Duenas K, Chwa WJ, Hoque F. Overview of Long COVID: Navigating the Aftermath. *Brown Hospital Medicine*. 2025;4(2):66-72. doi:10.56305/001c.133879. PMID:40391044

Brief Reviews

# Overview of Long COVID: Navigating the Aftermath

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Journal of Brown Hospital Medicine
Vol. 4, Issue 2, 2025

## Article Information

Keywords: Long COVID, COVID-19, Coronavirus, Post-COVID syndrome., Post COVID

https://doi.org/10.56305/001c.133879

Submitted: October 15, 2024 EDT

Accepted: March 31, 2025 EDT

Published: April 01, 2025 EDT

## Abstract

The coronavirus disease (COVID-19) pandemic was a global health crisis with far-reaching consequences. Among these were physical and mental health complications that emerged weeks or even months after the initial COVID-19 infection, collectively termed "long COVID" or "post-COVID syndrome." Identifying the epidemiology, risk factors, clinical manifestations, and management strategies for long COVID is crucial for both clinicians and patients, which is the focus of this review. The prevalence of long COVID varies across studies, generally ranging from 5% to 20%. Prominent risk factors include female sex, older age, a high number of acute symptoms, lower socioeconomic status, and underlying comorbidities such as diabetes, asthma, or chronic obstructive pulmonary disease. The clinical manifestations of long COVID are diverse; beyond the commonly reported symptoms of fatigue, malaise, ageusia, and anosmia, neuropsychiatric complications such as headache, cognitive deficits, and depression are also potential outcomes. Although there is currently no consensus on the management of long COVID, multidisciplinary care teams with appropriate referrals and follow-up diagnostic studies are essential in evaluating the clinical course of long COVID patients.

## BACKGROUND

The coronavirus disease (COVID-19) pandemic was a global public health crisis that resulted in numerous deaths, economic downturns, and unprecedented societal adjustments.[1,2] After over 765 million reported cases of COVID-19 and almost 7 million COVID-19-related deaths, on May 11, 2023, the World Health Organization (WHO) declared the end of the pandemic phase of COVID-19, slowly ushering a period of transition to normalcy.[3] Despite this declaration, cases of COVID-19 have continued to steadily vary.[4] Furthermore, the effects of COVID-19 are complicated by "long COVID", also known as a post-COVID syndrome, which is a condition experienced by a subset of individuals who initially recovered from COVID-19 but experience persistent and new symptoms lasting for weeks or months after the initial infection.[5] This review summarizes the prevalence, risk factors, clinical manifestations, and management of long COVID-19, to provide clarity for patients and clinicians managing this condition.

## PREVALENCE AND RISK FACTORS

Long COVID is most commonly characterized as a clinical syndrome that encapsulates a wide spectrum with regards to duration and severity of symptoms.[6] Attempts have been made to classify long COVID by duration of symptoms, with commonly cited thresholds ranging from 7 days to 2 months.[7,8] The Centers for Disease Control (CDC) defined "post-COVID conditions" as a wide range of physical and mental effects that may be present for at least 4 weeks after initial infection.[9] Regardless of thresholding, however, symptoms may last significantly longer and even potentially result in persistent illness, particularly after 12 weeks.[9]

Multiple studies have investigated the prevalence of long COVID. Prevalence of persistent symptoms past 12 weeks is variable: a prospective cohort study of 4,182 incident cases of COVID-19 from the COVID Symptom Study App illustrated 13.3% of participants reporting symptoms lasting past 28 days, of which 17% reported symptoms lasting longer than 12 weeks.[7,10] A cross-sectional survey of 3,042 United States individuals aged 18 or older estimated a 7.3% prevalence rate of symptoms such as fatigue, difficulty concentrating, or shortness of breath more than 4 weeks after initial infection of COVID-19.[11] A much higher risk is demonstrated in a 2020 international cross-sectional survey performed among patients with suspected and confirmed COVID-19, with the probability of symptoms lasting beyond 35 weeks at 91.8% with a 95% confidence interval

CI of 89.5-93.5%.[12] Another prospective cohort study performed in Germany in 2020 reported an intermediate prevalence of symptoms past 12 months, with 22.9% of 96 patients reporting to be symptom-free.[13] An inception cohort in Bangladesh of 2,198 participants with a previously confirmed COVID-19 diagnosis reported long COVID symptoms at 12 weeks at a 16.1% prevalence rate.[14] An extensive electronic healthcare record (EHR) review in the United Kingdom of over 1 million individuals estimated a long COVID prevalence rate of between 7.8 to 17%.[15] More recently, studies have attempted to characterize the prevalence of COVID longitudinally. In general, the prevalence of long COVID symptoms has decreased since the height of the pandemic in 2020. A multinational cohort study from European electronic health records datasets illustrated the prevalence of COVID-19 patients experiencing at least one symptom past 12 weeks of initial infection declining from 37.7% in late 2020 to early 2021 to 21.6% in May 2021.[16] Furthermore, in subsequent years, the CDC's data from the Census Bureau's Household Pulse Survey displayed prevalence of long COVID among noninstitutionalized United States adults decreased from 7.5% in June 2022 to 6.0% in June 2023.[17]

Despite numerous observational, cohort, and survey studies, factors such as age, gender, comorbidities, and presentation severity cause difficulty in reaching a consensus on an accurate prevalence statistic of long COVID, especially as most patients with COVID-19 are asymptomatic or experience only mild symptoms.[15,18,19]Older age and female gender are associated with a higher prevalence of long COVID.[18,20] Investigation of comorbidities as risk factors for long COVID has yielded diverse results. In a cohort study of 1,066 Japanese adults with long COVID, asthma was an associated risk factor of prolonged general fatigue.[21] A United States cohort study of 1,480 acute COVID patients identified the number of acute symptoms, lower socioeconomic status, established diagnosis of depression, and infection with earlier COVID variants as risk factors for developing long COVID.[22] A meta-analysis of 38 studies performed in 2022 suggested pulmonary disease, diabetes, obesity, and history of organ transplantation as potential risk factors for developing long COVID.[23] The EHR review in the United Kingdom corroborates these findings, particularly with increased long COVID risk from obesity and asthma, but cardio-metabolic conditions were inconclusive.[15] A community-based cross-sectional survey in France of 956 long COVID patients demonstrated smoking and hypertension as risk factors for long COVID.[24] Overall, general health, lifestyle, and social determinants of health are important considerations in assessing the vulnerability of COVID-19 patients to long COVID and associated persistent symptoms.

## CLINICAL MANIFESTATIONS

Long COVID frequently affects multiple organ systems that are more far-reaching than the initial acute infection.[6] In a landmark effort to better classify the clinical course of long COVID, the international Delphi consensus study, which consisted of 1,535 patients, patients' families, healthcare providers, and healthcare researchers from 71 countries synthesized 11 core outcomes for long COVID: cardiovascular outcomes, fatigue or exhaustion, pain, nervous system outcomes, cognitive outcomes, mental outcomes, respiratory outcomes, post-exertion symptoms, physical outcomes, work or occupational and study changes, survival, and recovery.[25] Many studies have investigated this wide spectrum of manifestations of long COVID. A cross-sectional study in Scotland of adults with confirmed long COVID reported the most prevalent symptoms to be malaise, fatigue, and cognitive impairment, with difficulty sleeping, general pain, nausea, and problems with activities of daily living (ADL) as among the most severe symptoms.[26] A longitudinal prospective cohort study of 442 patients in Germany 4 months after symptom onset reported the most common symptoms to be anosmia, ageusia, fatigue, and dyspnea.[27] An Israeli EHR review demonstrated similar findings in long COVID outcomes after 1 year, in addition to palpitations.[28] Younger patients exhibit similar manifestations. A Danish cohort study reported most common symptoms among pre-school children are fatigue, loss of smell, loss of taste, and muscle weakness, and among schoolchildren, the above symptoms as well as respiratory problems and dizziness.[29]

Neurological outcomes of COVID-19 have been a specific area of interest as patients, especially those who have underlying neurological disorders, have worse outcomes from COVID-19 in cognitive ability and functional status.[30] Previous literature has extensively documented potential neurological sequelae of COVID-19 infection past the acute period, such as stroke, cognitive disorders, migraines, seizures, encephalitis, and peripheral nervous system disorders, which are possibly contributed by cytokines that promote a pro-inflammatory state within the nervous system during peri and post-infectious periods.[31-33] An Austrian longitudinal cohort study illustrated cognitive deficits such as fatigue, concentration difficulties, forgetfulness, and sleep disturbances 1 year after initial infection, as well as signs of depression, anxiety, and post-traumatic stress disorder.[34] A 2022 meta-analysis revealed that the most common neurological manifestations of chronic COVID-19 were non-specific, consisting of headache, confusion, and fatigue.[35]

Notably, the risk of neurocognitive disorders such as Alzheimer's Disease with long COVID is unclear, though microglia-mediated neuroinflammation is one prevailing theory suggesting the potential of such an association.[36,

[37] In a cohort study done in the United States, out of 200 patients, there was evidence of worsened cognitive performance in COVID-19 patients compared to control, though this difference was not statistically significant.[38] A multicenter prospective cohort study in Germany suggested that after 6 months of initial COVID-19 infection, patients had a higher prevalence of mild cognitive impairment compared to controls, though they did not meet the criteria for dementia.[39] Further observational studies will be useful in delineating a more precise relationship between long COVID and cognitive function.

## MANAGEMENT

Long COVID is increasingly recognized as a driver of hospital admissions, with acute manifestations that cross multiple organ systems. Cardiovascular complications—such as myocardial inflammation, ischemic events, and arrhythmias—are prevalent even in patients without prior risk factors and often necessitate telemetry monitoring and advanced cardiac imaging during inpatient care.[40] Pulmonary complications, including fibrotic lung disease and thromboembolic events, may result in new or worsening hypoxemia that requires escalation to non-invasive or high-flow oxygen therapy.[41] These clinical trajectories demand that hospitalists adopt an integrated management approach, combining targeted diagnostics with early consultation from cardiology, pulmonology, and rehabilitation services. Discharge planning should begin early and include structured assessments of functional capacity, mobility, cognitive status, and caregiver support. For patients with persistent symptoms, deconditioning, or impaired activities of daily living, hospitalists should coordinate closely with care coordination teams to arrange transitions to skilled nursing facilities, long-term acute care hospitals, or home-based services as appropriate. Establishing regular follow-up with multidisciplinary post-COVID recovery clinics can also facilitate continuity of care and reduce the risk of readmissions.[42]Emerging evidence of endothelial dysfunction and a prothrombotic state in long COVID highlights the need for individualized thromboprophylaxis strategies during hospitalization and in the early post-discharge period, particularly for those at high risk.[40]

Hospitalists are uniquely positioned to bridge acute inpatient care with the longitudinal needs of this complex patient population. There is no set intervention for all patients afflicted with long COVID; rather, each patient requires a holistic clinical approach to determine the cause of the presented symptoms and subsequently formulate an individualized plan.[43-46] A Delphi study performed in the United Kingdom between 33 clinicians representing 14 different specialties stresses the importance of the primary doctor of long COVID patients to be a clinician who is well-versed in multisystem disorders and is part of an easily accessible network of specialists for potential patient referral.[43] Additionally, symptoms should be assessed for a possibility of a non-COVID-19-related cause, as long COVID is not a sufficient diagnosis without other more common diagnoses being excluded.[43,45-47]

Post-COVID patients with respiratory complications may be initially managed with oxygen saturation measurements and chest X-rays to assess for underlying lung pathology.[45-47] Lung function tests and chest computed tomography scans provide further utility in evaluating pulmonary abnormalities such as pulmonary fibrosis and interstitial lung disease (ILD) in these instances.[48] Furthermore, pulmonary rehabilitation has been demonstrated to improve the quality of life and exercise function of post-COVID patients suffering from exertional dyspnea, resting dyspnea, and underlying respiratory disorders such as chronic obstructive pulmonary disease and ILD.[46,49] A study done on 39 patients who underwent a supervised aerobic and resistance exercise program and found that the mean VO2 max improved by 2.1 ml/kg/min.[50] Perhaps, for inpatient scenarios, integrating such a routine with physical therapy (PT) and occupational therapy (OT) may help alleviate Long COVID patients experiencing respiratory symptoms. Another article supported the use of oxygen supplementation while undergoing pulmonary rehabilitation.[51] In addition, those that suffer pneumonia post COVID, it was seen that corticosteroids may resolve such symptoms.[50,51] Specifically dexamethasone treated patient were less likely to report long COVID symptoms at 8 month follow up in an observational study.[51]

Management of long COVID patients with neurologic and psychiatric complications is complex.[52] A German prospective cohort study suggested ANA titers to potentially be a helpful tool in assessing the role of autoimmunity in neurocognitive deficits and may be an evaluative measure in associating such complications with long COVID.[13] Specifically in patients with autonomic dysfunction, such as motor and sensory deficits leading to functional decline, a multidisciplinary approach involving occupational therapy and physiotherapy is recommended.[53] Additionally, supplementation with vitamins like B2, E, C have been recommended for neurorehabilitation.[54] Furthermore, due to long COVID's common associations with depression and anxiety, psychiatrists should also play a role in the care team, and their resources in psychopharmacology and cognitive behavioral therapy have proven to be effective in managing both somatic and psychiatric manifestations of long COVID.[55,56] Antidepressants may help such deficits by reducing peripheral inflammatory markers, which may help restore immune function.[51,54] Despite these recommendations, there is yet to be a formal consensus on an evidence-based, multidisciplinary management plan for long COVID.[50,51,54,57] Therefore, it becomes increas-

ingly important for long COVID patients to be managed by a multidisciplinary care team that can evaluate and treat the plethora of symptoms that long COVID may present with. While efforts have been made to synthesize the clinical outcomes and management goals set forth for long COVID patients, further review of the literature and consensus methodology should be employed to establish a well-corroborated treatment plan for this condition.

## Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosures/Conflicts of Interest

The authors declare they have no conflicts of interest

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