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Review Article

Long COVID: Epidemiology, post-COVID-19 manifestations, possible mechanisms, treatment, and prevention strategies – A review

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Abstract

***Background and objectives*:** The respiratory disease COVID-19 began in 2019 and quickly became a pandemic infecting millions of individuals across the globe. Many patients show lingering effects of the infection several days after testing negative for the disease. This has become known as "long COVID" and is defined by various sources as lasting anywhere from 4 weeks to undefined periods. This is a review of the existing literature on long COVID which offersextensive insights into its clinical features, diagnosis, and treatment.

***Materials and method*:** Information on clinical features, mechanisms, treatment options, preventive measures, and epidemiology of long COVID is derived from an extensive review of scientific journals and pertinent authoritative sources.

***Results*:** The virus enters the cells via angiotensin-converting enzyme 2(ACE2) receptors. ACE2 receptors are present on numerous cell types throughout the body and thus the virus can affect several organs resulting in avariety of different symptoms. Long COVID symptoms include fatigue, dyspnea,headache, brain fog,and symptoms related to cardiovascular and pulmonary systems. Fatigue can affect upwards of 93% of patients suffering from long COVID. Failure of the body to clear the virus could initiate this chronic effect. Studies indicate that theuse of antiviral drugs at the early phase of COVID-19 could prevent long COVID symptoms. Vaccines against SARS-CoV-2 also might help prevent long COVID.

Conclusion: Diagnosing and managing long COVID is challenging due to diverse symptoms, including mental health issues like anxiety and depression. Longitudinal studies and patient-oriented approaches are crucial for treatment, supported by policies and educational campaigns. Understanding the pathophysiology remains a top priority.

Introduction

The respiratory disease COVID-19, caused by SARS-CoV-2 first emerged in Wuhan, China, in November 2019 and quickly became a pandemic. As of this writing in 2023, over 768.9 million confirmed cases of COVID-19 have been recorded worldwide, and more than 6.9 million deaths have been reported by the World Health Organization[1]. Since this data is based on reported cases only, it can be presumed that many more cases have probably gone undocumented.

The clinical spectrum of COVID-19 ranges from

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asymptomatic to life-threatening infections [2]. The virus enters the cells via angiotensin-converting enzyme 2(ACE2) receptors. Once inside the cells, the virus undergoes replication, triggering immune responses [3]. ACE2 receptors are present on numerous cell types throughout the body, including those of the oral and nasal mucosa, lungs, heart, gastrointestinal tract, liver, kidneys, spleen, and brain, as well as arterial and venous endothelial cells, indicating how SARS-CoV-2 can potentially damage multiple organs [4,5].

Being a new disease, a lot of information on the manifestations of COVID-19 remains unexplained. Recent studies indicate that a segment of the patients who contracted and eventually tested negative for COVID-19 experienced prolonged and continued symptoms of the disease over varied periods. This prolonged post-disease illness, which cannot be explained by an alternative diagnosis, has been referred to as long COVID. Common manifestations of long COVID comprise of, but are not limited to cough, sore throat, shortness of breath, cardiovascular dysfunction, fatigue and weakness, anosmia, headaches, and diarrhea. An estimated 80 percent of people who recovered from COVID-19 could experience at least one long-term symptom [6,7].

The symptoms of long COVID can last for many weeks following SARS-CoV-2 infection. The term “long COVID” gained wide attention following a May 2020 report in BMJ Opinion, in which, an infectious disease professor shared his 7 weeks of negative health experience with unexplained symptoms following his COVID-19 infection [8]. The patient denoted his experience as “long COVID” [9], which is now a recognized term in scientific literature.

The National Institute for Health and Care Excellence (NICE) describes long COVID as a collective symptom that lingers or develops after acute COVID-19 infection, and which cannot be elucidated by an alternative diagnosis [10]. The US Centers for Disease Control and Prevention (CDC) describes long COVID as symptoms that extend beyond four weeks after initial infection [11]. The National Institute of Health (NIH) supports the US Centers for Disease Control and Prevention (CDC) definition of long COVID-19, stating that the lasting post-COVID-19 symptoms may prolong for 4 to 12 weeks beyond COVID-19 infection [12].

Studies indicate that developing long-COVID is unrelated to the severity of the infection, or the nature of treatments patients receive during COVID-19 infection [13].Patients with both mild and acute symptoms could develop long COVID [14,15]. A 2020 study suggests that the percentage of people who developed long COVID was similar among patients who were treated with oxygen alone and with invasive ventilation [14]. Similarly, studies reported that the prevalence of long COVID was not much different between hospitalized and non-hospitalized COVID-19 patients [16].

Although there is no founded consensus about defining long COVID syndrome, based on the available information, this review will mainly discuss the varied symptoms of long COVID, organ abnormalities and dysfunctions caused by the disease, and possible causes and mechanisms of organ dysfunctions [7].

Materials and Methods

The information presented in this narrative review encompasses insights from a comprehensive examination of scientific journals and authoritative sources, focusing on epidemiology, manifestations, organ abnormalities, systemic dysfunctions, possible mechanisms, and treatment related to COVID-19. The search strategy for this review involved utilizing keywords such as COVID-19, post-COVID symptoms, Long COVID, post-COVID conditions, long-haul COVID, post-acute COVID-19, post-COVID mechanisms, and post-COVID treatment regimen.

To gather relevant data, various search engines, including Google Scholar, MEDLINE, PubMed, Scopus, CDC, and WHO websites, were employed. The search scope was limited to the period from 2020 to 2023. Inclusion criteria encompassed articles that detailed manifestations, organ abnormalities, systemic dysfunctions, possible mechanisms, epidemiology, and treatment. Exclusion criteria were applied to non-English articles and articles lacking full text.

Researchers autonomously conducted article searches and evaluated the quality of each study, ultimately determining their inclusion in the review based on a thorough examination of the full text.

Results

Epidemiology

The sudden emergence of COVID-19 and the resultant pandemic threw the world's healthcare systems into chaos, confusion, panic, and uncertainty. Reported COVID-19 incidences and mortality rates varied across countries. It isnot so difficult to comprehend that at such a chaotic time, keeping or predicting an accurate incidence of SARS-CoV-2 infection and the mortality rate was not logistically possible.With this ambiguity concerning COVID-19 incidences, it is difficult to accurately predict the number of COVID-19 cases that could progress into long COVID. The disparity in the epidemiological data is mostly due to differences in the accuracy in diagnosis and the reporting methods used in reporting the incidences. All in all, a lot of COVID-19 cases probably went unreported or undocumented.

The National Institute of Health (NIH) and the Center for Disease Control and Prevention (CDC) defined long COVID as the ongoing post-COVID symptoms that persist beyond four weeks from the initial infection [12,11]. To this point, the data generated from various studies show a wide variation in long COVID prevalence. The UK Office for National Statistics reported that between April and December 2020, the estimated five-week prevalence of long COVID symptoms was 22.1%, and the 12-week prevalence was 9.9% [17]. Other studies reported that the prevalence was 96% at 90 days [18], 32.6% at 60 days [19], and 76% at 6 months [20].

In a 2022 publication, Hanson et al. revealed that a global total of 144.7 million individuals encountered any of the three symptom clusters associated with long COVID during the years 2020 and 2021. The prevalence rates for the fatigue, respiratory, and cognitive clusters were 51% (16.9–92.4), 60.4% (18.9–89.1), and 35.4% (9.4–75.1) among long COVID cases, respectively. Individuals with milder acute COVID-19 cases demonstrated a faster-estimated recovery (median duration 3.99 months) compared to those hospitalized for the acute infection (median duration 8.84 months). After twelve months, 15.1% (10.3–21.1) of individuals still experienced long COVID symptoms [21].

According to a recent review article, long COVID is observed in a minimum of 10% of severe SARS-CoV-2 infections. The study indicates that over 200 symptoms have been identified, affecting various organ systems. The estimated global prevalence of long COVID is reported to be at least 65 million individuals [22].

Although, due to the disparity in the epidemiological data, it is difficult to understand the epidemiology of the disease, the interest of the scientific community in long COVID is mounting, which might help create a better understanding of the epidemiology of COVID-19 and long COVID.

Common symptoms of long COVID

Data from a large study involving 3762 COVID patients from 56 countries revealed the presence of 205 symptoms involving 10 different organ systems, and of these, 66 symptoms persisted for over seven months after the patients tested negative for the disease. Some of these individuals could not resume their pre-COVID physical activities due to lingering post-COVID symptoms. About 77.7% of these patients reported fatigue as the most common symptom, 72.2% reported continued malaise, and 55.4% experienced cognitive dysfunction [18].

Ceban (2021) reported on the physical well-being of individuals 12 or more weeks following COVID-19 diagnosis and reported that about 32% and 22% were still experiencing fatigue and cognitive impairment, respectively [23].

Fatigue*:* Fatigue is a chronic symptom of post-COVID infections regardless of the severity of the disease. Goertz et al. (2020) reported that 92.9% of hospitalized and 93.5% of non-hospitalized patients suffered from fatigue at 79 days following the onset of the disease [16]. Post-COVID fatigue has been compared with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS), as both represent similar symptoms, such as fatigue, pain, autonomic, cognitive, and psychiatric dysfunctions [24].

It is difficult to pinpoint the causes of fatigue syndrome. Studies indicate that several factors may be responsible for post-COVID fatigue, such as

SARS-CoV-2 infection possibly damaging skeletal muscle, causing weakness, and inflammation of myofibers. Damage to neuromuscular junctions may also contribute to fatigue [25-28]. Wostyn (2020) suggested that SARS-CoV-2 infection may affect the lymphatic system, resulting in toxic build-up in the CNS causing fatigue symptoms [29]. Additionally, chronic fatigue could be a set of psychosomatic factors caused by negative psychological and social factors associated with SARS-CoV-2 infection [30,31].

Dyspnea: Dyspnea (breathlessness) is a common manifestation following COVID-19 infection [15,32]. Carfì et al. (2020) reported that dyspnea was present among 43.4% of 143 post-COVID patients 60 days after COVID-19 onset [33]. According to the UK Office for National Statistics (2020), regardless of the disease severity, shallow breathing is a common symptom in people with long COVID [17]. This is probably due to a slow recovery of lung functions in post-COVID patients. Total lung capacity, forced vital capacity, and forced expiratory volume could also be affected in long COVID patients [34].

SARS-CoV-2 replicates within the epithelial cells of the lung. Thus, the probable cause of dyspnea in post-COVID patients could be linked to extensive inflammatory damage to the endothelial cells in these organs [35,36]. Studies suggest that for most post-COVID patients, these damages may not be a long-term issue [37]. However, older patients and patients with pre-existing pulmonary conditions may develop pulmonary fibrosis caused by high levels of cytokines, such as interleukin-6 (IL-6) [38-40].

Cardiovascular abnormalities: Cardiovascular abnormalities, such as chest pain, tachycardia, myocarditis, and elevated serum troponin levels occur in SARS-CoV-2 patients [41-47]. Such manifestations have also been observed in long-COVID patients [48,33,49]. Residual myocarditis has been reported in young individuals and athletes long after recovery from COVID-19 [49].

Cardiac muscle cells express numerous ACE2 receptors providing SARS-CoV-2 pathways to the myocardium[50]. Cardiovascular manifestation in long COVID patients could also be caused by prolonged inflammation and fibrosis of the myocardium [51]. Persistent and intense immune responses to SARS-CoV-2 infection may damage the sarcomeres of cardiac muscle cells. Chronic hypoxia caused by SARS-CoV-2 infection may also damage the cardiac muscle cells [52,53]. Goldstein (2020) reported that SARS-CoV-2 infection may distress the autonomic nervous system which also may lead to irregular cardiac activities [52,54].

Headache: Persistent headaches are one of the most frequent symptoms that accompany long COVID. The headaches vary in duration and occurrence. This could beattributedtocontinued activation of the nervous system and the immune system, and the instigation of trigeminovascular function, an etiology in various headaches [7].

Organ abnormalities and systemic dysfunction

As stated earlier, SARS-CoV-2 enters cells via ACE2 receptors, therefore, cells, tissues, and organs with abundant ACE2 receptors, could be directly damaged by SARS-CoV-2 infection [50,55]. Crook et al. (2021) reported that SARS-CoV-2 could cause damage to the lungs, heart, blood vessels, brain, kidneys, GI tract, liver, pancreas, and spleen. Possible damage to skeletal muscles and neuromuscular junctions has been suspected in SARS-CoV-2 infection [25,27]. There is also very strong evidence of the consequences of SARS-CoV-2 and the endocrine system [56].

Dennis et al. (2020) reported that chronic systemic inflammation was commonly observed in post-COVID periods, long after the clearance of SARS-CoV-2 infection [14]. Such elevated inflammation could secondarily damage the tissues and organs, leading to multiple organ complications in long COVID patients [57-59].

Lungs: Long-term ongoing pulmonary complications have been observed in some post-COVID patients. The most common dysfunctions were breathing difficulties and shortness of breath. Studies suggest that about 25% of COVID-19 patients could experience insufficient pulmonary function for up to a year following the initial SARS-CoV-2 infection [60]. Post-COVID CT scans performed at 12 months following the infection revealed that almost 50% of the patients with severe SARS-CoV-2 infection had signs of fibrosis [61]. Such a change in pulmonary

tissue could lead to insufficient lung functions and pulmonary complications.

Heart and blood vessels: As stated earlier, cardiovascular abnormalities in long COVID patients include chest pain, tachycardia, myocarditis, and elevated serum troponin [41-46]. A study conducted between June 2020 and March 2021 evaluated 342 COVID-19 patients in 25 hospitals in the UK. The researchers observed elevated levels of troponin, a marker for acute myocardial injury and heart attack. MRI scans within 28 days following discharge showed myocardial scars and ventricular impairment [62].

Cytokine storms caused by SARS-CoV-2 infection can cause serious damage to cardiac tissues causing myocarditis, stress cardiomyopathy, damage to the endothelial lining of arteries and veins, and small blood vessels.This can lead to blood vessel inflammation, affecting heart rhythm including palpitations and ventricular arrhythmias. Symptoms of myocarditis may potentially mimic a heart attack [63].

Kidney: Subclinical acute kidney injury (AKI) as indicated by proteinuria and hematuria is relatively common in COVID-19 patients. Studies from theUS, Europe, and Brazil reported AKI in COVID-19 patients [64]. Data indicated that COVID-19-related AKI was present in 28-34% of all hospitalized patients and 46-77% of ICU patients [65,66]. Studies also reported that post-COVID patients have significant chances of developing chronic kidney disease (CKD) and CKD patients have higher risks of congestive heart failure and diabetes [67]. Decreased kidney function has also been reported in 35% of post-COVID patients even 6 months after they tested negative for the virus [20].

The mechanism of COVID-19's effects on kidneys is not clearly understood. However, one possible explanation could be due to the significant interaction of the SARS-CoV-2 virus with ACE2 receptors. Kidneys are among the key targets of the SARS-COV-2 virus as ACE2 receptors are in abundance on the renal parenchyma [68]. Additionally, podocyte cells of the glomerular capsule and the proximal convoluted tubules express ACE2 genes, indicating that nephrons could be the possible targets for SARS-C0V-2 [69]. Moreover, ACE2 receptors may also associate COVID-19 with the renin-angiotensin system (RAS), and the kallikrein-kinin system (KKS) [70,71]. RAS helps regulate blood pressure by maintaining salt and water retention and vascular tone, and KKS is associated with blood pressure regulation, inflammation, and coagulation. Thus, SARS-CoV-2 infection may contribute to abnormal functioning of the RAS and the KKS.

Gastrointestinal (GI) tract: Studies indicate that SARS CoV-2 infects the esophagus, stomach, small intestine, and colon. Mayo Clinic's Division of Public Health and Infectious Diseases reported that in a study involving 147 COVID-19 patients, 16 percent of the patients reported GI-related symptoms about 100 days after COVID-19 infection.The study also reported that abdominal pain, constipation, diarrhea, and vomiting were among the common symptoms of SARS-CoV-2 infection [72].

Significant changes in gut microbiota during and post-COVID periods have been reported. Such alterations include the depletion of anti-inflammatory symbionts, such as *Faecalibacterium,* and the enhancement of opportunistic pathogens, such as *Coprobacillus* and *Clostridium* species [73]. Such changes in microbiota could play a major role in GI-related complications in post-COVID patients.

The GI tract has a complex network of nerves. It is speculated that SARS-CoV-2 infection interferes with the gut-brain signaling processes causing post-COVID irritable bowel syndrome, resulting in abdominal pain and changes in bowel movements such as diarrhea or constipation. Such disorders are also known as DGBIs (Disordered Gut-brain Interactions) [74]. Nakhli et al. (2022) reported that the digestive symptoms observed in post-COVID were related to DGBI. DGBI also included heartburn, bloating, and swallowing difficulties [75].

Liver: Kolesova et al. (2021) reported possible liver fibrosis in about 5% of post-COVID patients [76]. Liver fibrosis was also reported by Heidari (2022) [77]. Milic et al. (2022) reported the prevalence of fatty liver in post-COVID patients [78]. De Lima et al. (2023) reported possible liver injury in long COVID patients indicated by abnormalliver enzymes and injury markers [79]. A study involving 243 patients, reported elevated levels of the liver enzymes alanine aminotransferase (ALT) and

aspartate aminotransferase (AST), along with other liver injury markers, such as lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), and ferritin [79]. In another study, researchers reported elevated levels of ALT and AST in post-COVID patients. The researchers found abnormalities in liver functions in 28.4% of 461 patients [80]. A meta-analysis of 64 studies involving 11,245 COVID-19 patients revealed that the prevalence of elevated ALT and AST was 21.2% and 23.2% respectively [81].The fibrosis of the liver could be due to a result of chronic inflammation of liver tissue caused by SARS-CoV-2 infection, and elevated liver enzymes could be correlated with liver injury.

Pancreas: Pancreatic cells express ample ACE2 receptors, and thus, the pancreas could be easily affected by SARS-CoV-2 infection [82].Hadi et al. (2020) reported acute pancreatitis in COVID-19 patients [83]. Liu et al. (2020) reported pancreatic injury caused by SARS-CoV-2 infection, detected by CT images and elevated blood serum lipase [51]. Researchers reported that 40% of the post-COVID patients showed mild impairment of pancreatic functions which was associated with diarrhea, fever, headache, and dyspnea even after 141 days following infection [14].

As stated earlier, ACE2 receptors are abundant in pancreatic cells possibly to a greater level than in pulmonarycells [82,51]. However, it is not known for certain if pancreatic damage is a direct result of viral infection within the pancreas or caused by the systemic inflammatory response seen during COVID-19 [84].

Spleen: Splenomegaly (enlarged spleen) in COVID-19 patients has been reported in several studies [14]. CT data indicated a moderate increase in spleen size and the increase was associated with COVID-19 severity [85]. Studies indicated that the impacts of COVID-19 on the spleen decreased the number of T and B lymphocytes leading to lymphocytopenia [86-88]. On the other hand, additional studies indicated a decrease in spleen size and T lymphocyte count [89]. Dennis et al. (2020) reported mild spleen damage in 4% of patients 141 days after they were tested negative for COVID-19 [14].

It is suggested that since the spleen expresses adequate ACE2 receptors, it could be directly attacked by SARS-CoV-2, and this could be the primary reason for splenic damage rather than intense systemic inflammation [4,86].

Muscle: SARS-CoV-2 infection negatively impacts skeletal muscle functions causing weakness, fatigue, and reduced mobility weeks after COVID-19 diagnosis. Skeletal muscles are essential for movement, posture maintenance, equilibrium, and normal physical activities.Thus, skeletal muscle dysfunction would reduce the quality of life.It has been suggested that respiratory muscle weakness could be used as a marker of the recovery process during long COVID [6].

SARS-CoV-2 invades the muscle cells through ACE 2 receptors. The virus-inflicted damage to the muscle cells could be direct as the virus replicates within the cells, interrupting cell function, or indirect via systemic inflammation, hypoxia, and myopathy [6]. Elevated levels of cytokines such as IL-2, IL-6, IL-10, and interferon-gamma impact muscle cell protein metabolism by decreasing anabolic functions and increasing catabolic functions, which could interfere with the safeguarding of muscle health and function [90].

Endocrine dysfunction: Endocrine organs express ACE2 receptors where the virus can trigger typical pro-inflammatory cytokines and acute phase reactants such as C-reactive protein.The damages include insufficient adrenal function and thyroid dysfunction, such as hypothyroidism, hyperthyroidism, and thyroiditis [57]. It has been noted that hyponatremia (low blood sodium) occurs in nearly a third of patients with COVID-19.In addition, the gonads and pancreas may be affected [91].

One clear area of concern is that endocrine failure due to long COVID may lead to progressive destruction of the pancreas.Data has shown that 10% of COVID-19 patients had newly diagnosed diabetes. However, Type 1 and Type 2 diabetics are more likely to have complications if they do get COVID-19 [92]. Studies also indicate that nondiabetic hospitalized COVID patients showed spikes in their blood sugar levels after leaving the hospital facility [93].

Immunological dysfunction: Another long-term effect of infection with COVID-19 is immune dysfunction which would make patients vulnerable to repeat infection as well as other infections [94]. Several reports have shown that infection with COVID-19 caused a severe decrease in CD8+ cytotoxic T cells and natural killer (NK) cells [95,96]. CD8+ T cells are important in controlling viral infections. Loss of CD8+ T cells has been observed in other viral infections and cancer so this is not unique to COVID [97]. Some claim that this loss is similar to that seen with HIV infections [94]. NK cells are also important for attacking virus-infected cells in an antigen-non-specific manner although recent reports suggest antigen-specific memory as well [98].

SARS-CoV-2 infection releases a flood of cytokines referred to as a cytokine storm. This amplified immune response may cause overwhelming inflammation in the body destroying healthy tissues and damaging vital organs [59]. Severe cytokine storm also occurs in Ebola infections [99].

Neurological dysfunction: Brain fog, headache, and fatigue arethe most common neurological symptoms among long COVID patients [100]. Fatigue, hyposmia, and cognitive impairments were the most common post-COVID symptoms likely caused by nervous system dysfunction [101].

Another study published by Shanley et al. reportedthat fatigue (89.3%) and headache (80.4%) were the two most common neurologic symptoms among post-COVID patients. At a 6-month follow-up, most symptoms subsided; about 33% reported complete recovery. However, memory impairment (68.8%) and decreased concentration (61.5%) persisted [102]. In the USA, among long COVID patients, about 15 million people are affected by extreme fatigue and brain fog, causing an estimated 2-4 million people to leave the workforce [103].

The possible causes of brain fog in COVID have been studied by several researchers [104-106]. Immune response to the virus induces chronic inflammation that leads to microclots and impaired brain cell functions [107,101]. Additionally, increased cytokine production due to the infection-activated microglia cells also hampers new neuron formationin the hippocampus [104]. Thus, increased cytokine activity impairs neurogenesis, particularly in parts of the brain that are associated with memory [107]. Therefore, persistent cytokine production and chronic inflammatory responses may be associated with numerous problems including brain fog in long COVID cases.

A study conducted in Bangladesh involved 385 post-COVID individuals, revealing persistent levels of depression (29.4%), anxiety (37.4%), and stress (18.2%). The study also noted extremely severe cases, with 3.6% experiencing depression, 6% anxiety, and 0.5% stress. Interestingly, there was no significant difference in depression and anxiety between suburban and rural populations, but stress levels were notably higher in the suburban group. Approximately 60% of participants had to reduce their heavy work schedules, yet moderate to minimal physical activities were less affected. Moreover, weakness and nervousness emerged as predominant factors hindering their socialization [108].

The key information concerning possible vital organ damage and systemic dysfunctions inflicted by SARS-CoV-2 infection, and long COVID manifestations are summarized in Table: 1.

Long COVID in children

Most long COVID information came from studies with adult patients. However, a few studies conducted on children or teen agers revealed that their symptoms were very much like those of adults. Crist (2022) indicated that there could be around 100 million people living with long-COVID, and its effects were equally disabling in both adults and young individuals. Even so, more studies are needed to validate such findings [109]. The UK Office for National Statistics indicated that in the United Kingdom alone, tens of thousands of younger subjects might have been suffering from long COVID. Among these long-COVID sufferers, about 44,000 were 2 to 11-year-olds and about 73,000 were 12 to 16-year-olds [110]. A large study from the United Kingdom involving young subjects (11 to 17-year-olds) revealed that two-thirds of the subjects reported three or more symptoms of long-COVID even three months after they were tested negative for the disease [111].

Table-1: *Summary of major systemic dysfunctions and manifestations in long COVID.*

Systems	Manifestations and dysfunctions
Respiratory system	Dyspnea, chest pain, cough, pneumonia, acute respiratory distress
Cardiovascular system	
Heart	Chest pain, myocardial inflammation, myocardial injury, arrhythmias, tachycardia/palpitation, elevated serum troponin
Blood vessel	Damage to blood vessel endothelium, leaky blood vessels,inflammation, coagulopathy, microangiopathy
Nervous system	Fatigue, sleep disturbances, anxiety, depression,brainfog, delirium, PTSD
Urinary system	Renal impairment, hematuria, elevated leucocytes in urine, acute kidney injury
Digestive system	
GI tract	Diarrhea, nausea, sore throat
Liver	Liver injury, elevated aspartate andaminotransferase, nausea, vomiting, diarrhea
Pancreas	Pancreatitis, diarrhea, fever, headache
Spleen	Reduced T and B lymphocyte, atrophy of lymphoid follicles
Muscular system	Muscle weakness, fatigue, reduced mobility
Endocrine system	Adrenal dysfunction, hypothyroidism, hyperthyroidism, thyroiditis, progressive destruction of the pancreas, complications with Type 1 and Type 2 diabetics
Reproductive system	Structural change of testis, altered testosterone level, altered spermatogenesis
Immune system	Production of immune molecules causing damage toendothelial cells, inflammation, and clot formation in the brain leading to the destruction of neurons

Note: PTSD: *post-traumatic stress disorder; GI: gastrointestinal*

Treatment and prevention strategies

At present, Long COVID lacks a definitive treatment. Collaborative efforts between patients and healthcare providers are crucial in planning personalized care strategies to effectively address post-COVID symptoms and enhance the overall quality of life.

In general, current clinical practice utilizes a symptom-oriented approach to address long COVID. This involves a thorough evaluation incorporating medical history and examinations. For a comprehensive assessment, it's advised to conduct various tests including full blood count, renal function, C-reactive protein, liver function, thyroid function, hemoglobin A1c (HbA1c), vitamin D, magnesium, B12, folate, and ferritin levels [112].

The approach to treating long COVID could extend beyond symptomatic treatments through the collaboration of a specialized team of physicians. For instance, the University of California, Los Angeles (UCLA), offers personalized treatments to long COVID patients with the expertise of specialists in internal medicine, neurology, cardiology, and pulmonology. Additionally, UCLA

Health (2024) highlights the provision of counseling and mental health support for individuals dealing with long COVID [113].

In a recent study, a synbiotic preparation (SIM01) was found to improve gut microbiota composition in patients with post-acute sequelae of SARS-CoV-2 (PACS). It increased beneficial bacteria and reduced pathogenic ones associated with PACS. The gut microbiota's connection to the immune response and blood cytokine profiling was noted. SIM01 also alleviated gastrointestinal symptoms resembling post-infectious irritable bowel syndrome. SIM01 helped reduce chronic fatigue syndrome by promoting butyrate-producing bacteria species. Prebiotic compounds in SIM01, including galacto-oligosaccharides, xylo-oligosaccharides and resistant dextrin, positively influenced gut microbiome composition. Furthermore, this study also indicated a possible connection between the gut, brain, and bacteria which could be related to mental symptoms, but more research is needed to fully understand it [114].

The National Institute for Health and Care Excellence (NICE) lays out evidence-backed methods for assessing and managing long COVID in patients [112]. Their guidelines suggest clinical examination for long COVID as early as 4 weeks after acute symptoms. Furthermore, the National Institute of Health Research (NIHR) has also provided recommendations regarding the assessment of long COVID symptoms, prioritizing care for specific populations [112,115].

Research suggests that monoclonal antibody treatments can target and neutralize the SARS-CoV-2 virus effectively. This sheds light on why certain individuals with long COVID experienced temporary symptom relief following their COVID-19 vaccination. Additionally, monoclonal antibodies might counter and replace nonfunctional antibodies that could inadvertently target our cells [116].

The World Health Organization (WHO) supports research priorities aimed at enhancing clinical understanding and creating treatments for long COVID. At the same time, healthcare experts are actively investigating clinical strategies to identify and address long COVID [112].

In addition to exploring treatment options, it would be beneficial for individuals experiencing long COVID to learn how to alleviate and handle the symptoms of the condition. The British Heart Foundation has released a Long COVID Recovery Guide that provides valuable tips on managing ailments like fatigue, breathlessness, brain fog, cognitive impairment, and joint and muscle pain. The guide also offers advice on boosting mood and supporting mental health [117].

Getting vaccinated against SARS-CoV-2 may reduce the risk of developing long COVID. According to the CDC, individuals who are not vaccinated against COVID-19 and contract the virus may be at a higher risk of experiencing long COVID compared to those who have been vaccinated. The CDC also highlights the possibility of multiple reinfections with SARS-CoV-2, with each instance carrying a potential risk of long COVID development. Additionally, it is noted that while most individuals with long COVID show evidence of infection or COVID-19 illness, there are cases where a person experiencing long COVID may not have tested positive for the virus or been aware of their infection [118].

Preventing long COVID should be a top priority for public and global health. New findings suggest that antiviral medications for SARS-CoV-2 could be effective in this prevention. Research indicates that nirmatrelvir (with ritonavir) reduced the risk of long COVID by 26%, and molnupiravir reduced it by 14% [119-121]. Exploratory analyses also showed that ensitrelvir may reduce the risk of long COVID [122]. Overall, these findings with nirmatrelvir, molnupiravir, and ensitrelvir suggest that using antivirals during the early phase of COVID-19 could be an important strategy to prevent long-lasting symptoms. Recently,Johns Hopkins Health Care has suggested the use of ICD-10 code U09.9 (International Classification of Disease) in the diagnosis and reporting of patients with Long COVID-19 [123].

Discussion

Long COVID is a possible risk factor, i.e., not all COVID-19 patients suffer from it. Indeed, most of the patients do not exhibit long COVID manifestations. The actual number of patients with

long COVID is unknown.However, it is estimated that between 7.7 to 23 million people are suffering from long COVID-related symptoms [124], whereas another study suggests that in the US, there are about 10-33 million working-age adults with long COVID [125].

What causes long COVID is also a challenging question to answer. The answer can be a mixture of speculations. One of the key reasons could be the duration of the virus in the infected patients.Viral RNA that remains in the body for longer than 14 days could cause long COVID.Studies indicate that about 42% of patients remain COVID-positive for 14 days or longer and for about 12% of patients, the duration is 90 days or longer [126]. Studies also suggest that in about 4% of the patients, viral RNA could be detected even 7 months after diagnosis with COVID-19, and in some immunocompromised patients, the virus might take about a year to be cleared from the body [125]. Viral elements were detected in intestinal, lung, appendix, and breast tissue for various lengths of time with a range of 100-462 days [127,128].

Several researchers believe that microclots that form in the body as a result of SARS-CoV-2 infection, could be involved with the sequelae of long COVID syndrome [129]. These microclots can block microcapillaries and prevent the exchange of oxygen in numerous organs and tissues. As these clots are resistant to fibrinolysis, this can cause a buildup and induce inflammatory responses as well [130,131]

According to a report from the Yale University Iwasaki Lab in collaboration with the Mount Sini School of Medicine, exposure to SARS-CoV-2 may elevate the humoral immune response against the coronavirus and other non-coronavirus pathogens, such as Epstein-Barr virus. Such infection could also decrease the stress hormone cortisol level. Iwasaki hypothesized that acute infection disturbs trillions of normal flora bacteria and viruses in our bodies. This induces inflammation causing an imbalance in the body’s homeostasis. Additionally, the reactivation of dormant viruses could induce autoimmunity by triggering B and T cells [132].

In a large study where 1.5 million unvaccinated COVID-19 patients were compared with over 25 thousand vaccinated patients with breakthrough infections, the vaccine significantly reduced the risk of developing long COVID [133].

Recent data also suggests that there may be a genetic risk factor involved with long COVID [134,135].One study determined that genetic variants in the FOXP4 locus were associated with an increased risk for Long COVID. This was due to increased expression of FOXP4 in the lungs (particularly alveolar and immune cells) which they believe increased the severity of COVID-19 [135].

Limitations

This review is constrained by the inherent bias associated with a literature review of a similar nature. The potential for bias could be mitigated through the adoption of a systematic review approach. Given that this study did not adhere to a systematic review methodology, the search strategies employed may not justify a thorough examination. Moreover, considering COVID-19's status as a novel disease, numerous uncertainties surround its understanding. The study's information spans approximately four years, yet the absence of a systematic method for bias assessment through meta-analysis raises concerns about potential bias in the study.

Conclusions

Due to nonspecific and diverse symptoms, the diagnosis and management of long COVID remains a challenge. Mental health illnesses such as anxiety and depression further aggravate the challenges. Moreover, the systemic nature of this condition, affecting multiple organs and bodily systems, complicates its management and requires close collaboration between patients and healthcare providers.

Studies indicate that the prolonged symptoms might be linked to the virus directly impacting various organ systems, including the immune system. Studies also suggest that the virus might persist in tissues, sustaining immune reactions and symptoms. Additionally, disruptions in cellular and molecular mechanisms, potentially affecting vascular function and causing microclotting issues across organs, are also suspected. Understanding

these mechanisms is crucial to determine the treatment options.

Longitudinal epidemiologic studies including clinical trials and patient-oriented approaches can bolster treatment strategies. Furthermore, educational campaigns, telemedicine integration, specialized care, and supportive policies would help to manage long COVID. Understanding the pathophysiology of long COVID illnesses and their management remains a priority.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of interest

The authors declare no conflict of interest, financial orotherwise.

Human and animal rights

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