Long COVID-19: Molecular Mechanisms, Multi-System Manifestations, and Current Therapeutic Strategies

Wania Ali Malik

1st Year BDS, Islamabad Medical and Dental College, Islamabad, Pakistan

Key points:

- Introduction
- Causes
- Symptoms and Clinical Manifestations
- Treatment and Management
- Conclusions

Introduction

Since its emergence in 2019, SARS-CoV-2 has become a major global health challenge. By 2025, the virus had infected over 700 million people and caused approximately 7 million deaths.[1] Although acute COVID-19 ranges from asymptomatic infection to severe respiratory failure and multi-organ dysfunction, its long-term effects have become an equally important public health concern. According to the WHO, Long COVID affects an estimated 10–30% of non-hospitalised individuals after a single infection.[2] COVID-19 may also cause clinically silent organ damage in people who experienced no acute symptoms, placing them at risk for long-term complications despite falling outside the conventional definition of Long COVID.[3]

The heterogeneity of Long COVID is remarkable: over 200 symptoms have been documented across virtually every organ system. Demographic risk factors include female sex, older age, higher BMI, pre-existing comorbidities and severity of the acute illness; however, even young, previously healthy individuals are affected.[4] Understanding the underlying pathophysiology is therefore essential both for developing targeted therapies and for guiding clinical management.

Causes

Long COVID is considered a multifactorial syndrome rather than a single disease. Multiple mechanisms likely act together or sequentially in different patients.[5]

Viral Persistence

One proposed mechanism is the persistence of SARS-CoV-2 viral reservoirs in host tissues beyond the acute phase. Viral RNA and spike protein have been detected in the gut, lymph nodes, brain, and cardiac tissue months after infection.[6] Persistent viral antigens may sustain immune activation and chronic inflammation.

Immune Dysregulation & Autoimmunity

Persistent immune dysregulation is a key feature of Long COVID. Patients often exhibit elevated pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ), reduced regulatory T-cell function, abnormal B-cell activity, and circulating autoantibodies that may contribute to tissue injury.[1,5]

Mitochondrial Dysfunction & Oxidative Stress

Recent proteomic studies have identified increased oxidative stress in Long COVID. Reactive oxygen species (ROS) damage lipids, proteins, and DNA,

impairing cellular metabolism.[7] Mitochondrial dysfunction may contribute to fatigue, cognitive impairment, and exercise intolerance by reducing cellular energy production.[5]

Endothelial Dysfunction & Microthrombi

SARS-CoV-2 directly infects vascular endothelial cells via ACE2 receptors, triggering endothelial inflammation, platelet activation, and the formation of microthrombi in small vessels. These microclots, composed of fibrin and amyloid-like proteins, resist fibrinolysis and impair microvascular perfusion in multiple organs, contributing to the diverse symptom burden of Long COVID.[4,6]

Reactivation of Latent Viruses

Elevated EBV reactivation titres correlate with fatigue severity, suggesting that viral reactivation may contribute to persistent symptoms.[5]

Gut Microbiome Dysbiosis

SARS-CoV-2 disrupts the intestinal microbiome, promoting chronic inflammation and increased gut permeability.[5]

Symptoms and Clinical Manifestations

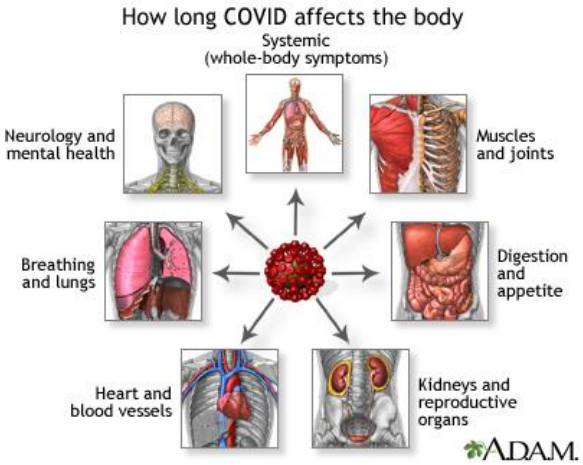


Figure 1: ***How long COVID affects the body***

Long COVID presents with a wide range of symptoms affecting multiple organ systems.Symptoms may persist after acute infection or develop weeks after apparent recovery.[1]

Respiratory System

Dyspnoea (shortness of breath) and chronic cough are among the most frequently reported respiratory symptoms.Chest CT may demonstrate ground-glass opacities or early pulmonary fibrosis in some patients.[4] Post-exertional malaise, a worsening of symptoms after physical or mental exertion is a cardinal feature that can severely limit functional capacity.

Neurological Symptoms

Neurological manifestations are among the most disabling.Brain fog, characterised by impaired memory, concentration, and slowed thinking, is reported in 20–30% of patients.[2] Additional neurological symptoms include headache, peripheral neuropathy, sleep disturbances, and in severe cases, seizures and stroke. Possible mechanisms include neuroinflammation, microvascular injury, and viral persistence.[6]

Cardiovascular Manifestations

Cardiovascular complications include myocarditis, pericarditis, arrhythmias, and Postural Orthostatic Tachycardia Syndrome (POTS), characterised by a heart rate increase of ≥30 bpm on standing.Cardiac MRI studies have demonstrated persistent myocardial inflammation months after infection.Patients may also have an increased long-term risk of major adverse cardiovascular events (MACE).[3,4]

Gastrointestinal Symptoms

Persistent gastrointestinal symptoms include nausea, diarrhoea, abdominal pain, and dysphagia.Gut microbiome alterations may contribute to gastrointestinal symptoms.[5]

Psychological Manifestations

Anxiety, depression, and post-traumatic stress disorder (PTSD) are more common in Long COVID patients compared to age-matched controls. The bidirectional relationship between neuroinflammation

and mood disorders,may worsen psychological symptoms.[1]

Additional manifestations include persistent fatigue, loss of smell (anosmia) and taste (ageusia), musculoskeletal pain, hair loss (telogen effluvium), skin rashes, and endocrine dysfunction including new-onset diabetes mellitus and thyroid disorders.[4]

Treatment and Management

There is currently no curative treatment for Long COVID. Management is multidisciplinary, symptom-directed, and based on current clinical evidence.[5]

Pharmacological Interventions

Anti-inflammatory agents, including low-dose corticosteroids and colchicine, are used in patients with evidence of persistent systemic inflammation. Anticoagulation therapy with low-molecular-weight heparin (LMWH) is under investigation for patients with microthrombus burden. Intravenous immunoglobulin (IVIG) may benefit selected patients with autoimmune manifestations.[5,6]

For symptom management, SSRIs, low-dose naltrexone, and fluvoxamine are being investigated for neurological and fatigue symptoms. Beta-blockers and ivabradine are commonly used to manage POTS.[1]

Non-Pharmacological Approaches

Pacing and energy management are central to managing post-exertional malaise. Graded exercise therapy is generally not recommended because it may worsen symptoms.[2] Cognitive rehabilitation may improve brain fog and cognitive impairment. Pulmonary rehabilitation is recommended for persistent respiratory symptoms.

Nutritional & Microbiome-Targeted Strategies

Probiotics and dietary interventions may help restore gut microbiome diversity and reduce inflammation.[5] Vitamin D, vitamin C, zinc, and omega-3 supplements are widely used, although evidence for their effectiveness remains limited.[7]

Vaccination as Prevention

COVID-19 vaccination reduces the risk and severity of Long COVID after breakthrough infection. Vaccinated individuals have a 50–70% lower risk of persistent symptoms than unvaccinated individuals.[1,2]

Multidisciplinary Care

Management often requires input from respiratory physicians, cardiologists, neurologists, psychiatrists, physiotherapists, and primary care physicians. Dedicated Long COVID clinics provide coordinated assessment and follow-up.[3]

Conclusion

Long COVID is a complex, multi-system condition that continues to pose significant clinical and public health challenges. Its pathophysiology involves viral persistence, immune dysregulation, endothelial dysfunction, oxidative stress, and gut microbiome disruption. Although no definitive cure exists, early recognition, multidisciplinary care, and continued research are essential to improve patient outcomes.[5]

References

1. He S, et al. Long COVID: The latest manifestations, mechanisms, and potential therapeutic interventions. **Mol Clin Oncol.** 2022.
2. Hakem Zadeh F, et al. Long COVID: Complications, underlying mechanisms, and treatment strategies. 2023.
3. Ewing AG, et al. Review of organ damage from COVID and Long COVID: A disease with a spectrum of pathology. 2024.
4. Andrade BS, Siqueira S, de Assis Soares WR, de Souza Rangel F, dos Santos NO, Santos Freitas A, et al. Long-COVID and post-COVID health complications: An up-to-date review on clinical conditions and their possible molecular mechanisms. **Viruses.** 2021;13(4):700.
5. Long COVID: Mechanisms of disease, multisystem sequelae, and prospects for treatment. 2025.
6. Michalak KP, et al. Acute COVID-19 and Long COVID syndrome: Molecular implications for therapeutic strategies. **Front Immunol.** 2025.
7. Molecular insights into Long COVID: Plasma proteomics reveals oxidative stress, coagulation

cascade activation, and glycolytic imbalance. **bioRxiv** [Preprint]. 2025.
8. MedlinePlus. COVID-19 illustration [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: MedlinePlus.