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■ Review Article

Long COVID: A Comprehensive Overview of the Signs and Symptoms across Multiple Organ Systems

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Long coronavirus disease (COVID), also known as the post-acute sequelae of coronavirus disease 2019 (COVID-19) (PASC), is a significant concern since the end of the COVID-19 pandemic, as it still manifests in individuals with persistent symptoms and complications beyond the acute phase of infection. Defining this disease is challenging, as it manifests as a spectrum of symptoms varying in severity among individuals who have previously tested positive for COVID-19. Long COVID is more prevalent in hospitalized COVID-19 patients and presents in various ways, ranging from pulmonary to extrapulmonary symptoms. This literature review examines the current body of research on long COVID with a focus on its effects on the cardiovascular, hematological, respiratory, renal, and neurological systems with systematically analyzed, peer-reviewed articles retrieved from the PubMed database. There have been several proposed pathophysiological mechanisms by which severe acute respiratory syndrome coronavirus 2 affects the aforementioned organ systems; however, research on the definite mechanisms is lacking, especially when considering the management of long COVID in the perioperative setting. The impact of post-COVID sequelae necessitates individualized management strategies tailored to each symptomatic profile, particularly in patients with comorbidities. The COVID-19 pandemic affected millions of people and had a profound impact on those who developed PASC, lowering their quality of life and increasing potential surgical risks. However, there is still uncertainty regarding the specific risk factors for long COVID and who is most susceptible to it. Further research is required to fill these gaps and explore potential avenues for preventing PASC.

Keywords: COVID; Long COVID; Epidemiology; Cardiology; Hematology; Pulmonology; Nephrology; Neurology

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INSTRUCTION

Long coronavirus disease (COVID), or post-coronavirus disease 2019 (COVID-19) syndrome, is a term used to represent the continuation or development of new COVID-19 symptoms 3 months after the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with symptoms lasting for at least 2 months with no other explanation, regardless of the age or severity of the original symptoms.[1] The consequences of the infection go far beyond those of the respiratory system, often leading to various manifestations of extrapulmonary symptoms.[2] Most survivors of COVID-19 recover normally without complications after viral clearance; however, recent research has indicated that a small percentage of patients have sequelae for a longer period, leading to persistent pulmonary and extrapulmonary symptoms.[2] Long COVID has become a disease that is difficult to define as patients exhibit more than 200 different symptoms with differing levels of severity.[2,3] In some cases, patients can test positive for COVID-19 long after the completion of their disease course.[1] For example, in the United Kingdom, one patient tested positive for COVID-19 for more than 500 days until death.[1]

Long COVID has an estimated prevalence and incidence of roughly 50%–70% and up to 85% versus 10% and 10%–35% in hospitalized versus non-hospitalized patients, respectively.[2,4] In a meta-analysis of 194 studies with a total of 735,006 participants, at least 45% of COVID-19 survivors, regardless of hospitalization status, experienced at least one unresolved symptom (mean follow-up time, 126 days).[5] Fatigue was frequently reported across 28.4% of hospitalized and 34.8% of non-hospitalized patients with 95% confidence interval (CI) of 24.7%–32.5% and 17.7%–34.6%, respectively.[5] When assessing the hospitalized cohort, 45.3% had abnormal computed tomography patterns or radiographs (95% CI, 35.3%–55.7%), 41.1% were found to have ground glass opacification (95% CI, 25.7%–58.5%), and 31.7% had impaired diffusion capacity for carbon monoxide (95% CI, 25.8%–3.2%).[5] Another study reported that, although fatigue was the most common symptom reported in post-COVID cases, it was closely followed by residual dyspnea in 10%–40% of patients, mental health problems such as anxiety and depression in up to 26%, chest pain in up to 22%, and olfactory and gustatory dysfunction in up to 11%.[4] One cluster analysis study showed that of the 164 individuals who contracted COVID-19, 115 (70%) reported persistent symptoms.[6] The analysis revealed that most Long COVID symptoms were characterized by sensory disturbances, such as anosmia and dysgeusia, and fatigue-like symptoms, such as weakness and tiredness.[6,7] Additionally, 23 (20; 1/5) of these individuals had additional symptoms, including dyspnea, tachycardia, headache, sleep disturbances, anxiety, and chronic muscle aches, compared to those whose symptoms had rapidly disappeared.[6,7]

Multiple studies have been completed, with others still ongoing, to explain the molecular processes at play.[2] Contributing factors such as exacerbated cytokine production, procoagulant states, direct cellular damage, and dysfunctional brainstem/vagal signaling are all directly or indirectly caused by COVID-19 and play major roles in the development of long-term symptoms.[2,8] Further, both induced, and inactivity-induced changes may increase mitochondrial dysfunction and myofibril breakdown, and decrease mitochondrial biogenesis and muscle synthesis.[8] One primary example is NSP4 and ORF9b, which are COVID-19-related proteins responsible for the assembly of cytoplasmic double-membrane vesicles required for viral replication and interferon antagonism, respectively.[8] These two proteins cause structural changes in the mitochondria, formation of outer membrane macropores, and release of mitochondrial DNA-laden inner membrane vesicles.[8] This, as well as many other examples of mitochondrial dysfunction, is seen as one of the earliest and most prominent neurodegenerative features of COVID-19-induced neuropathy, defined as being more prevalent among those with metabolic syndromes, such as diabetes, obesity, and cardiovascular and liver diseases, leading to susceptibility to adverse outcomes of the infection.[8] Additionally, cardiac mitochondrial disruption after infection, reactive oxygen species production, and energy stress lead to mitochondrial alterations and cardiovascular dysfunction in COVID-19-infected patients, and the incidence of adverse cardiovascular events increases in recovered COVID-19 patients.[8]

The effects of long COVID span a wide range of symptoms and influence a range of organ systems.[3] Cardiorespiratory symptoms include shortness of breath, coughing, chest pain, and palpitations; musculoskeletal symptoms include joint pain and myalgia; and neuropsychiatric symptoms include brain fog, depression, insomnia, and stroke.[3] Ear, nose, and throat symptoms include anosmia; gastrointestinal (GI) symptoms include changes in bowel habits, nausea, dyspepsia, and abdominal pain; dermatological symptoms include rash, pustules, and hair loss; and generalized or multi-system symptoms include fatigue and reduced exercise tolerance.[3] Notably, with over 200 reported symptoms across hundreds of articles, the listed symptoms are some of those that are more commonly reported and should not be considered a comprehensive list. For example, in the United States, it was discovered that in the 30 days to 12-month period post-COVID-19 infection, patients had an increased risk of ischemic heart disease, pericarditis, myocarditis, arrhythmias, and heart failure compared to matched controls.[9] It is also important to know that more than one-third of patients with long COVID symptoms have pre-existing comorbidities, with hypertension and diabetes mellitus being the most common.[4]

Furthermore, the effects of prolonged COVID's effects on the body are influenced by factors such as sex, age, viral strain, vaccination status, and other environmental or psychosocial factors.[10] Long-term exposure to air pollution is significantly associated with an increased risk of long COVID in young adults.[11] Education level, marital status, and medication use are important prognostic factors for the development of symptoms such as persistent fatigue, which is up to 4 times more likely to develop after COVID-19 infection.[10] In children, infection with a pre-Omicron variant and older age led to an increased risk of developing long-term COVID or post-acute sequelae of COVID-19 (PASC), with some patients reporting persistent symptoms up to 18 months af-

ter COVID-19 infection, while infection with an Omicron variant was associated with shorter recovery times.[12] Associations between hospitalization during the acute phase of infection and the development of symptoms affecting specific systems such as the musculoskeletal and GI systems have also been observed.[12]

Although more common short-term vaccine side effects such as myalgia, fever, headache, and chills are often reported, additional research stratified by vaccine type is ongoing regarding potential short- and long-term vaccine side effects.[13,14] However, the prevention of COVID-19 remains the best way to reduce the risk of PASC, and studies suggest that the benefit-to-risk ratio of vaccination remains favorable across age and sex, even considering reports of the development of rare side effects.[15] Additional studies also suggested that vaccination in patients with long COVID symptoms is safe and can even lead to symptomatic improvement in some cases.[16] Other studies suggest that vaccinating an adult population leads to a decreased likelihood of long COVID symptom development.[17] It is important to note that a subset of studies has shown a lack of association between vaccination status, infection variants, and viral load during the acute phase with the development of persistent COVID-19 symptoms, suggesting the need to include other strategies in addition to vaccination promotion.[15] Patients who already present long COVID symptoms such as anosmia, dyspnea, fatigue, and cognitive dysfunction frequently try a variety of methods to try to mitigate symptoms. These include dietary change, positive thinking, group support, and pacing, but they still experience frustration in life, in part due to limited clinical help and the burden of associated costs, which also demonstrates the necessity of researching additional treatments and therapy to help improve the lives of patients with PASC.[18]

Research in this field is critical to improving long COVID interest and awareness. For example, accurately identifying the infectious strains prevalent during a specific season could improve targeted therapies for acute and PASC symptoms.[12] The involvement of long COVID in particular systems such as the GI or musculoskeletal are also points of important, as the GI system has been theorized to serve as a reservoir for COVID-19 and could be linked to multisystem inflammatory syndrome in adult (MIS-A) development.[12] One possible research benefit is that if the likelihood of long COVID symptom development can be predicted by monitoring previously identified risk factors, then the screening of patients who have been discharged after COVID-19 could also lead to better resource allocation and overall treatment improvement for patients.[19] Another seldom discussed benefit would be the reduced burden on healthcare systems already strained by the global pandemic, particularly with healthcare workers who have reported exhaustion and increased workload at alarming rates that still resonate 4 years after the outbreak of the pandemic.[20]

METHODS

Peer-reviewed articles were retrieved from the PubMed database and systematically analyzed. Search terms used included "What is long COVID," "long COVID AND risk factors," long COVID AND cardiovascular complications, "long COVID AND respiratory complications," "long COVID AND hematologic complications," "long COVID and anesthesia," and "anesthesia complications in long COVID patients." The exclusion criteria were pediatric populations and articles that did not explore the mechanism or prevalence of symptoms. Only articles published between 2019–2024 were considered, with a few exceptions that provided background information on specific disease processes or epidemiological contexts.

BODY SYSTEM EFFECTS

This study outlines the long-term effects of COVID-19 on the cardiovascular, hematological, respiratory, renal, and neurological systems. There have also been several cases of the development of post-COVID MIS-A and multisystem inflammatory syndrome in children documented; this review will focus on long COVID-19 syndromes in adults.[21]

The pathophysiology of the effects of prolonged COVID-19 is still not fully understood; however, it is proposed that angiotensin-converting enzyme 2 (ACE-2) is downregulated due to the S1 spike on SARS-CoV-2 binding to ACE-2 its subunits found on cardiac, respiratory, and endothelial myocytes.[22] Downregulation of ACE-2 prevents vasodilation and regulates tissue repair, inflammation, cell proliferation, and platelet aggregation by inhibiting the kallikrein-kinin system.[23] Additionally, it has been proposed that overactivation of CD4 + T cells can cause hyperinflammation due to the substantial release of proinflammatory cytokines and interferons.[22] Dysregulation of the immune system and T cell exhaustion secondary to upregulation can increase the risk of blood clots through endothelial inflammation.[22] It has even been shown that a higher viral load is positively correlated with higher cytokine levels and greater inflammation.[22] These body system effects are summarized in Table 1.

1. Cardiovascular and Hematological

Cardiovascular abnormalities can lead to conditions such as arrhythmias, postural tachycardia syndrome (POTS), sinus tachycardia or bradycardia, cardiomyopathies, pulmonary embolisms, left ventricular or right ventricular dysfunction, heart failure, acute coronary syndrome leading to chest pain, and PASC MIS-A.[21,22,24,25] The long-term cardiovascular effects of COVID-19 are vast and can be caused by a combination of hypercoagulability, microvascular dysfunction, endothelial dysfunction, dysrhythmias, and dysautonomia resulting from the negative effects of the virus on cells.[22] Hematological indications of long COVID have been reported less frequently in the literature when compared with cardiovascular sequelae of long COVID; however, its implications are clinically significant, especially when considering anesthesia and having patients immobilized for prolonged surgeries/procedures.

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Table 1. Summary of main findings

System	Condition	Mechanism(s)	Sign(s)/symptom(s)	Proposed treatments
Cardiovascular & hematological	Hypercoagulability	Dysfunction in clotting proteins and protein breakdown, causing an increase in inflammatory molecules, circulating microclots, hyperactive platelets, and plasma resistant to fibrinolysis.[26]	Increased risk of thrombotic events.[26]	Direct thrombin inhibitors.[27]
	Thrombotic events	Either excessive and prolonged inflammation, triggering platelet aggregation, activation of coagulation factors, or intravascular coagulation.[30] Direct impact of virus entering cells due to overexpression of ACE-2, causing endothelial inflammation and dysfunction.[31,32]	Typical signs and symptoms associated with various thrombotic events, such as elevated D-dimer, prothrombin, IL-6, and fibrinogen.[30]	Typical treatment modalities for various thrombotic events.
	Cardiovascular PASC (PASC-induced myocarditis, pericarditis, and POTS)	Inflammation of pericardial vasculature (e.g., intercostal and esophageal branches of the aorta and internal thoracic arteries).[35] Inflammation of the pleura or prolonged effect of cardiac injury due to high level of inflammation caused by initial infection.[36]	Chest pain, chest tightness, palpitations, dizziness, and tachycardia.[33] Preformed amyloid clots in plasma due to elevated SAA and α2p2 and elevated troponin.[26]	Intravenous and oral corticosteroids with inotropes.[39,40] Antibiotics necessary in select cases. Walking >2,000 steps per day, pulmonary rehabilitation, and possibly Liuzijue.[42,44]
	POTS	A form of PASC potentially associated with autonomic nerve destruction.[41]	Overlaps with that of PASC, but can include dizziness, palpitations, fatigue, headache, nausea, vision changes, and brain fog.[41]	Same treatment modalities as PASC.
	MIS-A	Potentially due to the ability of the virus to cause autoimmune dysregulation.[23]	Persistent cardiomyopathy and hypothyroidism.[23]	Corticosteroids.[23]
	BBRVT	Aortitis from the aortic arch to root causing ventricular storm which led to bundle branch reentry ventricular arrhythmia.[39]	Tachycardia.[39]	Temporary pacemaker, radiofrequency ablation, prednisolone.[39]
Respiratory	Dyspnea	Diffuse alveolar damage by the virus binding to ACE-2 on type 2 pneumocytes, viral occlusion of alveoli microvasculature via thrombi, and increases in respiratory inflammatory mediators.[49]	Prolonged dyspnea for >6 months to 1 year following discharge from hospitalization.[25]	Typical symptomatic treatment modalities for shortness of breath.
	Cough	Lung fibrosis, causing increased sensitivity of the cough reflex, wherein the virus infects the vagal sensory nerves, and causing inflammation and immune interactions.[53]	Continued cough >3 months after initial infection symptom onset.[53]	Typical symptomatic treatment modalities for shortness of cough.
Renal	AKI	Viral spiral proteins attach to receptors of the ACE-2-releasing proteins in the collecting ducts and proximal tubule epithelial cells, mesangial cells, and podocytes.[57]	>8% longitudinal decline in GFR and typical signs and symptoms associated with AKI.[56]	Typical treatment modalities for AKI.
	Decreased GFR	Caused by AKI due to viral spiral protein attachment to renal tubular cells.[57]	Significant decrease in renal function >1-year post-hospitalization.[60]	Typical treatment modalities for decreased GFR.
	CKD	Caused by decreased GFR due to viral spiral protein attachment to renal tubular cells.[57]	Significant reduction in renal function or worsening of existing CKD >1-year post-hospitalization.[60]	Typical treatment modalities for CKD.
Neurological	Brain fog	Direct infection of the virus to brain microvascular endothelium, weakening the BBB, invoking an inflammatory response. Activation of microglia and astrocytes cause dysregulated autophagy, disrupting neurotransmitter production.[66]	Feelings of mental lethargy, feelings of fuzziness, inability to concentrate, or spacing out with impairment in executive function.[66,68,69]	No specific treatments are known for brain fog.
	Memory impairments	Same mechanisms described for brain fog. Direct viral invasion of neurons through transcellular BBB endothelium access.[66]	Advanced form of brain fog with a wide degree of severity from forgetfulness to the inability to remember dates, names, events, and specific details of one's life.[65]	Typical treatment modalities that work to reverse memory impairments.
	Fatigue	Same mechanisms described for brain fog, specifically associated with the surge of cytokines in initial infection.[66]	>6 months of feelings of tiredness or lethargy, mental and/or physical.[66]	Typical symptomatic treatment modalities for chronic fatigue.

(Continued on next page)

Table 1. Continued

System	Condition	Mechanism(s)	Sign(s)/symptom(s)	Proposed treatments
	Neuropsychiatric disturbances	Same mechanisms described for brain fog and memory impairments, specifically associated with the surge of cytokines in initial infection. Possible contributing factors include external circumstances, such as quarantine, isolation, financial worry, and stress associated with either the pandemic or being ill.[66]	Anxiety, post-traumatic stress disorder, obsessive compulsive disorder, and depression.[66]	Typical symptomatic treatment modalities for individual psychiatric concerns.
	Sleep disturbances	Same mechanisms described for brain fog, neuropsychiatric disturbances, and memory impairments. Due to mental health issues that were exacerbated by the stress of COVID.[66,67]	Difficulties initiating or maintaining sleep, nightmares, and lucid dreaming.[66,67]	Typical symptomatic treatment modalities for sleep disturbances.
	Headache	Same mechanisms described for brain fog. Hypoxia, immunologic events, or vascular events.[70]	Intermittent but deep, stabbing, tension-like or migraine-like headaches >6 months post-infection.[66,70]	Typical symptomatic treatment modalities for headaches and migraines.

ACE-2, angiotensin-converting enzyme 2; IL-6, interleukin 6; PASC, post-acute sequelae of COVID-19; COVID-19, coronavirus disease 2019; POTS, postural tachycardia syndrome; SAA, serum amyloid A; α2p2, alpha(2)-antiplasmin; MIS-A, multisystem inflammatory syndrome in adult; BBRVT, block and bundle branch reentry ventricular arrhythmia; AKI, acute kidney injury; GFR, glomerular filtration rate; CKD, chronic kidney disease; BBB, blood–brain barrier; COVID, coronavirus disease.

1) Hypercoagulability

A study by Pretorius et al.[26] in 2021 used proteomics and fluorescence microscopy to study the plasma of patients with long COVID/PASC, which they defined as patients that have been experiencing persistent symptoms for at least 6 months after COVID-19 infection. The main findings of this study were that the underlying cause of hypercoagulability in PASC is dysfunction in clotting proteins and protein breakdown that causes an increase in inflammatory molecules (such as serum amyloid A 4 [SAA4] and alpha(2)-antiplasmin [α2p2]), circulating microclots, hyperactive platelets, and plasma resistance to fibrinolysis.[26] This study also found that those who were concurrently infected with type 2 diabetes mellitus (T2DM) were especially susceptible to hypercoagulability because patients with T2DM are predisposed to hyperactive platelets.[26]

Therapeutic approaches to hypercoagulability in PASC patients suggest the use of direct thrombin inhibitors such as Argatroban for hypercoagulability issues in this population; however, therapeutic approaches are still being explored and further research is needed in this field.[27]

Hypercoagulability is already a concern in patients who are undergoing surgery and will be subjected to prolonged immobilization, and patients who are already at a higher risk of clotting may also be at a higher risk of developing PACS.[28] Examples of those with a higher clotting risk include obese patients, women of reproductive age or on hormone replacement therapy, patients with T2DM, and hyperlipidemia.[28] The question remains whether these are associations/confounders or whether these patient populations are at an even further increased risk of developing thrombotic complications of PACS. More research must be conducted so that these patients can be prophylactically treated appropriately, possibly with the use of direct thrombin inhibitors or dual antiplatelet therapy over the standard mono-antiplatelet therapy with subcutaneous heparin, especially when these patients are immobilized after surgery.

2) Thrombotic events

There are reports of thrombotic complications in patients infected with COVID-19; the incidence of these complications among patients with COVID-19 ranges from 7.7% to 49% with more venous than arterial thrombi.[29] These rates were much higher than those reported in patients without COVID-19.[29]

The pathophysiological mechanism of thrombotic events in patients with COVID-19 is not fully understood; however, it is suspected that these complications could be due to either excessive and prolonged inflammation, triggering of platelet aggregation, activation of coagulation factors, or intravascular coagulation, as correlations have been found between elevated D-dimer, prothrombin, interleukin (IL)-6, and fibrinogen.[30] Another suspected mechanism of hypercoagulability in COVID-19 can be attributed to the direct impact of the virus entering the cell due to ACE-2 overexpression, which causes endothelial inflammation and dysfunction.[31,32] Thrombotic complications have also been shown to be a persistent issue in patients previously infected with COVID-19.

3) Cardiovascular PASC

The cardiovascular effects of PASC are rarely caused by direct injury of SARS-CoV-2 COVID-19 on myocardial tissue but are rather a consequence of PASC-induced myocarditis, pericarditis, and POTS.[33] The most common cardiovascular symptoms of PASC are chest pain, chest tightness, palpitations, dizziness, and tachycardia.[33] Chest pain and tightness have been reported in a substantial number of patients suffering from long COVID-19.[25] Results from a five-database systematic review revealed that 16% of patients reported chest pain 3 months after hospital discharge.[34]

Currently, one of the proposed mechanisms underlying these symp-

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toms is inflammation of the pericardial vasculature, namely the intercostal and esophageal branches of the aorta, internal thoracic arteries, and anastomoses of the coronary arteries with pericardial fat.[35] The second mechanism is that chest pain may be due to pleural inflammation or the prolonged effects of cardiac injury.[36] Rohun et al.[37] in 2022 presented a case series of PASC myocarditis leading to heart failure and suggested that this may be one of the more severe complications of PASC. The three patients presented in this case series were all male: a 46-year-old previously healthy athlete, a 33-year-old previously healthy bodybuilder, and a 53-year-old with a history of hypertension; all developed heart failure after the development of PASC myocarditis.[37] The authors attributed the severity of myocarditis to the high degree of inflammation caused by COVID-19.[37]

Examining the blood and its breakdown products can also be indicative of the prognosis of patients with COVID-19. Patients with PASC were found to exhibit a significant number of preformed amyloid clots in their plasma, which was attributed to elevated levels of SAA and α2p2. Furthermore, patients within this population demonstrate poor prognosis.[26] In a study by Knight et al.[38] in 2020, 29 patients who were previously hospitalized with COVID-19 presented with elevated troponin levels of unknown cause and underwent cardiac magnetic resonance imaging, indicating that 13 of these patients developed myocarditis following COVID-19. These patients had no myocardial scarring prior to hospitalization for COVID-19.[38] Rather, myocarditis was diagnosed using late gadolinium enhancement patterns with adenosine stress perfusion testing and was able to provide an explanation for myocardial ischemia.[38] Cardiovascular effects of PASC are effectively managed with corticosteroids (both intravenous and oral), inotropes, and antibiotics, which are also necessary in some cases.[39,40]

4) Postural tachycardia syndrome

POTS occurs when there is an inappropriate increase in heart rate (>30 beats per min) without an increase in blood pressure within 10 minutes of standing from a seated position and with symptoms lasting longer than 3 months.[41] The symptoms of POTS can overlap with some of the other symptoms of PASC including dizziness, palpitations, fatigue, headache, nausea, vision changes, and brain fog.[41] The pathophysiology of PASC-inducing POTS is unclear; however, it has been speculated that this may be due to autonomic nerve destruction.[41]

5) Multisystem inflammatory syndrome-adult

In a case report by Bhatt et al.[23] in 2023, the patient presented with cardiac dysfunction, hepatitis, and acute kidney injury (AKI) and was diagnosed with MIS-A. Upon completion of corticosteroid therapy, the patient recovered; however, cardiomyopathy and hypothyroidism.[23] The exact pathophysiology of how MIS-A leads to further sequelae is unknown; however, Bhatt et al.[23] in 2023 speculated that it could be due to the ability of SARS-CoV-2 to cause autoimmune dysregulation.

6) Other conditions

Rare complications can also arise from long COVID. A rare case of aortitis from the aortic arch to the root caused tachycardia that eventually progressed to a ventricular storm with intermittent third-degree atrioventricular block and bundle branch reentry ventricular arrhythmia.[39] The patient's condition was resistant to amiodarone, lidocaine, and adenosine; therefore, they were treated with prednisolone and radiofrequency ablation after placing a temporary pacemaker.[39] Prior to the COVID-19 infection, the 69-year-old patient did not have any myocardial conduction abnormalities.[39]

7) Proposed treatments

Physical activity effectively reduces cardiovascular complications of long COVID. Yates et al.[42] in 2023 demonstrated that performing at least 2,000 steps per day reduced the risk of cardiovascular adverse events by 10% in a large cohort study consisting of 9,306 participants. Another study showed that pulmonary rehabilitation could be imperative for the recovery and prevention of the long-term sequelae of COVID-19.[43] Tang et al.[44] in 2023 also showed that implementing an at-home exercise program incorporating Liuzijue, a traditional Chinese exercise, in patients recovering from COVID-19 improved functional capacity and overall quality of life. Comorbidities must also be considered in patients treated for long COVID. One study in particular found that selective serotonin reuptake inhibitor and tricyclic antidepressant treatments may worsen symptoms related to inappropriate sinus tachycardia or POTS, specifically.[45]

2. Respiratory

The primary organ system affected by COVID-19 is the respiratory tract, and the extent of lung damage can correlate with the degree of infection.[46] The injured lungs become evident through the symptoms of respiratory failure and pneumonia.[47] The most commonly reported respiratory symptoms of long COVID are dyspnea, cough, and chest discomfort.[25] Data collected from studies following the discharge of patients with previous COVID-19 infections depict pulmonary function tests with a mix of low diffusion and restrictive patterns.[48] The virus can possibly harm the lungs via three separate mechanisms.[49]

The first mechanism is through diffuse alveolar damage, resulting in acute respiratory distress syndrome.[49] This damage to the alveoli is thought to be caused by virus binding to ACE-2 on the surface of type 2 pneumocytes, leading to their destruction.[49] The destroyed alveoli pose an issue, as reduced alveolar epithelial integrity affects the efficacy of adequate gas exchange.[49] Autopsy of lung tissue post-COVID-19 infection has depicted fibroproliferative alveolar damage diffusely spread throughout the tissue, in addition to pneumocyte desquamation and the formation of hyaline membranes.[48]

The second mechanism through which the virus harms the lungs is occlusion of the alveolar microvasculature via thrombi.[49] Through ACE-2 receptors, the virus binds to and activates endothelial cells of the lung vasculature, inducing thrombus formation by upregulating adhesion molecules such as P-selectin, E-selectin, intracellular adhesion molecule-1, and von Willebrand factor leading to platelet aggregation.[49]

The last mechanism involves airway inflammation via inflammatory mediators.[49] Inflammatory mediators spread through the trachea, bronchioles, and bronchi, resulting in damage.[49] A study comparing intensive care unit (ICU)-admitted COVID-19 patients and non-ICU patients found increased levels of IL-10, granulocyte colony-stimulating factor, IP1, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, IL-7, and tumor necrosis factor in ICU-admitted patients.[49]

1) Dyspnea

Results from a prospective observational study in the United Kingdom showed that 51% of 769 patients reported prolonged dyspnea 1 year after discharge from COVID-19 hospitalization.[50] Current literature shows that prolonged breathlessness is a symptom of prolonged COVID-19 in hospitalized patients.[25] A study of patients 6 months after hospital discharge found that the average distance walked in 6 minutes was significantly lower than the reference range because of the participant's dyspneic challenges.[51] Lung function test results from a multicenter cohort study revealed that 6 months after hospitalization for COVID-19, approximately 30% of patients had suboptimal forced vital capacity and forced expiratory volume in 1 second.[25] A longitudinal cohort study discovered that pulmonary function testing at 1-year post-discharge showed unremarkable lung volume measurements; however, significant impairment in diffusion capabilities was noted.[52]

2) Cough

Following dyspnea, the second most commonly reported persistent respiratory-related symptom is cough.[53] In an online survey conducted in the United Kingdom, 30% of symptomatic patients reported a continued cough 3 months after the initial onset of COVID-19 symptoms.[53] A Norwegian-based study reported that 10% of non-hospitalized patients experienced continuous cough 4 months after the onset of acute symptoms.[54] The current literature states that prolonged cough in patients with COVID-19 may be due to lung fibrosis, causing increased sensitivity of the cough reflex in these individuals.[53] The proposed mechanism of increased sensitivity is thought to be caused by a virus infecting the vagal sensory nerves. Thus, inflammation and immune interactions result in increased sensitivity.[53]

3. Renal

Literature supports the idea that the degree of initial COVID-19 infection is highly correlated with the risk of kidney injury.[55,56] Although more research is required on the pathophysiology of viral damage to the kidneys, the mechanism underlying COVID-19-related kidney involvement is due to the viral spiral proteins attached to the receptors of ACE-2-releasing proteases.[57] The released proteases and ACE-2 receptors are localized in the collecting duct, proximal tubule epithelial cells, mesangial cells, and podocytes.[57] The literature shows that following COVID-19 infection, individuals are at an increased risk of developing AKI and a declining glomerular filtration rate (GFR), leading to chronic kidney disease (CKD).[55]

1) Acute kidney injury

Current studies posit that kidney injury due to COVID-19 is a result of the virus infecting the parenchyma and/or microthrombus formation within the organ.[58] A cohort study involving 89,216 individuals post-infection with COVID-19 determined an increased risk of kidney injury in patients previously infected with COVID-19, irrespective of whether they developed AKI during the initial infection.[55] Autopsy data from patients with COVID-19 have shown virus-like particles within the epithelium of the proximal tubules, suggesting that the virus can elicit damage within the organ itself.[59] Individuals who develop AKI have an increased risk of developing more severe kidney injuries, including AKI with progression to CKD.[56] A study following patients 1-year post-discharge from hospitalization determined that those who had AKI had a longitudinal decline of 8.5% in GFR.[56]

2) Glomerular filtration rate

The rate of glomerular filtration has been shown to decrease faster longitudinally in patients with previous COVID-19 than in controls.[55] In a study of 2,212 patients 1-year post-COVID-19 infection, there was a significant decrease in estimated GFR (eGFR; a calculated estimation of the GFR through the use of blood test parameters, age, sex, and body habitus), with the highest decline recorded in hospitalized patients.[60] Additionally, a study comparing COVID-19-infected individuals to uninfected controls revealed a significant reduction in the eGFR of infected individuals.[56] The study also stated that after 1 year of observation, the infected individuals demonstrated a decrease in eGFR level similar to that after 4 years of aging in the uninfected population.[56] Notably, the highest degree of eGFR decline was observed in individuals previously hospitalized during the initial COVID-19 infection period.[60]

3) Chronic kidney disease

The inflammation and damage that occur during initial COVID-19 infection can last for months, resulting in the development of CKD.[61] A longitudinal study following patients 1-year post infection with COVID-19 reported that 40% of patients were at risk of developing CKD.[60] An observational study reported that 45% of the patients with a previous CKD diagnosis experienced significant disease worsening after disease post-infection.[62] Moreover, a prospective cohort study reported continued kidney function decline 1-year post-COVID hospitalization.[63] While the literature strongly supports the development of CKD after long periods of COVID-19, it is imperative to recall the reciprocal relationship between these two conditions. Patients with CKD are at a higher risk of developing COVID-19; as such, additional follow-up is imperative for these patients.[64] After reviewing the literature, we found that there is no specific treatment for COVID-induced injury; and dialysis remains the treatment of choice for CKD.

4. Neurological

Persistent neurological and neuropsychiatric symptoms due to long COVID also affect some of those who have recovered from COV-

ID-19.[65] The current understanding of the mechanisms is that as the virus is known to directly infect cultured human brain microvascular endothelium, it is thought that in doing so, the virus can weaken the blood–brain barrier (BBB) and provoke an inflammatory response.[66] Autophagy can be dysregulated by the activation of microglia and astrocytes and neurotransmitter production can be disrupted.[66] In addition to the problems caused by hyperinflation, neurological and neuropsychiatric symptoms may also result from direct viral invasion of neurons through transcellular BBB endothelium access.[66] The direct effects of viruses on the brain are not yet well understood. However, many long-term effects have been studied in recent years, showing how damaging and debilitating they can be.[67] Of all the long-term neurological and neuropsychiatric effects that have been noted, those more commonly observed include impaired thinking, memory problems, fatigue, sleep disturbances, and headaches.[66,68]

1) Brain fog

Long-term thinking or cognitive impairment, also referred to as brain fog, has been reported in 7.2% of patients who have recovered from their initial COVID-19 symptoms.[68,69] Brain fog is often used to describe feelings of mental lethargy, fuzziness, inability to concentrate, or spacing out.[66,68,69] Certain risk factors are related to a higher likelihood of developing brain fog, including those with respiratory problems (odds ratio [OR], 1.9), women (OR, 1.4), and those who had ICU admission during the initial illness (OR, 1.7).[69] In another study, 50% of those who had recovered from COVID-19 suffered from some level of executive function impairment even months after recovering from their initial illness.[65] Additionally, 33% of the patients reported a decrease in attention and information processing speed.[65]

2) Memory impairments

Memory impairment is a specific instance of a more severe level of brain fog, as it begins to affect one's ability to remember specific details about one's life, such as dates, names, and events, and increases one's forgetfulness.[65] One study reported that among those who were 3 months post-COVID-19 infection, 24% of patients had deficits in their working memory and 10% had deficits in their verbal memory.[65] Another study showed that episodic memory, irrespective of the type of stimulus, was negatively impacted in those affected by long-term COVID.[67]

3) Fatigue

Fatigue is arguably one of the most common symptoms of long COVID with reports affecting more than 33% of patients who have recovered from COVID-19, persisting up to 6 months or more in certain cases.[65,66] The decrease in physical and/or mental performance due to chronic fatigue can be traced back to central nervous system (CNS) changes that are initiated by the initial infection as a result of systemic inflammatory processes that affect the brain, including a surge in cytokines.[66]

4) Neuropsychiatric disturbances

Anxiety, post-traumatic stress disorder, obsessive compulsive disorder, and depression, with increased severity seen specifically in females, have all been commonly correlated to long COVID with the help of many studies in recent years.[66] Many factors can cause these symptoms, and whether they should be considered as biological causes remains unclear. Development of these symptoms is possibly influenced by external circumstances, such as quarantines, isolation, financial worry, stress from the pandemic, to name a few.[66] These circumstances increase a sense of loneliness, incite behavioral changes, provoke avoidance behaviors, and increase anxiety levels.[66] These circumstances cause physical changes to the permeability of the BBB, allowing for an overload of cytokines, inflammation, and direct viral invasion of neurons with subsequent CNS damage.[66]

5) Sleep disturbances

Long-term sleep disturbances are another symptom among the most commonly reported neurological effects of long COVID.[66,67,69] Although sleep disturbances are a relatively broad descriptor, the most common disturbances experienced have been reported as trouble falling or staying asleep, nightmares, and lucid dreaming.[66,67] In a study of patients with long COVID, it was reported that 26% of patients had recurring sleep disturbances.[66] Another study reported that 41.8% of patients with long COVID experienced insomnia, specifically, at 1-month post-COVID-19 and 25.5% at 3 months post-COVID-19.[66] One theory states that the sleep disturbances experienced by these patients are less likely due to the direct effects of the virus; rather, they are the result of mental health issues exacerbated by the stress of the pandemic.[66,67]

6) Headaches

Severe, migraine-like headaches are highly common both in the initial infection with COVID-19 as well as in long COVID with roughly 77% of patients experiencing headaches 6 months post-COVID-19 infection.[66,70] These headaches affect those of all ages and have been reported to be a crucial part of the long COVID sequelae, which are known to affect one's ability to work as well as their quality of life.[66,70] In the months following an acute infection, patients report intermittent but deep, stabbing, tension-like, or migraine-like headaches, which are often thought to be caused by cerebrovascular complications, such as stroke or nosebleed.[70] Owing to the nature of these patients' headaches, it can sometimes be difficult to discern whether they are caused by primary or secondary headache disorders as long COVID headache episodes are clinically indistinguishable from migraines, even in patients without a history of migraines.[70] Hypoxia, ongoing immunologic events, or vascular events are all consequences that can arise from long COVID exacerbated headache episodes, causing functional impairment and psychological or psychiatric comorbidities.[70]

DISCUSSION

This literature review was conducted using a multitude of peer-re-

viewed studies on the prevalence of long COVID as well as its impact on various organ systems. Long COVID has a spectrum of presentations ranging from pulmonary to extrapulmonary symptoms. Examples of extrapulmonary manifestations include but are not limited to, the CNS via retrograde hematogenous or neuronal routes and the digestive system as a result of the intestinal epithelium expressing the ACE-2 receptor, allowing the virus to attach, replicate, and have an immune response.[2] There are not enough data to conclude why a certain set of symptoms appears in some individuals; however, it is clear that long COVID is more prevalent in those who have been hospitalized due to COVID.[1] Specifically, while most COVID-19 survivors recover normally after clearance of the virus, the disease effects 10% of recovered non-hospitalized COVID-19 patients and 50%–70% of hospitalized patients with over 200 documented symptoms with varying levels of severity.[2] Some of the presentations of long COVID, such as those pertaining to the circulatory system, have a molecular process to explain the pathophysiology, in which both COVID-19 viral particles and endothelial cells express ACE-2 TMRPSS2, a gene that encodes a protein in the serine protease family, and heparan sulfate, which enhances virus binding and activity.[2] This process involves transcellular movement and loss of endothelial integrity, ultimately causing dysfunction, resulting in the disruption of cardiomyocytes, interstitial cells, and macrophages, as well as altered renin-angiotensinogen-aldosterone and bradykinin-kallikrein pathways.[2] It manifests as small-vessel coronary artery disease, acute myocardial infarction, and other potential cardiac events.[2] There are still additional processes lacking an answer as to the pathophysiological mechanisms.

These processes also impact the perioperative setting and management.[71] Vaccination is also important in preventing long COVID. In a systematic review by Watanabe et al.[72] in 2023, the study found that those administered two doses of the COVID-19 vaccine were associated with a lower risk of long-term COVID than those who were not vaccinated. This study also suggested that about 20% of patients experiencing long COVID had symptomatic improvement after 2 weeks to 6 months of COVID-19 vaccination, indicating that the vaccine is a potential treatment option as well as a preventative measure.[72] The strategies and treatment of post-COVID sequelae vary greatly depending on the symptomatic profile and needs of each patient. These should include physician examination of patients with mapping of current symptoms or medical concerns, establishing COVID-19 exposure status and potential disease history, screening for possible non-COVID-19 comorbidities or chronic conditions, administering appropriate medical treatments for acute symptoms or established underlying conditions, educating patients on possible manifestations of post-COVID-19, and continuing regular patient follow-up, and informing the patient to seek medical care at the onset of worsening symptoms.[71] Considering the acute management of patients experiencing sequelae of long COVID, treatment of inflammation with the use of corticosteroids can effectively manage the effects of long COVID on the cardiovascular and hematologic systems.[39] Specifically, regarding MIS-A management, steroids are effective; however, in severe cases, the integration of vasopressors, inotropes, and antibiotics was also necessary to stabilize patients.[40]

Long COVID has had a significant impact on some while leaving others untouched. Those affected by it, as well as those who are at an increased risk (e.g., hospitalized patients), have the potential to experience a decreased quality of life.[73] There is no conclusive evidence on what the risk factors are and who is at risk of suffering from long COVID; therefore, further studies should be done to compare those who have received COVID with and without long COVID to observe what commonalities and differences exist (e.g., age, sex, past medical history, family history, blood type, genes, and so forth) as well as to learn if there are further avenues to explore in hopes of preventing long COVID symptoms in the future.

CONCLUSION

Long COVID has the potential to affect several organ systems, manifesting as symptoms that fluctuate in duration and severity and differ across patients. The disease affects the cardiovascular system, with the development of POTS and myocarditis, potentially leading to heart failure. Hypercoagulability and thrombus formation are the most evident hematological symptoms reported in long COVID patients, while dyspnea, cough, and chest pain are the respiratory outcomes generally seen. The most commonly observed effects on the renal system include a rapid decline in eGFR and the development of AKI, which increases the risk of CKD. Headaches, fatigue, memory, neuropsychiatric symptoms, and sleep disturbances are the most notable neurological symptoms in long COVID patients. Due to how recently the COVID-19 pandemic took place, there are limited and discrepant data and literature providing insights into addressing long COVID and preventing it. The variations in presentation and ambiguity in pathophysiological etiology imply that individualized clinical evaluations need to be performed when treating long-term COVID.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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