Review and Prospect of Post-COVID-19 Syndrome: New Challenges Faced by Public Health Nursing in the Future

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Abstract

Objective: This paper aims to review research progress on COVID-19 sequelae to enhance attention to their complexity and social impacts. Study design: A systematic review was conducted by integrating global epidemiological data, clinical studies, and mechanistic analyses to systematically summarize existing findings. Methods: Published literature was screened and analyzed, covering the epidemiological characteristics of sequelae (e.g., incidence, population distribution), clinical manifestations (multisystem impacts on respiratory, neurological, cardiovascular systems, etc.), potential mechanisms (viral persistence, immune dysregulation, organ damage), and prevention/treatment strategies (vaccination, rehabilitation therapy, etc.). Results: Approximately 5%-10% of infected individuals develop long-term sequelae, with higher risks observed in women, severe cases, and those with underlying conditions. Neurocognitive impairment, pulmonary fibrosis, and cardiovascular damage are major manifestations, with mechanisms closely linked to viral persistence, chronic inflammation, and immune disorders. Vaccination may reduce sequelae risk, though more evidence is needed to support its efficacy. Conclusion: COVID-19 sequelae represent a multisystem, multifactorial health challenge that requires enhanced mechanistic research, optimized diagnostic and treatment systems, and global responses through interdisciplinary collaboration and social support.

Keywords

Novel coronavirus, Aftereffects, Urban health development, Public health

Introduction

In December 2019, COVID-19 was first reported in Wuhan, China, with its pathogen identified as SARS-CoV-2, a β-coronavirus. The disease was declared a pandemic in March 2020 [1]. As an enveloped single-stranded positive RNA virus, SARS-CoV-2 features spike proteins that effectively bind to human cells, enhancing its infectivity and influencing disease severity and the development of sequelae [2]. COVID-19 sequelae are characterized by complex symptoms, prolonged duration, and significant social impacts. However, their onset mechanisms, causative factors, and specific symptoms remain incompletely understood, posing great challenges for diagnosis and treatment. Consensus on “long COVID” has not yet been reached [3]. This article summarizes current research to highlight the importance of paying attention to COVID-19 sequelae.

Epidemiological characteristics

Incidence rate and duration

Globally, approximately 5.0%-10.0% of COVID-19 infected individuals experience long-term sequelae. Stratified by infection severity, the incidence rates are 5.7%, 27.5%, and 43.1% for non-hospitalized, hospitalized, and ICU patients, respectively. Symptom duration varies significantly: Mild cases last an average of 4 months, severe cases can extend beyond 9 months, and some symptoms persist for 2 years [4].

Forty-five percent of survivors still have unresolved symptoms at the four month mark. A long-term follow-up study in Wuhan, China, showed that 55.0% of hospitalized patients still had at least one sequela (e.g., fatigue, muscle weakness, sleep disorders) two years after infection [5]. However, due to limitations in follow-up duration and measurement methods, there is currently no authoritative data source on the duration of sequelae.

Characteristics of population distribution

Gender differences: Women have a higher disease risk (OR value 1.65). Influenced by X chromosome genes and hormonal factors, both the innate and adaptive immune responses of females are stronger than those of males [6]. Which may cause their immune systems to generate more autoimmune symptoms when combating viruses, especially in terms of anxiety, depression, and pulmonary function impairment. Prospective studies have shown that the COVID-19 pandemic has had a significant impact on women's sexual quality of life, frequency, as well as stress and anxiety levels [7]. From a physiological perspective, women's smaller airways and lungs, along with the pro-inflammatory effects of estrogen, may make pulmonary function impairment and clinical consequences more severe after infection.

Age and pediatric risk: A study in *Nature Medicine* developed an age data model and found that individuals under 20 years old were approximately half as likely to contract COVID-19 as those aged 20 and above, with more confirmed cases observed in older adults [8]. However, a telephone follow-up survey in Israel of pediatric COVID-19 patients aged 3-18 showed that 11.2% of children experienced long-term symptoms such as breathing difficulties and fatigue, among whom 1.8% were under 12 years old, and approximately 4.6% of adolescents aged 12-18 had sequelae lasting more than six months [9]. A Norwegian study of over 700,000 pediatric COVID-19 patients revealed that preschool-aged children had a higher risk of sequelae and required longer recovery times [10]. Suggesting that age should be an important focus in epidemiological research on post-COVID sequelae. Underlying medical conditions and infection severity: Patients with comorbidities or severe infections are more prone to organ dysfunction such as pulmonary fibrosis and cognitive impairment. Underlying medical conditions not only increase mortality during illness but also lead to more severe sequelae, requiring heightened vigilance for such patients. Almost all studies have shown a close association between the severity of acute COVID-19 symptoms and post-infection sequel, the more severe the acute symptoms, the higher the likelihood of developing sequelae [11-13].

Clinical manifestations and effects on organ systems

Respiratory system

COVID-19 primarily invades the respiratory system, and its induced sequelae often manifests as pulmonary function abnormalities. A U.S. study showed that 62.2% of recovered patients exhibited persistent damage via pulmonary function tests and imaging examinations, specifically presenting as dyspnea, restrictive ventilation disorders, and pulmonary fibrosis [14]. A July 2024 study revealed that pulmonary fibrosis is closely associated with the aggregation of monocyte-derived pulmonary macrophages triggered by interferon-γ signaling pathway activation [15]. Among severe patients, 54% have pulmonary diffusion dysfunction, whose pathological mechanisms involve multiple factors such as immune abnormalities, persistent inflammation, and tissue structure remodeling. Current diagnosis of respiratory sequelae requires integrating multidisciplinary assessments including immunology, pathology, and imaging. The complexity of pathogenic mechanisms indicates that long-term follow-up studies should be strengthened in the future, with interdisciplinary collaboration to improve the diagnosis and treatment system and provide a basis for precise interventions.

Nervous system

Central nervous system: Approximately 31.0% and

27.0% of recovered patients experience persistent attention disorders and memory loss, respectively, with brain fog (scattered attention, cognitive slowness) being the most common neurological symptom. In a Northwestern University study, it was listed as the primary complaint among long-term (>6 weeks) post-COVID sequelae [16]. Patients exhibit a 35.0% elevated risk of anxiety and a 39.0% elevated risk of depression relative to the general population [17]. Possibly related to disease stress, social isolation, and the uncertainty of the disease course, though the changes in suicide rates during the pandemic remain inconclusive. Severe patients may develop complications such as stroke or intracerebral hemorrhage, with mechanisms linked to virus-induced vascular endothelial damage and thrombosis [18]. Other studies suggest that some patients exhibit hippocampal atrophy and cognitive decline similar to Alzheimer's disease, with MRI showing significantly reduced hippocampal volume [19].

Peripheral nerves: Involvement of the peripheral nervous system often manifests as autonomic nervous system dysfunction, with postural orthostatic tachycardia syndrome (POTS) being a prominent feature. Infected individuals have a 2.12-fold higher risk of developing POTS than non-infected individuals [20]. Olfactory/gustatory dysfunction often persists for months or longer, with mechanisms potentially related to direct viral damage to olfactory neurons or inflammation-mediated apoptosis [21,22]. Additionally, there is a potential association between COVID-19 infection and Guillain-Barré syndrome (GBS), a disease characterized by symmetrical limb weakness and sensory abnormalities. A systematic analysis pooling 436 COVID-19-related GBS cases showed that males accounted for 67.2% of cases, with an average age of 61.38 years, though the causal relationship between the two remains unconfirmed [23,24].

Cardiovascular system

The damage of long COVID to the cardiovascular system has become increasingly prominent, primarily manifesting as palpitations, myocarditis, and arrhythmias. Studies show that 17.0% of COVID-19 hospitalized patients and 44.0% of ICU patients experience arrhythmias [25]. Data from the Mayo Clinic indicates that approximately 20.0% of hospitalized patients have cardiac injury, independent of pre-existing health conditions [26]. The mechanism of myocarditis is mostly related to the virus directly invading cardiomyocytes via the ACE2 receptor, triggering inflammation and functional impairment [27]. Current clinical diagnosis relies on medical history, electrocardiogram, cardiac MRI, and other assessments of myocardial injury and microvascular status [28]. But due to the uneven quality of existing research data, more high-quality clinical studies are needed for support. Additionally, some COVID-19 treatment drugs may induce cardiac complications.

Systemic symptoms

Long COVID often presents with systemic symptoms, such as fatigue (20%-52%), sleep disorders (25%-31%), arthralgia, gastrointestinal dysfunction, and alopecia. While some symptoms may be resolved, dyspnea and psychological issues may persist and worsen [29-32]. As a core symptom, the mechanisms of fatigue remain unclear but are hypothesized to be associated with neurofunctional abnormalities, chronic inflammation triggered by excessive immune activation, and micro thrombosis [33,34]. Currently, there is a lack of targeted therapies, with clinical management primarily relying on multidisciplinary symptom management that requires individualized intervention strategies based on patient-specific differences.

Progress in mechanism research

Virus residues and chronic inflammation

In the structural proteins of SARS-CoV-2, the spike protein (S protein) mediates infection by binding to the host ACE2 receptor and persists long-term in the cranial nervous system after viral clearance, triggering persistent inflammation. Its mechanisms include: (1) activation of Toll-like receptors TLR2/TLR4; (2) formation of pro-inflammatory

thrombi by binding to fibrin; (3) induction of neutrophil degranulation, exacerbating tissue damage. Meanwhile, the spike protein induces neuronal stress through activating the mitogen-activated protein kinase (MAPK)-c-Jun N-terminal kinase (JNK) signaling pathway, and markedly elevated Tau protein levels in acute-phase patients suggest its potential association with neurodegeneration [35,36].

Residual viruses can also activate macrophages and NK cells, intensifying chronic inflammation. Proteomics research has unveiled potential mechanisms of long COVID: Analysis of plasma samples two years post-infection found that some proteins related to immune response, complement coagulation, and cholesterol metabolism gradually recovered within two years, while pathways such as Fc receptor signaling and neuronal differentiation showed delayed recovery. The study identified 11 protein markers associated with pulmonary function repair and 2 related to olfactory dysfunction, providing targets for intervention [37]. However, most existing studies focus on the acute disease phase, with short follow-up periods, limited sample sizes, and a lack of dynamic protein data from the acute phase, restricting a comprehensive understanding of long COVID mechanisms.

Abnormal immune system

Long COVID patients exhibit significant immune dysregulation, including cytokine storms, autoimmune abnormalities, and coagulation dysfunction, leading to multi-organ damage. Studies show that specific and adaptive immune responses persist for 6-12 months in over 95% recovered patients, with prolonged immune activation potentially triggering endothelial damage and micro thrombosis, exacerbating cardiovascular and neurological symptoms [38,39]. Additionally, the durability of immune memory from COVID-19 vaccines and infections remains a key research focus [40]. Future therapies need to balance virus neutralization with reversing adaptive immune suppression to improve long-term outcomes [41].

Direct organ injury

SARS-CoV-2 invades organs such as the lungs, heart, and kidneys through the ACE2 receptor, directly damaging cells and inducing fibrosis. Impaired tissue repair after acute infection can lead to long COVID, manifested as pulmonary fibrosis and myocardial injury, causing long-term respiratory and cardiovascular symptoms [42-44]. Studies have also found that the virus may damage muscle mitochondrial function, leading to abnormal energy metabolism and triggering fatigue and muscle weakness [45]. Currently, there is no specific therapy for organ damage, but a 2023 study showed that nintedanib and pirfenidone can improve patients' pulmonary function and imaging scores [46].

Psychological and social factors

Long-term isolation, social stigma, and unemployment stress may exacerbate mental symptoms such as anxiety and depression. From a psychological mechanism perspective, physical discomfort from infection, long-term isolation, social stigma, unemployment stress [47-49], as well as loss of smell and taste [50]. All exacerbate anxiety, depression, and other mental symptoms. Additionally, fear of vaccines and their effects have also had a negative impact on mental health, directly influencing the mortality rate of unvaccinated COVID-19 patients [51]. In terms of social factors, social skill degradation, lack of social interest, psychological distress caused by illnesses (such as erectile difficulties), and economic pressure are all risk factors for personal and family well-being. Conversely, good family companionship and friend support can enhance psychological resilience [52,53].

Studies have found a potential association between inflammatory biomarkers and COVID-19-related depressive symptoms [54]. But no specific pharmacotherapeutic protocols for patients with long COVID have been identified. Of course, at the psychological and social levels, patients can also seek traditional psychological interventions, such as counseling from psychotherapists, for self-healing. This highlights the importance of launching multidisciplinary comprehensive intervention

clinical trials once again.

Prevention and control strategies

Vaccination

Studies on the preventive effect and mechanisms of vaccination against long COVID show that the Pfizer/BioNTech vaccine (BNT162b2) can reduce the risk of residual brain spike protein and related neural damage. Mouse experiments indicate that in mice vaccinated before infection with the Omicron variant, spike protein levels in the brain and meninges were 50.0% lower than in unvaccinated groups. The mechanism is associated with vaccine-induced neutralizing antibodies and T-cell immunity, which accelerate viral clearance, reduce viral replication, and limit spike protein release. Spike protein triggers neuronal stress and neuroinflammation (e.g., microglial activation, Tau protein deposition) by activating the MAPK-JNK pathway, while vaccines indirectly inhibit inflammatory responses by reducing spike protein accumulation [55]. In humans, vaccines reduce long COVID risk through multiple mechanisms: (1) Neutralizing antibodies block spike protein binding to ACE2 receptors, reducing initial viral load, alleviating excessive immune activation, and decreasing the release of inflammatory cytokines (e.g., IL-6, TNF-α) to avoid "cytokine storms". (2) Inducing memory T/B cell formation, where memory T cells directly kill infected cells and assist B cells in differentiating into plasma cells to rapidly produce high-efficiency antibodies for viral clearance. (3) Regulating immune cell metabolism (e.g., enhancing glycolysis and fatty acid oxidation) to improve antiviral and tissue repair capabilities. Additionally, the detection of residual spike protein in cranial bone marrow after infection suggests vaccines may reduce its persistence by shortening viral exposure time, thereby lowering the risk of neurological sequelae [56,57].

However, due to individual differences in age, underlying conditions, etc., fluctuating symptoms across different assessment time points, diverse symptoms involving multiple systems with a lack of single metrics and limitations in study design (e.g., sample size, follow-up duration), data on the impact of post-infection vaccination on long COVID symptoms are difficult to interpret. Moreover, much of the data supporting vaccines for reducing long COVID symptoms has low credibility, clearly indicating ongoing controversies [58]. Some studies even directly highlight a range of side effects of vaccination. Thus, preventive strategies via vaccines currently lack definitive, high-confidence research with clear directions.

Rehabilitation treatment

The "Rehabilitation Treatment Plan for Discharged COVID-19 Patients" in China advocates multidisciplinary collaborative intervention, covering respiratory, cardiac, psychological, and motor function rehabilitation, to address the diverse and individualized rehabilitation needs of long COVID patients [59]. Current rehabilitation for long periods of COVID primarily focuses on respiratory and psychological interventions, often using physical therapy. In clinical exploration, hyperbaric oxygen therapy has achieved breakthroughs in improving cerebral perfusion, cognitive function, and cardiopulmonary capabilities. The first case showed it can repair cerebral white matter microstructure and enhance cardiopulmonary capacity [60]. Patients with olfactory dysfunction can promote recovery by sniffing strong odorants to activate neural pathways [61]. A survey in Austria indicated the need to strengthen interdisciplinary rehabilitation training for physical therapists and optimize multi-domain collaborative models to improve comprehensive management of long COVID [62].

Construction of the medical system

The development of healthcare systems for long COVID has emerged as a new global public health challenge. The UK's National Health Service (NHS) previously established 90 specialized long COVID clinics to provide multidisciplinary assessments, but a March 17th, 2025, BBC News investigation via freedom-of-information requests revealed a significant reduction in their numbers. The news noted that this decline reflects broader systemic

challenges faced by long COVID patients during diagnosis and treatment [63,64]. The United States has launched a "Long COVID Response Plan" that prioritizes research, care, and public education while emphasizing the importance of multidisciplinary collaboration [65].

Long COVID poses challenges due to its complex, inconsistently defined symptoms, leading to inaccurate diagnostics, and is intertwined with numerous social issues [66]. Studies show that healthcare utilization and costs increase within six months of long COVID diagnosis, imposing a long-term burden on the U.S. healthcare system [67]. Building effective healthcare systems requires focusing on long-term patient management and rehabilitation to achieve dual psychological and physical healing, along with policy support, resource investment, innovation in diagnostic technologies and treatments, and enhanced training for healthcare professionals to address long COVID's complex symptomatology.

Challenges and prospects

Research limitations

Most existing long COVID studies are primarily based on the original virus strain, and the characteristics of post-COVID-19 sequelae for new variants such as Omicron still require in-depth observation. Although some progress has been made, the high mutability of SARS-CoV-2 has led to the continuous emergence of new variants, resulting in research content that cannot be updated in a timely manner. For example, the research on the characteristics of sequelae after infection with variants such as Omicron is still insufficient. However, the proportion of patients infected with the Omicron variant who develop long-term symptoms is relatively low, only 24% to 50% of those infected with the Delta variant [68]. The small research base and the imperfect follow-up plan have caused great difficulties for further research. Moreover, as mentioned earlier, the mechanism of long COVID is complex, and the specific pathogenesis remains unclear, which also limits the development and research of targeted treatment methods [69].

Bottlenecks in diagnosis and treatment

Long COVID sequelae present profound challenges in diagnosis and targeted treatment due to their diverse symptoms (involving over 200 types) and the lack of specific biomarkers [70]. Existing research shows that patients with long-term pulmonary sequelae exhibit upregulated neutrophil-associated immune signatures, yet this cannot explain why some patients fully recover while others experience persistent illness, nor does it provide objective indicators to distinguish sequelae risk [71]. In clinical practice, two core issues have emerged: First, the high uncertainty in symptom attribution due to the absence of specific markers; second, the fragmented post-COVID care system, which lacks coordination with other medical services and exacerbates the diagnostic and treatment burden on patients [72]. The root of these challenges lies in the lagging mechanistic research and the lack of a unified pathological hypothesis, which constrains the optimization of diagnostic criteria and the development of precise intervention protocols.

Social support needs

Long COVID patients face multifaceted social support needs: Limited work and daily life capabilities due to physical function decline, coupled with psychological issues like anxiety and depression caused by prolonged illness, and urgently required mental health services intervention. The disease is not only a medical challenge but also demands coordinated responses from social systems. Studies recommend that employers should offer flexible work arrangements and role adjustments for patients, while governments should improve employment security policies [73]. At the family support level, a combination of online and offline approaches (such as health lectures and mutual aid groups) can enhance caregiving capabilities. Meanwhile, telemedicine can be used to achieve dynamic condition monitoring, rehabilitation guidance, and psychological interventions, forming a multi-

dimensional support network [74]. Such measures aim to alleviate patients' social burdens and promote their physical and mental recovery processes.

Conclusion

Post-covid-19 sequelae are multi-system and multi-dimensional health issues. Their mechanisms are complex and prevention and treatment require a combination of individualized and comprehensive approaches. Human beings have relied on wisdom to overcome many difficulties in the occurrence and development of COVID-19. In future research, efforts should be focused on the analysis of pathological mechanisms, the exploration of biomarkers, and the optimization of long-term rehabilitation plans to address this global health challenge about population gathering and urban development. It is believed that the day when the long COVID problem is solved is not far away.

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Conflicts of Interest

The authors declare no conflict of interest.

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