract. The lungs are particularly vulnerable to the virus because the virus can access human type II alveolar cells via the angiotensin-converting enzyme 2 (ACE2). The SARS-CoV uses specific host cell factors throughout its infection cycle because it cannot reproduce on its own. The virus replicates within cells by diverting the body's own cellular machinery and binds the virion to the receptor ACE2 (Murgolo et al., 2021).

The SARS-CoV-2 has surface glycoproteins called *spikes* that connect to the ACE2 receptor to enter the host cell. The S-protein spike is the viral element that attaches to the host receptor via the ACE2 receptors, and there are two subunit S-proteins known as S1 and S2. The S1-protein determines the virus-host range and cellular tropism via the receptor-binding domain and binds to the host receptor ACE2 (Astuti & Ysrafil, 2020). Once the virus is on the ACE2 cell surfaces, it causes leukocytic infiltration and alveolar wall and blood vessel permeability and reduces lung surfactants. This leads to respiratory symptoms and inflammation that may result in a cytokine storm and eventually a systemic inflammatory response syndrome. The S2-protein mediates fusion of the virus with the cell host via the H1 and HR2 receptors by forming a six-helical bundle. It is the S1 domain that induces immunoglobin G and immunoglobulin A antibody activity. The M-protein of SARs-CoV-2 controls transmembrane transport of nutrients and the formation of the viral envelope. There are also N- and E-proteins that restrict the host's immune response. The N-protein (nucleocapsid) is in the endoplasmic reticulum Golgi region connected to the nucleic acid material of the virus. Because the N-protein is bound to RNA, it is involved with viral replication and viral infections. These structural features of SARS-CoV-2 increase its ACE2-binding affinity and improve the specificity of reverse transcription polymerase chain reaction test for the genome sequence (Walls et al., 2020).

Surveys obtained from persons with post-COVID-19 syndrome have shown persistent symptoms such as fatigue, diffuse myalgia, and joint and musculoskeletal pain. These symptoms are all linked to mitochondrial dysfunction, oxidative stress, and reduced antioxidants. The mitochondria may play a role in understanding the pathophysiology and treatment of post-COVID-19 syndrome fatigue. Mitochondrial bioenergetic dysfunction may lead to anaerobic glycolysis to compensate for dysfunctional oxidative phosphorylation. An increase in glycolysis causes cellular damage, and glycolysis may inhibit lactate levels and other metabolic pathways. A possible explanation for muscle aches and fatigue is that the virus selectively infects neurons because this enables the virus to evade the host's immune system. SARS CoV-2 can invade the host immune system by going into a state of latency with low replication while infecting neurons. Activation of inflammasomes, part of the innate immune system receptors, can be related to a cytokine storm and hypercoagulopathy in the infected host. Thus, the person with post-COVID-19 syndrome may have lifelong infections that can be reactivated whenever some stress weakens the host's immune system (Gedefaw et al., 2021).

With SARS-CoV-2, the body has a persistent, excessive inflammatory response to clear the virus, mainly in the respiratory system. This inflammation is both beneficial and harmful, depending upon the duration of the infection. There are two significant categories of inflammation stimulation that initiate immune responses: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMP detection of the SARS-CoV-2 activates antiviral genes to establish a cellular antiviral state, enabling cells to limit and clear the infection. With the introduction of SARS-CoV-2, neutrophils are activated and release neutrophil extracellular traps, which then activate DAMPs. Particularly in the lungs, cells release DAMPs to alert the innate immune system to begin cell death. In addition, heat shock proteins and high-mobility group Box 1 stimulate mitogen-activated protein kinases and nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF-κB) to activate the inflammatory response (Bolourani et al., 2021).

When activated in the central nervous system, the PAMPs and DAMPs bind to receptors to stimulate the intracellular inflammasomes and the central nervous system defense system (Eze & Starkweather, 2021). Inflammasomes induce inflammation in response to infectious microbes, but excessive inflammation can result in chronic or systemic inflammatory diseases (Guo et al., 2015). Eze and Starkweather (2021) have hypothesized that the symptoms of post-COVID-19 syndrome are associated with similar pathophysiological events such as the development and maintenance of pain by the microglial

release of proinflammatory mediators and initialization of the inflammasomes.

METHODS

An integrative review of published empirical and theoretical literature was conducted to better understand the definition, classification, and pathophysiology of post-COVID-19 syndrome. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and the integrative review methodology by Whittemore and Knafl (2005) guided the integrative review. Problem identification, literature search, data evaluation, data analysis, and presentation were the five strategies used to address the concerns of rigor, inaccuracy, and bias (Whittemore & Knafl, 2005).

Search Strategy and Outcome

Search terms were derived from key concepts and review questions developed to enhance the understanding of post-COVID-19 syndrome. The PubMed, CINAHL, and Web of Science databases were searched for articles published as of August 30, 2021, using combinations of the following key words: post-COVID-19 syndrome, post-SARS-CoV-2, long COVID-19, long COVID-19 syndrome, and pathophysiology of post-COVID-19. A total of 27,929 articles were identified (Table 1). Figure 1 depicts the flowchart outlining the search strategy. Article titles were assessed for relevance, and a total of 324 were selected for further review. We read the abstracts of these 324 articles and thoroughly reviewed 51 articles. The 51 articles were chosen because they related to the pathophysiology of post-COVID-19 syndrome. Exclusion criteria were articles on children under 18 years of age and animals. We hand-searched reference lists during a full-text review; three articles were added from official scientific and public health websites such as the Advisory Council to the National Institutes of Health task force on post-acute COVID-19 sequelae and the Centers for Disease Control and Prevention. Finally, 54 articles were included in the review based on their relevance.

Data Evaluation

Evaluating the data and quality of studies in an integrative analysis is complex because of the variety of articles included and lack of standards for evaluation; therefore, the quality of the articles was reviewed by two investigators (Whittemore, 2005). Each article was studied using the framework developed by Hawker et al. (2002) to grade the reliability of the results from empirical and theoretical articles using the critical appraisal tool. The tool grades on a scale that includes "very poor," "poor," "fair," and "good." Articles with two or more "poor" or "very poor" scores were removed from the evaluation. The two investigators discussed any articles with the significant discrepancy in scores until a conclusion was reached.

Data Analysis

Data analysis was completed using a constant comparison method whereby data could be examined in systematic categories to identify patterns, variations, and relationships. Thus, data from all articles were extracted, coded, and divided into three groups according to their focus: definition and classification of post-COVID-19 syndrome, long-term manifestations of post-COVID-19 syndrome, and post-COVID-19 pathophysiological variations. Each group reviewed the data using an iterative compare and contrast method to integrate results across articles.

RESULTS

Prior to 2020, most studies related to COVID-19 did not address long-term sequelae of post-COVID-19 syndrome. Many articles focused on the nomenclature and epidemiologic data related to the syndrome and not the pathophysiology. Thus, we included the definitions, classifications, and manifestations related to post-COVID-19 syndrome to clarify current terminology and indicators of the syndrome. When examining the pathophysiology of post-COVID-19 syndrome, we found the following major categories: (a) virus-specific pathophysiological variations, (b) oxidative stress, (c) immunologic abnormalities, and (d) inflammatory damage.

Definition and Classifications of Post-COVID-19 Syndrome

As of mid-2021, there is still no commonly accepted definition of post-COVID-19 syndrome. Greenhalgh et al. (2020) were the first to define post-COVID-19 as an extended illness for more than 3 weeks after the acute onset of symptoms. More than 10% of persons with COVID-19 experience prolonged illness. However, the term *chronic COVID-19* has been defined as persistent symptoms extending beyond 12 weeks after the

TABLE 1. Numerical Results/Articles From Search Terms and Search Engines

Search terms	PubMed	CINAHL Complete	Web of Science	All
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	Total = 27,929

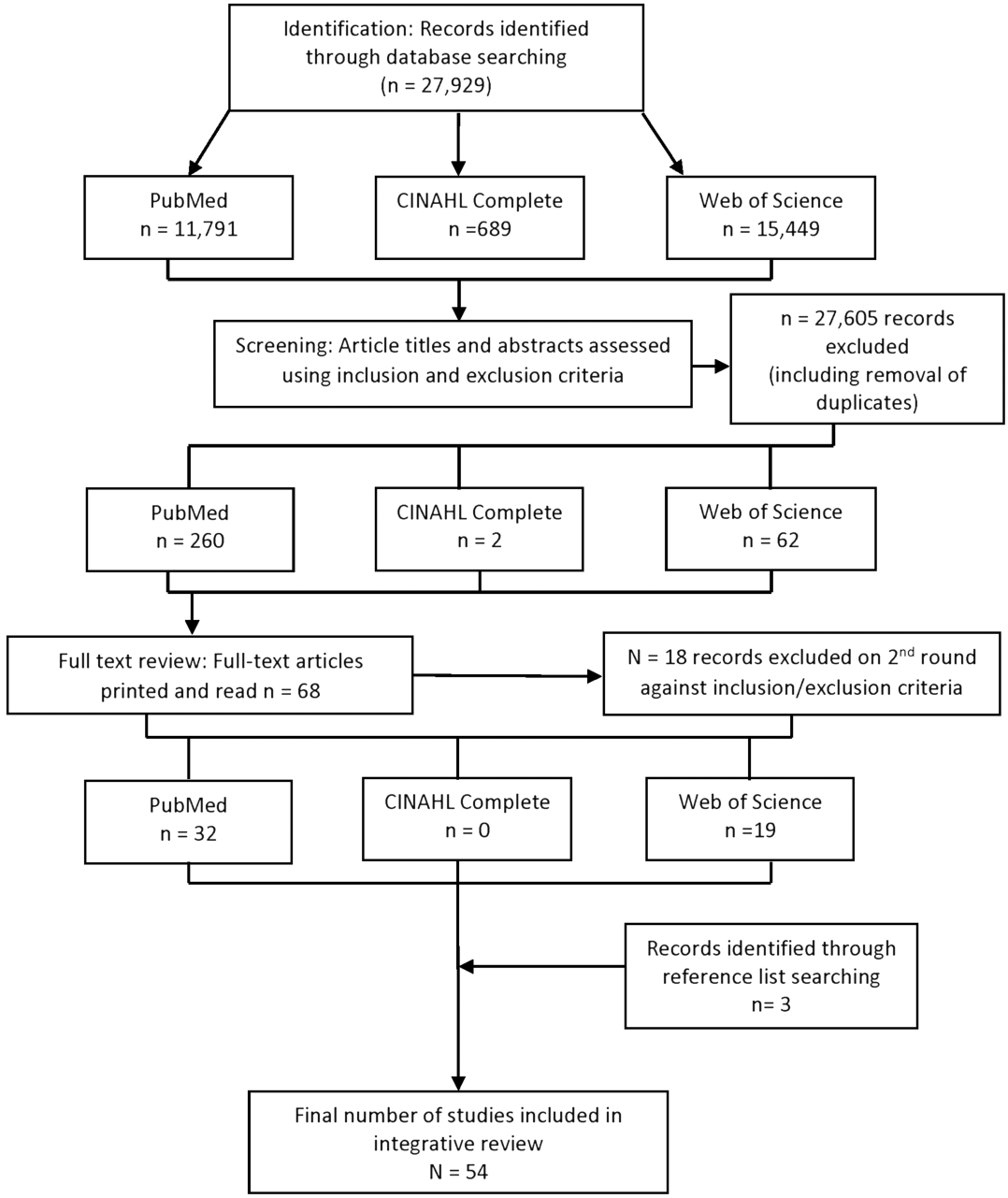

FIGURE 1. PRISMA flow chart of search strategy.

onset of symptoms. Some investigators and clinicians have expanded Greenhalgh's definition to exclude hospitalized time, starting the post-acute COVID-19 period after discharge from the hospital (Amenta et al., 2020).

There are five categories of post-COVID-19 syndrome labeled Type 1 through Type 5 with criteria based on initial symptoms, duration of symptoms, delayed onset of symptoms, and period of quiescence (Table 2). Persons with Type 1 have initial COVID-19 symptoms, variable duration of the symptoms, and no delayed onset of symptoms or period of quiescence. These persons have a different duration of recovery because of the severity of their illness and complications. Persons with Type 2 have mild initial symptoms, duration of symptoms of more than 6 weeks, and no delayed onset of symptoms or period of quiescence. Persons with Type 3 have mild initial symptoms but with duration of symptoms of more than 3 months, no delayed onset of symptoms, and a period of quiescence. Persons with Type 4 are asymptomatic (no initial symptoms) with a positive SARS-CoV-2 test, delayed symptoms of variable duration once they have symptoms, and no period of quiescence. Type 5 persons have a positive SARS-CoV-2 test with no symptoms and then delayed onset of symptoms with no period of

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).
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quiescence (Table 2; Pavli et al., 2021). Other clinicians classify only the acute phase of post-COVID-19 into these categories: (a) residual symptoms from an acute infection that continues after the infection, (b) continued organ dysfunction after initial recovery, and (c) new symptoms after being initially asymptomatic (Amenta et al., 2020).

Long-Term Manifestations of Post-COVID-19 Syndrome

Persons with post-COVID-19 syndrome have a variety of complex abnormalities that could alter the progression of the healing process. Often, the therapeutic interventions—particularly when persons are hospitalized for adult respiratory distress syndrome (ARDS)—lead to complications that require lengthy recovery (Matsuishi et al., 2021). Miwa et al. (2021) found that 47% of patients not on mechanical ventilation had significant persistent abnormal pulmonary function, whereas 90% of those who underwent invasive mechanical ventilation still had pulmonary problems at 100 days. Many persons who survived hospitalization for acute COVID-19 now have post-acute infections. Chopra et al. (2021) reviewed the outcome data of 1,250 COVID-19 patients from 38 U.S. hospitals who were still alive after 60 days. Data showed that 6.7% of patients died after 60 days, and 15.1% were readmitted to the hospital for post-COVID-19 complications. These investigators also conducted telephone interviews with post-COVID-19 patients (n = 488) and found that 32% still had persistent COVID-19 symptoms, with 18.9% having new or deteriorating symptoms. The most common reported symptoms were dyspnea walking up the stairs, coughing, and loss of olfactory and gustatory function.

The multitude of symptoms experienced by persons with post-COVID-19 syndrome that persist for more than 4 weeks are often due to damage to the respiratory, cardiovascular, neurological, gastrointestinal, and other systems. Approximately 70% of persons with these symptoms had been physically fit before the illness and have become sedentary because of the severity of the symptoms (Carfi et al., 2020). Table 3 is a list of the top 10 symptoms reported by persons with post-COVID-19 syndrome. Almost 70% of these persons have dyspnea, and 60% complain of fatigue or being severely tired (Levison, 2020).

Post-COVID-19 Pathophysiological Variations

The following are major potential pathophysiological mechanisms for post-COVID-19 syndrome: (a) virus-specific pathophysiological variations, (b) oxidative stress, (c) immunologic abnormalities, and (d) inflammatory damage (Figure 2). Most of the symptoms observed in persons with post-COVID-19 syndrome are likely a consequence of direct viral injury. It is not possible to comprehensively discuss all mechanisms involved in post-COVID-19 syndrome in this review. Thus, we will discuss a few significant pathways associated with predominant symptoms, such as dyspnea, fatigue, and headaches.

Post-COVID-19 Viral-Specific Variations The pathogen responsible for COVID-19, SARS-CoV-2, causes cellular damage by inflammatory cytokines, maladaptation of the ACE2 pathway, procoagulation, and other immune abnormalities. Viral toxicity probably contributes to sequela seen in post-COVID-19 syndrome. Persons ill from similar viruses such as the SARS-CoV in 2003 or Middle East respiratory syndrome in 2012 had similar patterns of symptoms now observed in persons with post-COVID-19 syndrome (Nalbandian et al., 2021). The pathological condition resulting from SARS-CoV-2 or its sequelae leads to multiple organ dysfunction and infections. With the invasion of alveolar epithelial and endothelial cells by SARS-CoV-2, a cascade of neutrophils, monocytes, and immune cells leads to diffuse alveolar damage. In turn, numerous mechanisms and pathways are activated, causing various sequelae such as heart failure, neuropsychiatric dysfunction, thromboembolism,

TABLE 3. Top 10 Symptoms of Post-COVID-19 Syndrome

1.	Dyspnea
2.	Fatigue
3.	Loss of olfactory and gustatory function
4.	Tightness of the chest
5.	Chills or sweats
6.	Muscle or body aches
7.	Dry cough
8.	Sore throat
9.	Fever
10.	Headache or brain fog

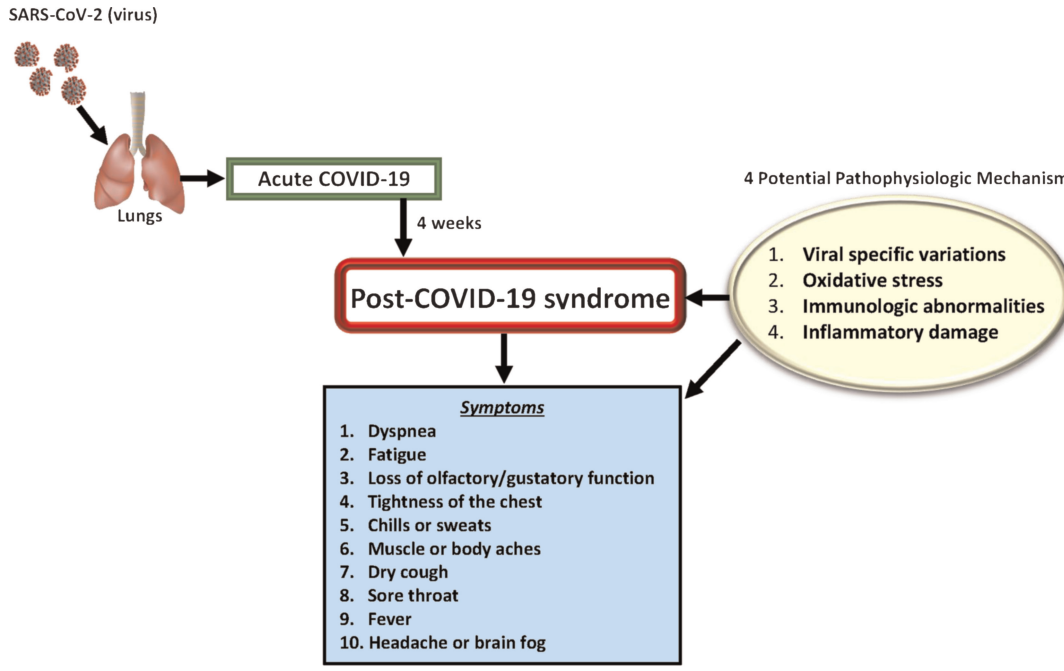

FIGURE 2. Potential pathophysiological mechanisms of post-COVID-19 syndrome.

renal injury, dermatological disorders, diabetic ketoacidosis, sensory defects, and irritable bowel syndrome (Onishi et al., 2021).

Post-COVID-19 and Oxidative Stress Many persons with post-COVID-19 syndrome had respiratory problems during the acute phase of their disease. SARS-CoV-2 often causes viral pneumonia leading to lung tissue injury and damage. Viral infections, especially coronavirus infections, stimulate overactivation of the immune system in the lungs to reduce viral replication. If SARS-CoV-2 causes severe pneumonia by infecting Type II pneumocytes, the numerous mitochondria synthesizing acetyl-CoA needed for pulmonary surfactants are damaged. Also, the ability of the mitochondria to produce antioxidants is reduced, leading to oxidative stress. Oxidative stress is a phenomenon in which there is an imbalance between the production and accumulation of cellular reactive oxygen species (ROS) and antioxidant defenses. In both SARS-CoV and SARS-CoV-2, investigators have shown that oxidative stress plays a significant role that may lead to mitochondrial DNA mutations, injury to the mitochondrial respiratory chain, modifications of membrane permeability, and activation of the mitochondrial defense systems (Derouiche, 2020).

In addition, oxygen supplementation often used to treat patients with acute COVID-19 can induce excess ROS generation in the mitochondria. This can damage the mitochondrial complexes and reduce oxidative phosphorylation leading to decreased production of adenosine triphosphate and increased cellular apoptosis. Mitochondria ROS also can affect immune and defense responses against the DAMPs of the virus by activating antiviral innate immune responses. If the mitochondria are damaged with hyperoxia, then the antiviral reactions are reduced, and there can be increased viral damage. The increase in oxidative stress has been hypothesized to be one of the pathophysiological causes of the various organ sequelae observed in persons with post-COVID-19 syndrome (West et al., 2011).

Lowering oxidative stress with the administration of antioxidants could decrease viral load and assist with recovery in persons with post-COVID-19 syndrome. For example, Codo et al. (2020) found that when peripheral blood monocytes from healthy individuals were exposed to SARS-CoV-2, there was decreased viral replication when adding *N*-acetylcysteine and MitoQ to the cells. This indicates that reducing ROS with antioxidants and maintaining mitochondrial function may significantly lower coronavirus replication. Thus, mitochondrial-targeted antioxidants may be a potential approach to decrease oxidative stress in persons with post-COVID-19 syndrome. However, further research is needed in both animals and humans.

Post-COVID-19 Immunologic Abnormalities When SARS-CoV-2 enters the respiratory system, there is a host immune response. First, the S-protein spike of the virus attaches to the ACE2 receptor of different human cells. Next, innate immunity helps to protect the host against the virus invasion. Recognition of the virus causes subsequent cytolytic immune responses via Type I interferons (IFN) and natural killer cells. This type of immunity is vital in dissipating the virus by activating both T-cells that destroy virus-infected cells and antibody-producing B-cells that assist in producing antibodies that specifically target SARS-CoV-2. In acute COVID-19, patients with severe pneumonia or ARDS show a decrease in the lymphocyte

counts and increased cytokines, particularly tumor necrosis factor and inflammatory cytokines called *interleukins*. These various proinflammatory T-cells are extremely prevalent in the lungs (Liu et al., 2020).

With the invasion of SARS-CoV-2, the antiviral immune response is critical to remove the virus, but the continual response with enormous amounts of inflammatory cytokines may cause a cytokine storm. A cytokine storm occurs when an overabundance of cytokines causes a positive immune feedback loop producing excess cytokines that damage cells and tissues in an injured organ such as the lung. SARS-CoV-2 targets alveolar macrophage expression, and the result is activated macrophages that produce the cytokine storm (Oronsky et al., 2021). With cytokine storms, immediate treatments such as immune modulators, cytokine-specific therapies, and antivirals are administered to reduce the damage. These treatments reduce the immune response in an attempt to decrease tissue and organ damage. However, if the inflammatory response is greatly depressed by these agents, the patient might enter a prolonged immunosuppression state (Misra et al., 2020).

Some persons with post-COVID-19 syndrome have survived the cytokine storm that occurred with pneumonia or ARDS and may have pulmonary injury or fibrosis. These persons have exercise-induced dyspnea and chronic dry cough and may require supplemental oxygen and pulmonary rehabilitation (Oronsky et al., 2021). The cytokine storm also damages other tissues and organs, such as the myocardium. Cytokines cause myocardial injury, and the cardiac tissue is remodeled, leading to both hypertrophy and fibrosis of the left ventricular wall. This hypertrophy decreases myocardial contractility and impairs cardiac function. The major cytokine for this damage is transforming growth factor-beta 1 (Q. Wu et al., 2017).

Post-COVID-19 Inflammatory Damage With a disease such as COVID-19, there is an overwhelming inflammatory response called *systemic inflammatory response syndrome*. In this syndrome, the body activates a long-lasting, counterbalancing, compensatory anti-inflammatory response syndrome to help dampen the proinflammatory state and return to immunologic homeostasis to prevent multiple-organ dysfunction (Sugimoto et al., 2016).

In COVID-19 patients with both IFN-αβ and IFN-γ, there was inflammatory cell infiltration involving Fas–Fas ligand or TRAIL–death receptor 5 that cause airway and alveolar epithelial apoptosis. This inflammatory pathway leads to alveolar edema, hypoxia, and increased disease severity in other organs, such as heart failure. Multisystem inflammatory syndrome in adults or children following COVID-19 infection has a wide variety of organ involvement and causes many of the symptoms observed in post-COVID-19 syndromes such as dyspnea, fatigue, pain, and fever. A new term, *post-COVID-19 inflammation syndrome*, is now being used by clinicians who have observed patients with nonspecific inflammation and postviral arthritis. These persons respond to short-term administrations of nonsteroidal anti-inflammatory drugs and hydroxychloroquine. With these drugs, some persons with post-COVID-19 syndrome alleviate their symptoms (Chandrashekara et al., 2020).

DISCUSSION

This integrative review chose to include studies involving a wide range of terms used to describe post-COVID-19 syndrome. Our overarching aim was to determine if we could describe the pathophysiology of post-COVID-19 based on the available evidence. Examination of 54 studies published as of August 30, 2021, revealed a handful of possible mechanisms involved in the physiological processes associated with this syndrome. We found that post-COVID-19 syndrome is not a hallmark of critically ill patients. Still, it also represents a significant proportion of those presenting only mild to moderate symptoms after the acute infection (Soriano et al., 2021).

There are many terms to describe the persistent symptoms and/or complications following COVID-19 syndrome. The three most common terms used are *post-COVID-19 syndrome*, *long COVID-19*, and *post-COVID-19 condition* (Soriano et al., 2021). This syndrome should not be confused with the acute phase of COVID-19 and the pathophysiological changes that occur early in the disease. However, comprehending the pathophysiological mechanisms that cause the various sequelae in persons with post-COVID-19 syndrome is essential. Because there are over 19 sequelae of this syndrome, five categories of post-COVID-19 syndrome have been developed.

A better understanding and appreciation of several potentially modifiable factors that influence the post-COVID-19 syndrome is critical, particularly in reducing the symptom burden of these persons. Five studies reported continuous immunologic changes 4 weeks after persons were infected with SARS-CoV-2. These studies found that persons with post-COVID-19 symptoms were immunocompromised for a prolonged period. The pathophysiological mechanisms underlying post-acute COVID-19 syndrome are multifactorial, with dysregulation of the immune and autonomic nervous system. These persons with prolonged symptoms have augmented SARS-CoV-20-specific immune responses, particularly immune dysregulation (Dan et al., 2021; Nalbandian et al., 2021; Patterson et al., 2021; Ramakrishnan et al., 2021; J. Wu et al., 2021). Therefore, future research is needed to understand the underlying pathophysiological process that may enable innate and adaptive immune responses, including the phenotypes associated with post-COVID-19 syndrome (Nalbandian et al., 2021; Ramakrishnan et al., 2021).

Despite the significant gaps in the literature related to pathophysiology of post-COVID-19 syndrome, current evidence suggests one of the major contributors is viral toxicity (Mallakpour et al., 2021). SARS-CoV-2 produces cellular damage by alterations of the ACE2 pathway, various inflammatory cytokines, mitochondrial dysfunction, procoagulation, and other

TABLE 4. Ongoing Clinical Trials Investigating Therapies to Reduce Post-COVID-19 Syndrome

Therapy	NCT number	estimated Enrollment	Design	Description	Primary outcome
Naltrexone, NAD+	NCT04604704	60 participants	Randomized, parallel assignment	Patients will receive low-dose naltrexone and NAD+ treatment or a corresponding placebo tablet and patch for 12 weeks.	Assess fatigue and quality of life using validated surveys
Hyperbaric oxygen	NCT04647656	70 participants	Prospective, randomized, double-blinded	HBOT administrated in a multiplace chamber with 40 daily sessions, 5 sessions per week for 2 months. Treatment group will be subjected to 100% oxygen by mask for 90 minutes with 5-minute air breaks every 20 minutes. Sham group will be subjected to 21% oxygen by mask for 90 minutes.	Memory, attention, and information process with post-COVID-19 symptom.
Autologous HB-adMSCs	NCT04798066	Exact number not known, using intermediate-sized population access protocol	Randomized	The dose to use for this intermediate-sized patient population expanded access protocol is 200 million HB-adMSCs, administered through intravenous infusion only, with a treatment duration of 14 weeks, infusion rate of 4–5 ml/min, and total volume of 250 ml sodium chloride 0.9%. A total of 5 administrations and a dosing interval of 2 weeks for the first two HB-adMSCs administrations and 1 month after that.	Evaluate the safety and efficacy of HB-adMSCs for the treatment of post-COVID-19 syndrome
Nebulized platelet lysate	NCT04487691	40 patients	Double-blind, randomized, placebo controlled single-center study	Nebulized platelet lysate compared to placebo control of saline administered via handheld nebulizer 1× daily for 8 weeks to determine effect on lung function in patients with post-COVID-19 adult respiratory distress syndrome.	Spirometry-FVC and FEV1/FVC changes in pre- and posttreatment spirometry measures
Multicomponent exercise training	NCT04718506	56 participants	Randomized, parallel assignment	Tailored, multicomponent exercise training with post-COVID-19 syndrome (i.e., patients who present symptoms >12 weeks after the acute phase of the disease). Evaluate the clinical efficacy and safety of a tailored exercise-based treatment relative to the control arm in improving the subject clinical status in ambulatory patients.	Post-COVID-19 functional status on a 5-point ordinal scale (0–4 grades) and medical screening
Explore gut–lung axis with microbiomes	NCT04813718	20 participants	Randomized, parallel assignment	Examine the microbiome of gut to investigate the gut–lung axis as a link between dysbiosis, barrier dysfunction, translocation of bacterial products, and hyperinflammation.	Microbiome composition; 16 sRNA sequencing intestinal barrier; change in zonulin levels over time and with/without the intervention; sCD14; endotoxin levels; serum tumor necrosis factor alpha; several interleukins; other immune cells

(continues)

TABLE 4. Ongoing Clinical Trials Investigating Therapies to Reduce Post-COVID-19 Syndrome, Continued

Therapy	NCT number	estimated Enrollment	Design	Description	Primary outcome
Resistance-based exercise	NCT04900961	220 participants	Randomized, parallel assignment	A personalized, resistance-based exercise intervention for patients during the convalescence phase in-hospital through to 3-months postdischarge, a duration reflecting chronic, maintenance treatment studies. The intervention may be initiated in-hospital or in the community postdischarge. Resistance bands may be used according to the exercise guideline.	Incremental shuttle walk test
Exercise-based rehabilitation program	NCT04841759	30 participants	Nonrandomized, parallel assignment	SARS-CoV2 survivor who attends the exercise program and have post-COVID-19 fatigue syndrome with measurements at baseline, 4 weeks, and 8 weeks.	Change of maximum oxygen uptake assessed during cardiopulmonary exercise testing
C1 esterase inhibitor recombinant	NCT04705831	40 participants	Randomized, crossover assignment	In this study, subjects receive 19 weeks including 16 infusions total of C1 esterase inhibitor that are each 1 week apart. This is to help patients who have developed postviral fatigue syndrome to reduce extreme fatigue, loss of taste, brain fog, and/or seizures.	Behavior Rating Inventory of Executive Function–Adult; Repeatable Battery for the Assessment of Neuropsychological Status; Beck Depression Inventory II; Montreal Cognitive Assessment; Fatigue Severity Scale; Migraine Disability Assessment; Headache Impact Scale; activities of Daily Living Sliding Scale and Questionnaire; SF McGill Pain Questionnaire; Gastrointestinal Symptoms Rating Scale

Note. NAD+ = nicotinamide adenine dinucleotide; HBOT = hyperbaric oxygen therapy; COVID-19 = coronavirus 2019; Autologous HB-adMSCs = autologous adipose-derived mesenchymal stem cells; FEV1/FVC = forced expiratory volume/forced vital capacity; sRNA = small ribonucleic acid; sCD14 = soluble cluster of differentiation 14.

immune aberrations (Kaundal et al., 2021; Whiteside, 2021). In post-COVID-19 syndrome, there is cellular damage in multiple organ systems, causing various symptoms from the residual effects of SARS-CoV-2 infection (Nalbandian et al., 2021). Future research to address identified gaps in this review may potentially discover underlying pathophysiological mechanisms and potential therapeutic interventions to reduce the severity of the symptoms. Many unknowns remain as to the proportion of COVID-19 survivors who will require multidisciplinary post-COVID-19 clinics to address both persistent symptoms and potential long-term respiratory and other complications. Clinicians and researchers need to continue investigating the pathophysiological pathways of post-COVID-19 syndrome and develop potential therapeutics for persons exposed to this deadly virus.

Therapies to Reduce Post-COVID-19 Syndrome

Therapeutic treatments for persons who have post-COVID-19 syndrome should be based on the molecular and integrative physiological pathways that are damaged or dysfunctional. Several recent clinical trials are focused on prevention and treatment interventions for post-COVID-19 syndrome based on antioxidant supplements, exercise, and other pharmacological approaches. A selected list of ongoing clinical trials investigating therapies to reduce post-COVID-19 syndrome is presented in Table 4.

Implications for Research

The management and care of individuals with post-COVID-19 syndrome are likely to become a substantial burden for healthcare systems worldwide. The research to date suggests essential directions for future study specifically related to the mechanisms involved in the pathophysiology of post-COVID-19 syndrome. This review provides significant evidence for understanding long-term complications of this syndrome and the need for future research in the areas of virus-specific pathophysiological variations, oxidative stress, immunologic

abnormalities, and inflammatory damage. Understanding the physiological changes that occur following COVID-19 illness may explain the development of later pathologies that emerge.

As the COVID-19 pandemic began, initial symptomology descriptions were mainly related to the acute clinical presentation. Now that there are many persons with post-COVID-19 syndrome, priorities for research should include investigating the symptom science related to post-COVID-19 to include identification of symptoms or cluster of symptoms, followed by the characterization into a phenotype. Once these phenotypes are determined, genomic and other omics discoveries should be used to uncover potential biomarkers that can lead to targeted therapeutic and clinical interventions.

Strengths and Limitations

A strength of this integrative review was using PRISMA guidelines to assist with our critical appraisal of published articles using a standard framework. Using these guidelines, we managed the literature to form comprehensive inclusion criteria to avoid premature closure and consensus among the authors on extracting data and summarizing findings. However, this is an evolving new study area, and many of the articles used retrospective and case–control designs. There were very few articles reporting examination of only the post-COVID-19 pathophysiology. Most of the studies did not control for age, comorbidities, or pharmacological effects of drugs at the time of data collection. Also, data extracted were limited to studies published in English and the appraised level of evidence of the articles reviewed; thus, this review did not summarize recommendations for clinical practice. Although all studies investigated post-COVID-19 syndrome, it is possible that other researchers did not use our key words, and hence, studies were missed. Finally, despite consultation with a librarian and a systematic search, we may not have included all relevant articles.

Conclusion

This integrative review summarizes the definitions, classifications, manifestations, and pathophysiology related to post-COVID-19 syndrome. Numerous articles related to post-COVID-19 syndrome exist with very complex biological descriptions. However, there are existing gaps in synthesizing physiological mechanisms and pathways. Consequently, we aimed to integrate the current literature to highlight the four major categories of manifestation (viral injury, oxidative stress, immunologic abnormalities, and inflammatory damage). Understanding the role of the pathophysiological pathways involved with this syndrome may assist in developing and testing potential therapeutics such as antioxidants and mitochondrial supplements. Long-term complications of COVID-19 are still unfolding, and in the future, more evidence will be available to guide therapeutic management of this syndrome.

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