INTERNATIONAL MULTI DISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
eISSN 2394-6334 Impact factor: 8.854 Volume 13, issue 04 (2026)

POST-COVID-19 COMPLICATIONS: PATHOPHYSIOLOGY, CLINICAL SPECTRUM, AND LONG-TERM HEALTH IMPLICATIONS

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ABSTRACT: Background: The SARS-CoV-2 pandemic has generated an unprecedented global health burden, not only through acute illness but through a protracted syndrome of post-infection sequelae collectively termed 'Long COVID' or Post-Acute Sequelae of SARS-CoV-2 infection (PASC). Objective: This article reviews the pathophysiological mechanisms, clinical manifestations, and organ-specific complications of COVID-19, with emphasis on the long-term burden of PASC. Methods: A narrative review of peer-reviewed studies, clinical registries, and WHO situation reports published between 2020 and 2024 was conducted. Results: COVID-19 complications span multiple organ systems, including the respiratory, cardiovascular, neurological, renal, and immune systems. PASC affects an estimated 10–35% of COVID-19 survivors and represents a major unresolved public health challenge. Conclusion: Multidisciplinary post-COVID care pathways, sustained biomedical research, and long-term surveillance systems are urgently needed to address the growing burden of PASC globally.

1. INTRODUCTION

The emergence of SARS-CoV-2 in late 2019 and its subsequent pandemic spread precipitated a global health crisis of historic proportions. By mid-2024, over 775 million confirmed cases and more than 7 million deaths had been reported to the WHO. While acute COVID-19 severity ranges from asymptomatic infection to fatal respiratory failure, a substantial proportion of survivors experience persistent or newly emerging symptoms well beyond the initial recovery period, a phenomenon variously termed Long COVID, Post-COVID Syndrome, or Post-Acute Sequelae of SARS-CoV-2 infection (PASC).

PASC was formally recognized by the WHO in October 2021, defined as symptoms persisting or emerging beyond three months from the onset of SARS-CoV-2 infection, lasting at least two months, and not explained by an alternative diagnosis. Its heterogeneous symptom profile — encompassing fatigue, cognitive impairment, dyspnea, chest pain, and more than 200 other symptoms across organ systems — has challenged clinicians, researchers, and health systems worldwide.

The mechanisms underlying PASC remain incompletely understood, with emerging evidence implicating viral persistence, immune dysregulation, autoimmunity, endothelial dysfunction, microbiome disruption, and reactivation of latent herpesviruses such as Epstein-Barr virus. The condition disproportionately affects women, individuals aged 35–69 years, those with pre-existing comorbidities, and, paradoxically, those with initially mild acute illness, challenging the assumption that severe acute disease predicts worse long-term outcomes.

This review synthesizes current evidence on the pathophysiology, clinical spectrum, and management of COVID-19 complications, with the aim of informing clinicians and policymakers about the scope and complexity of post-COVID care needs.

2. METHODS

A comprehensive narrative review was conducted by searching PubMed, Embase, Cochrane Library, and medRxiv using the terms: 'COVID-19 complications,' 'Long COVID,' 'PASC,' 'post-acute sequelae SARS-CoV-2,' 'COVID-19 cardiovascular,' 'neurological COVID,' 'COVID-19 renal,' and 'COVID-19 immune dysregulation.' Publications from January 2020 to December 2024, including original research, systematic reviews, meta-analyses, case series, and WHO and NIH technical documents, were reviewed. Given the rapidly evolving nature of COVID-19 research, preprint servers were consulted where peer-reviewed data were unavailable. Studies of all design types were included given the novelty of the condition. Data were synthesized by organ system and by proposed pathophysiological mechanism.

3. RESULTS

3.1 Acute Complications

Respiratory: Acute COVID-19 most prominently affects the lower respiratory tract, causing pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure. A meta-analysis of 45 studies encompassing over 9,000 hospitalized patients found that ARDS developed in 17% of cases, with an associated in-hospital mortality of 52%. Pulmonary thromboembolism occurs in 8–30% of critically ill COVID-19 patients, driven by hypercoagulability and endothelial injury.

Cardiovascular: Myocardial injury, defined by elevated troponin levels, occurs in 7–28% of hospitalized patients and is independently associated with in-hospital mortality. COVID-19-associated myocarditis, while less common, has been documented in athletes and young adults and may manifest as cardiomegaly, reduced ejection fraction, and sudden cardiac death. Cytokine storm-mediated systemic inflammation promotes coronary plaque instability and acute myocardial infarction even in the absence of prior cardiovascular disease.

Neurological: Neurological manifestations occur in approximately 36% of hospitalized COVID-19 patients. These include ischemic and hemorrhagic stroke, encephalopathy, Guillain-Barre syndrome, transverse myelitis, and seizures. The mechanisms include direct viral neuroinvasion via the olfactory bulb and blood-brain barrier disruption, as well as para-infectious immune-mediated injury.

Renal: Acute kidney injury (AKI) complicates COVID-19 in 20–37% of hospitalized patients, driven by direct tubular cytopathic injury from SARS-CoV-2 via the ACE2 receptor, hemodynamic compromise, immune complex deposition, and nephrotoxic medications. AKI requiring renal replacement therapy carries a mortality exceeding 70%.

3.2 Post-Acute Sequelae (PASC / Long COVID)

Prevalence and demographic patterns: The WHO-led global burden of disease initiative estimated that approximately 145 million individuals had experienced PASC by 2022. Prevalence estimates vary widely (10–35%) due to inconsistent case definitions and surveillance methods. Women are 1.5–2 times more likely than men to develop PASC, consistent with their higher rates of autoimmune diseases. Notably, vaccination before infection substantially reduces PASC risk, with meta-analyses suggesting a 50–70% reduction in odds among vaccinated individuals.

Fatigue and post-exertional malaise (PEM): Fatigue is the most frequently reported PASC symptom, affecting 50–80% of PASC patients. Many experience PEM — a hallmark symptom

of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) — in which physical or cognitive exertion triggers disproportionate worsening of symptoms. Mitochondrial dysfunction, autonomic nervous system dysregulation, and impaired oxygen extraction at the tissue level have been proposed as mechanisms.

Cognitive impairment ('Brain Fog'): Approximately 20–30% of PASC patients report cognitive symptoms including memory deficits, impaired concentration, processing speed reduction, and word-finding difficulties. Neuroimaging studies have identified structural brain changes including reduced gray matter volume and white matter hyperintensities in PASC patients compared to controls. Cerebrospinal fluid analysis in a subset of patients revealed neuroinflammatory markers and viral spike protein fragments, suggesting ongoing neuroinflammation.

Cardiovascular sequelae: A landmark retrospective cohort study using VA healthcare data encompassing over 150,000 COVID-19 survivors found significantly elevated risks of heart failure (hazard ratio 1.72), atrial fibrillation (HR 1.84), stroke (HR 1.52), and deep vein thrombosis (HR 2.09) in the year following acute infection compared to contemporary controls. These risks persisted even in patients with initially mild acute illness.

Respiratory sequelae: Persistent dyspnea, reduced exercise tolerance, and pulmonary function abnormalities are documented in 10–25% of COVID-19 survivors at 6–12 months. High-resolution CT imaging demonstrates residual ground-glass opacities, fibrotic changes, and bronchiectasis in a proportion of cases. Pulmonary function tests reveal restrictive or mixed patterns, with reduced diffusion capacity (DLCO) being the most common abnormality.

4. DISCUSSION

The breadth and complexity of COVID-19 complications challenge traditional disease categorization and require integrated, multidisciplinary care models. The conventional division between 'acute' and 'chronic' illness is inadequate for PASC, which may reflect multiple distinct pathophysiological processes operating simultaneously or sequentially — including viral persistence in tissue reservoirs, persistent immune activation, autonomic dysfunction (particularly POTS — postural orthostatic tachycardia syndrome), and microbiome disruption.

From a healthcare system perspective, the magnitude of PASC creates an enormous demand for specialist services — pulmonology, cardiology, neurology, psychiatry, and rehabilitation medicine — that exceeds current capacity in most health systems, including those in Central Asia. Integrated post-COVID clinics, following models developed in the United Kingdom, Germany, and Italy, offer a coordinated approach that may improve efficiency and patient outcomes.

The global research agenda must prioritize: (1) standardized, internationally harmonized PASC case definitions; (2) pathophysiology-targeted clinical trials (e.g., antivirals targeting viral persistence, JAK inhibitors for immune dysregulation, low-dose naltrexone for neuroinflammation); (3) longitudinal cohort studies tracking PASC outcomes over years to decades; and (4) health system strengthening to ensure equitable access to post-COVID care in LMICs.

Children and adolescents present an additional concern through the phenomenon of Multisystem Inflammatory Syndrome in Children (MIS-C), a rare but severe post-infectious complication temporally associated with SARS-CoV-2 characterized by fever, multiorgan inflammation, and shock. Though distinct from adult PASC, MIS-C underscores that no age group is exempt from the long-term consequences of COVID-19 infection.

5. CONCLUSION

COVID-19 is not a transient acute illness for a substantial proportion of those infected. Its complications span every major organ system and persist for months to years in millions of individuals globally. PASC, in particular, represents a new chronic disease burden that threatens to reshape healthcare demand and workforce productivity for decades. Urgent investment in research, clinician education, health system adaptation, and equitable access to post-COVID care is imperative to address this evolving epidemic within an epidemic.

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