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Review Article

Understanding Long COVID: A Comprehensive Review for Clinicians

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ABSTRACT

Long COVID is defined as a chronic condition that develops following a SARS-CoV-2 infection, persisting for at least three months. It presents as a complex and multifaceted syndrome, most common symptoms include fatigue, breathlessness, and neurological impairments, with researchers identifying patterns of respiratory and multi-system complaints. According to a CDC survey, an estimated 6.4% of U.S. adults have experienced Long COVID, with prevalence varying geographically. Factors such as age, sex, genetics, acute disease severity, pre-existing conditions, and socioeconomic status are potential predictors of long COVID. Vaccination has shown promise in reducing the likelihood of developing Long COVID. The impact of long COVID extends beyond individuals, affecting health systems, economies, and societies. Currently, no standardized diagnostic or treatment guidelines exist for Long COVID. Management strategies focus on symptom relief, with non-pharmacological interventions and conservative therapies for respiratory and neurological symptoms. Emerging diagnostic tools and treatments, such as micro clot detection, biomarker assays, and antiviral drugs like Paxlovid, show potential in improving patient outcomes. Despite the official end of the pandemic, millions continue to suffer from Long COVID, highlighting the need for ongoing research and tailored management approaches to address this persistent public health challenge.

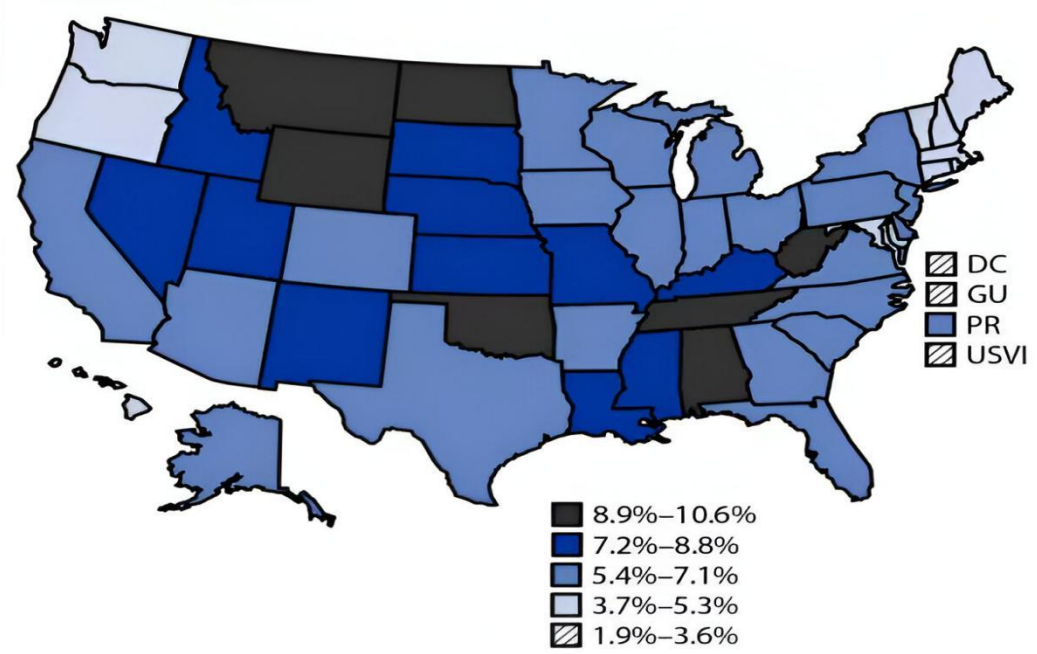
Key Words: Long COVID (LC), LC, Post-COVID, PCC, COVID-19, Epidemic, infection-associated chronic condition (IACC)

Defining and Understanding Long COVID

Long COVID, defined in 2024 by the U.S. Department of Health and Human Services (HHS) and the National Academies of Sciences, Engineering, and Medicine (NASEM), stands as an infection-associated chronic condition (IACC) that develops following a SARS-CoV-2 infection and persists for at least three months. Long COVID displays a vast range of manifestations, highlighting its complexity as a multifaceted condition. A comprehensive list of associated signs, symptoms, and diagnosable conditions includes hundreds of entries, reflecting its broad effects on the body.[1] Patients with Long COVID report diverse symptoms, such as shortness of breath, cough, persistent fatigue, post-exertional malaise, cognitive difficulties, memory issues, recurring headaches, dizziness, rapid heart rate, sleep disturbances, altered taste or smell, bloating, constipation, and diarrhea. Long COVID also presents as diagnosable conditions like interstitial lung disease, hypoxemia, cardiovascular disease, arrhythmias, cognitive impairment, mood disorders, anxiety, migraines, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS), dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders, including lupus, rheumatoid arthritis, and Sjögren's syndrome.[1] The extensive symptom range in Long COVID suggests it is a multi-syndromic and multi-phasic condition rather than a single disease phenomenon.[2]

Long COVID: Prevalence and Risk Factors

Understanding the epidemiology of Long COVID is crucial for comprehensively addressing its impact on public health. CDC highlights that 6.4% of noninstitutionalized U.S. adults report experiencing Long COVID nationally (95% CI = 6.2%–6.5%).[3] The prevalence ranged from 1.9% to 10.6%, with lower prevalence in New England and the Pacific and higher prevalence in the South, Midwest, and West.[3] Researchers in New York (NY) conducted a population-representative survey from June 30th to July 2nd, 2022, consisting of a random sample of 3,042 adults in the United States.[4]



Abbreviations: DC = District of Columbia; GU = Guam; PR = Puerto Rico; USVI = U.S. Virgin Islands.

Figure 1: Prevalence of reported experience of Long COVID among adults aged ≥18 years, by jurisdiction — Behavioral Risk Factor Surveillance System, United States, 2022 (Source: https://www.cdc.gov/mmwr/volumes/73/wr/mm7306a4.htm) [2]

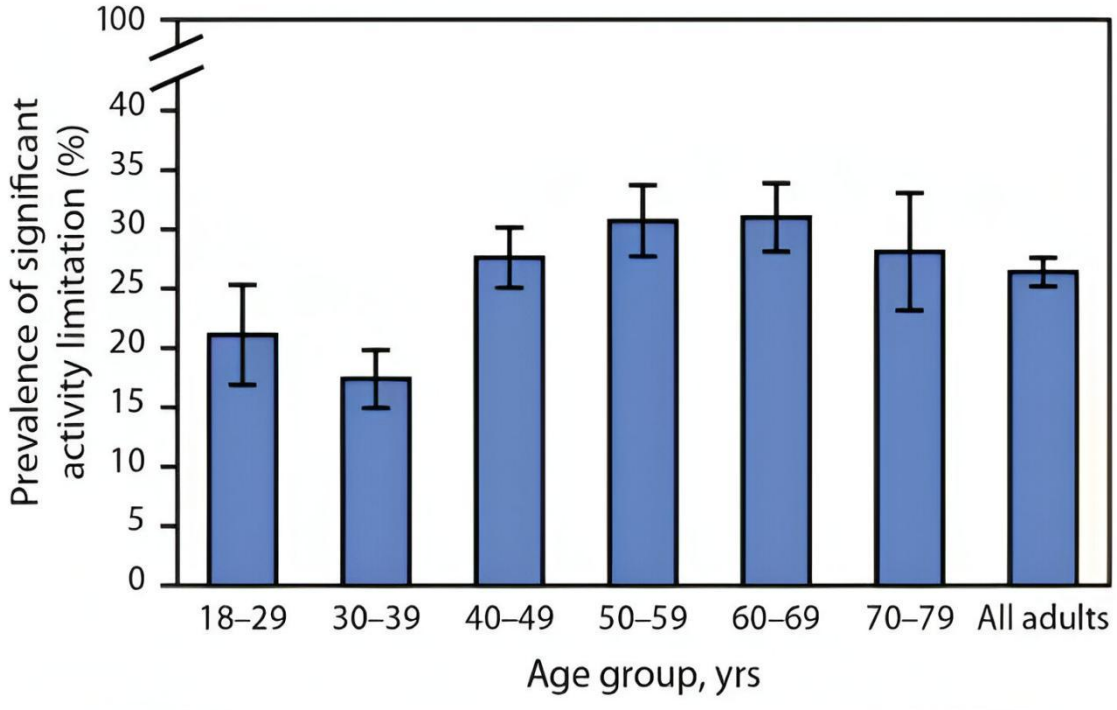
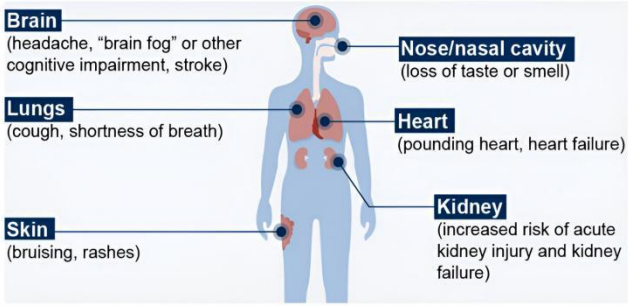


Figure 2: Prevalence of significant activity limitation among adults reporting long COVID* — Household Pulse Survey, United States, June 7–19, 2023 (Source: https://www.cdc.gov/mmwr/volumes/72/wr/mm7232a3.htm) [5]

An estimated 7.3% of all respondents reported Long COVID, which they defined as symptoms of fatigue, difficulty concentrating, shortness of breath, or a reduced ability to carry out daily functions for more than four weeks since their COVID-19 infection, which are not explained by anything else. The U.S. Household Pulse Survey estimated that 7.5% of people were experiencing Long COVID during this time period.[4] Notably, approximately 25% of respondents stated that their ability to carry out daily functions was diminished by "a lot." These percentages extrapolate to approximately 18 million adults experiencing symptoms during this two-week study period.[4] Factors such as age, sex, genetics, acute disease severity, pre-existing conditions, and socioeconomic status are potential predictors of long COVID. [4,15]

Symptoms of Long COVID

The most common symptoms are profound fatigue, breathlessness, cough, chest pain, palpitations, headache, joint pain, myalgia, insomnia, neuropathy, diarrhea, rash, hair loss, ataxia, and difficulties with memory and concentration.[5] Researchers identified two main patterns of symptoms: 1) fatigue, headache, and upper respiratory complaints such as sore throat, shortness of breath, persistent cough, and loss of smell; and 2) multi-system complaints such as ongoing fever and gastrointestinal problems.[5]



Source: GAO analysis of Centers for Disease Control and Prevention information and medical literature. | GAO-22-105666

Figure 3: Some reported symptoms of long COVID [6]

Long COVID shows heterogeneity, stemming from various underlying pathophysiologic processes, such as organ damage from the acute infection phase, complications from dysregulated inflammation, microvascular dysfunction, persistent viral activity, and autoimmunity.[3,10,11] Its sequelae affect multiple organ systems, underscoring the complexity of researching and treating this condition. Broadly, researchers theorize that the COVID triggers a persistent immune response, leading to the symptoms of fatigue, general malaise, and myalgia.[2] Long-term shortness of breath may be explained by elevated T cells in the lungs of patients with Long COVID.[2] In addition, elevated spontaneous IFN-gamma production has been interpreted as the presence of persistent virus.[2] One study showed that the spike protein was found in 60% of patients with Long COVID at 12 months post-infection.[2] The gastrointestinal symptoms are supported by the presence of viral shedding in the stool seven months after infection. Another theory is that Long COVID may be caused by immunity to self-antigens triggered by COVID-19.[2] Autoreactive T cells have been identified in severely sick patients and may persist, causing Long COVID. Furthermore, there is a correlation between the number of autoantibodies and the severity of the disease. Lastly, a third theory suggests that immune dysregulation is the culprit.[2] Histamine receptor antagonists have been used as a treatment for Long COVID, reducing symptom burden and T-cell perturbations, suggesting its causal role. Notably, some symptoms of Long COVID overlap with Mast Cell Activation Syndrome and multisystem inflammatory syndrome in children. Fatigue refers to unrelenting exhaustion and a constant state of weariness that reduces a person's energy, motivation, and concentration.

This is one of the most common symptoms, with a five-week prevalence of fatigue in 11.9% of patients who were infected with COVID-19.[6] One cross-sectional study found that 92.9% and 93.5% of hospitalized and non-hospitalized COVID-19 patients, respectively, reported ongoing fatigue 79 days after being diagnosed.[6] These studies report no association between the severity of COVID-19 and long-term fatigue.

Researchers hypothesize that this may be due to a range of central, peripheral, and psychological factors. Reduced metabolism in the frontal lobe and cerebellum has been implicated in COVID-19 patients with fatigue and is likely caused by systemic inflammation and cell-mediated immune mechanisms, though it is unknown if this is present in Long COVID.[6] Another review hypothesizes that congestion of the lymphatic system and subsequent toxin buildup in the central nervous system may contribute.[6] Shortness of breath is another common symptom, estimated to have a prevalence of 4.6% at five weeks post-COVID-19 infection, regardless of the presence of acute respiratory symptoms or disease severity.[6] Another study consisting of 143 patients reported that 43.4% of patients were still experiencing dyspnea 60 days after their infection. One month following infection, abnormalities in diffusion capacity for carbon monoxide, total lung capacity, forced expiratory volume in the first second, forced vital capacity, and small airway function demonstrated how lung function may take time to recover.[6] Researchers hypothesize that the virus causes substantial damage to the lungs and respiratory tract by replicating within the endothelial cells, causing an intense immune and inflammatory reaction.[6] Risk factors for developing fibrotic-like changes to lung tissue include older age, an extended hospital stay, and pre-existing lung conditions.[6] Cytokines such as IL-6 are raised in COVID-19 and are known to lead to the formation of pulmonary fibrosis. Long COVID has been associated with multiple neurological symptoms, such as cognitive impairment, delirium, headache, and stroke. One study found that at three months post-discharge, 40% of ICU-treated patients had cognitive scores like patients with moderate traumatic brain injury, while 26% had scores similar to those with mild Alzheimer's disease.[6] Additionally, 10.1% of all COVID-19 survivors experienced stroke and headache five weeks post-discharge. Coronaviruses can infect the central nervous system through hematogenous or neuronal retrograde neuro-invasive routes, explaining the high incidence of inflammation in the nervous system.[6] COVID-19 also alters the permeability of the blood-brain barrier, enabling peripheral cytokines to enter the central nervous system and further worsen inflammation.[6] Increased levels of systemic inflammation, observed in some patients as a "cytokine storm," in addition to the activation of glial cells, increase the likelihood of neurological manifestations, such as encephalitis and stroke.[6]

Prevention of Long COVID

More than four years since the emergence of SARS-CoV-2, an estimated 65 million people worldwide are living with long COVID. This escalating public health challenge underscores the urgent need for preventive, rehabilitative, and therapeutic strategies.[15] Vaccination against COVID-19 has been shown to be the most effective mechanism for preventing symptoms of Long COVID.[7,15] A meta-analysis found that 7 out of 9 studies reported that the vaccine was associated with a lower incidence of Long COVID compared to unvaccinated individuals.[7] These studies differed in the magnitude of the protective effect, with a 78.0% to 41.1% decrease in the odds or risk of self-reported Long COVID.[7] One study consisting of 64,571 individuals found that the hazard rate of post-acute sequelae was 13% lower in the vaccinated group. Notably, the protective effects of vaccination against Long COVID decreased as the interval between vaccination and infection increased.[7] Specifically, those who were vaccinated and tested positive for COVID-19 had a reduced risk of post-acute sequelae in the cardiovascular, coagulation, metabolic, and pulmonary organ systems, as well as a reduced risk of fatigue.[7] There were no statistically significant differences in post-acute sequelae for the renal, gastrointestinal, psychiatric, and neurological organ systems. One study with 3,388 participants found that those who received two doses of the COVID-19 vaccine were less likely than unvaccinated individuals to report post-COVID fatigue by 64%, headache by 54%, and myalgia by 68%.[7]

Management of Long COVID

Currently, there are no distinct guidelines for diagnosing and treating Long COVID, likely because this disease is new and has many different clinical presentations.[11] Medical management of long COVID primarily aims to optimize patients' function and quality of life through targeted symptom management. This approach includes addressing the most bothersome symptoms identified by the patient, creating a comprehensive rehabilitation plan through shared decision making, optimizing underlying medical conditions, and using diaries or calendars to monitor health changes.[12,13,14,15] Patients with long COVID may experience symptoms like those in conditions like myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia, post-treatment Lyme disease syndrome, dysautonomia, and mast cell activation syndrome, and may benefit from similar management strategies.[8] Additionally, further tests may be ordered based on their symptoms. For example, if patients are experiencing cardiopulmonary symptoms, tests such as a D-Dimer, Troponin, chest X-ray, echocardiogram, and pulmonary function tests may be ordered.[8] Overall, the primary management strategy is through conservative symptom management. Cough, pain, and myalgia are managed with NSAIDs, acetaminophen, and cough suppressants.[5] Beta-blockers are used to treat POTS, while IV immunoglobulin treats immune dysfunction.[11]

Non-pharmacological management includes increasing salt intake for POTS, cognitive pacing for cognitive dysfunction, and elimination diets for gastrointestinal symptoms.[11,15] Chest physiotherapy and neurorehabilitation are beneficial for patients with pulmonary and neuromuscular sequelae.[5] Sally J. Singh and colleagues examine respiratory sequelae and discuss the potential of pulmonary rehabilitation programs and breathing physiotherapy to aid recovery.[15] If patients present with a pulmonary embolism or stroke, management follows the standard protocol.[5]

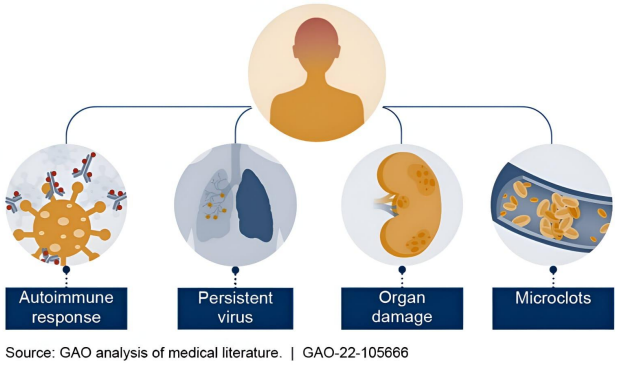


Figure 4: Some possible causes of long COVID as suggested by researchers. [6]

Diagnostic tools specific to Long COVID are in development and include imaging to detect micro clots, corneal microscopy to identify small fiber neuropathy, new fragmentation of QRS complexes on EKGs indicative of cardiac injury, and the use of hyperpolarized MRI to detect pulmonary gas exchange abnormalities.[11] There is also preliminary research suggesting that high levels of extracellular vesicles and immune markers indicating high cytotoxicity could be indicative of Long COVID.[11] Biomarker research in myalgic encephalomyelitis and chronic fatigue syndrome may also be applicable to Long COVID.

These include electrical impedance blood tests, saliva tests, erythrocyte deformation, sex-specific plasma lipid profiles, and variables related to isocapnic buffering.[2,11.15] Treatments specifically directed for Long COVID are also currently in the developmental stage, primarily based on small studies and case reports.[2] Anticoagulants have preliminarily shown a reduction in the risk of microclotting.[2,11] Similarly, apheresis helps through this mechanism, as well as by reducing markers of inflammation, autoantibodies, and lipids.[2,11] BC007, an aptamer, blocks autoantibody binding to G-protein-coupled receptors and has shown promise in clinical trials.[2] Paxlovid is also being studied as a potential treatment for Long COVID. It is currently approved to treat outpatients with COVID-19 infection who are at high risk for progression to severe COVID-19.[11]

One study showed that treating acute COVID-19 with Paxlovid reduced the incidence of Long COVID by 25%.[11] As a result, the NIH has recently launched a double-blind, placebo-controlled study to determine whether this drug may improve outcomes for Long COVID.[10] Notably, a recent RCT demonstrated that early outpatient treatment with metformin during the acute phase reduced the incidence of long COVID, although its mechanism of action remains unclear.[15] Clinicians should set achievable care goals through shared decision-making, focus on specific symptoms, validate patients' experiences, and connect them to appropriate care and support services.[13,14] Further research in diagnostic tools and targeted treatments for Long COVID is necessary to effectively treat this disease.

Conclusion

Despite the World Health Organization's declaration on May 5, 2023, that COVID-19 no longer constitutes a public health emergency of international concern, the long-term consequences of the pandemic represent an escalating global health crisis. Long COVID represents a unique challenge through its multiple clinical presentations and symptoms.

Vaccination against COVID-19 has been shown to reduce the likelihood of being diagnosed with Long COVID. Currently, diagnostic testing and treatment for Long COVID are primarily dictated by the patient's symptoms, given the variety of presentations. Many clinical trials and preliminary research suggest promising diagnostic tests and treatments specific to Long COVID, such as biomarker assays for immunological dysregulation and drugs like Paxlovid.[16]

As our understanding of this complex condition continues to evolve, it is imperative that we prioritize ongoing research efforts to elucidate its underlying pathophysiology, long-term outcomes, and subsequent treatments. Challenges in research include reliance on patient self-reporting and difficulties differentiating COVID-19-specific effects from pre-existing comorbidities or overlapping conditions. Coordinated multidisciplinary research is essential to uncover mechanisms, identify biomarkers, and develop targeted interventions, demanding a focused, well-resourced, and patient-centered approach.[15]

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