Volume 5, Issue 1

Eurasian Journal of Chemical, Medicinal and Petroleum Research

Journal homepage: https://www.ejcmpr.com/

DOI: https://doi.org/10.5281/zenodo.17482318

The Pathophysiology of Long COVID: Mechanisms and Management Strategies

Davoud Azizpour Maghvan
Department of Medicine, Islamic Azad University of Tabriz, Tabriz, Iran

Article info
Received: 05.10.20225
Accepted: 30.10.20225
Available Online: 30.10.20225
Checked for Plagiarism: Yes

Keywords:
COVID, Anticoagulants, Healthcare Systems, SARS-CoV-2 Infection (PASC), Pharmacological Interventions

ABSTRACT

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), has emerged as a significant public health challenge, affecting millions of individuals globally. It is characterized by persistent or new symptoms lasting weeks to months beyond the acute phase of COVID-19, including fatigue, dyspnea, cognitive impairment, autonomic dysfunction, and musculoskeletal pain. The underlying pathophysiology is multifactorial and remains under investigation. Current evidence suggests that persistent viral reservoirs in tissues, chronic immune activation, autoimmunity, endothelial dysfunction, microvascular injury, and mitochondrial impairment play major roles. Neurological and autonomic disturbances, along with psychosocial and epigenetic influences, further contribute to the complexity of the syndrome. Management strategies are primarily supportive and multidisciplinary, focusing on symptom relief, rehabilitation, and psychosocial care. Approaches include pulmonary and cardiovascular rehabilitation, pacing and energy conservation for fatigue, pharmacological interventions for dysautonomia, and cognitive therapy for neurocognitive symptoms. Emerging treatments such as immunomodulators, antiviral agents, anticoagulants, and mitochondrial support therapies are under investigation. Despite progress, challenges remain in defining diagnostic criteria, identifying biomarkers, and tailoring personalized interventions. Long COVID represents not only a biomedical issue but also a socioeconomic burden, requiring coordinated healthcare strategies and global research efforts. Understanding its mechanisms and developing effective management approaches are essential to mitigate its long-term impact on individuals and healthcare systems.

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has reshaped modern medicine, public health, and global socioeconomic dynamics. While the acute manifestations of COVID-19 ranging from asymptomatic infection to severe respiratory failure have been extensively studied, attention has increasingly shifted toward the persistent and often debilitating symptoms that linger long after the resolution of acute infection [1].

This condition, widely referred to as Long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), represents one of the most pressing post-pandemic challenges.

Long COVID is not a single disease entity but rather a heterogeneous syndrome encompassing multiple organ systems. Patients report a broad range of symptoms including chronic fatigue, post-exertional malaise, dyspnea, chest pain, palpitations, cognitive impairment (often described as “brain fog”), sleep disturbances, anosmia, dysautonomia, and musculoskeletal pain [2]. Psychiatric symptoms such as anxiety, depression, and post-traumatic stress disorder (PTSD) are also common, further complicating the clinical picture [3].

Corresponding Author: **Davoud Azizpour Maghvan (davidromani777@gmail.com- ORCID: 0000-0001-5317-4272)*
1 Email: asghar_elmi@yahoo.com- ORCID: 0000-0002-8936-3857)

These manifestations may persist for weeks, months, or even years following the initial infection, significantly impairing quality of life and productivity. Epidemiological estimates vary, but studies suggest that between 10–30% of individuals infected with SARS-CoV-2 develop some form of prolonged symptoms. Considering the scale of the pandemic, this translates into tens of millions of individual's worldwide living with the consequences of Long COVID.

From a pathophysiological perspective, Long COVID presents a unique puzzle [4]. Traditional models of post-viral syndromes, such as those following Epstein-Barr virus or influenza infection, offer partial analogies, yet the scope and severity of Long COVID exceed previous observations. Multiple overlapping mechanisms have been proposed. Persistent viral reservoirs may continue to drive immune activation and inflammation even in the absence of detectable viremia. Dysregulated immune responses including altered T-cell function, persistent cytokine elevations, and the presence of autoantibodies suggest a sustained state of immune imbalance [5]. Furthermore, SARS-CoV-2 is recognized for its vascular tropism, and evidence of endothelial damage, microvascular thrombosis, and impaired nitric oxide signaling highlight the importance of vascular dysfunction in symptom persistence. Neurological and autonomic pathways appear particularly vulnerable, with many patients experiencing postural orthostatic tachycardia syndrome (POTS), neuropathic pain, and cognitive deficits likely stemming from neuroinflammation and microvascular compromise [6].

Mitochondrial dysfunction has also emerged as a central hypothesis in the pathogenesis of Long COVID. Persistent inflammation and oxidative stress impair mitochondrial energy production, leading to reduced ATP availability and abnormal metabolic responses to exertion. This mechanism aligns with the hallmark symptom of post-exertional malaise, drawing parallels to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Additionally, psychosocial factors such as chronic stress, trauma, and social determinants of health may exacerbate symptoms and prolong recovery, while epigenetic modifications induced by SARS-CoV-2 could sustain immune and metabolic dysregulation.

The multisystem nature of Long COVID requires a broad lens for both research and clinical management. Unlike acute COVID-19, which was primarily approached through respiratory and critical care frameworks, Long COVID spans pulmonology, cardiology, neurology, psychiatry, immunology, and rehabilitation medicine. The challenge lies in both understanding the underlying biology and translating this knowledge into effective treatment strategies. Current management is largely symptomatic and multidisciplinary, focusing on rehabilitation, supportive care, and psychosocial interventions. Symptom-directed therapies such as pacing for fatigue, pulmonary rehabilitation for dyspnea, beta-blockers or ivabradine for dysautonomia, and cognitive rehabilitation for brain fog form the cornerstone of care. Pharmacological approaches remain experimental, with ongoing trials investigating immunomodulatory, antivirals, anticoagulants, and metabolic support therapies [7].

Despite these emerging strategies, significant gaps remain in our understanding. The absence of universally accepted diagnostic criteria complicates both clinical care and research efforts. Biomarker discovery is urgently needed to identify subgroups of patients with distinct pathophysiological mechanisms, allowing for more personalized interventions. Moreover, the trajectory of Long COVID is highly variable: while some individuals experience gradual improvement, others report worsening or relapsing symptoms, and a subset may face lifelong disability. This variability underscores the importance of longitudinal studies and patient registries to map outcomes over time.

The implications of Long COVID extend far beyond individual health. At a societal level, the syndrome imposes a heavy burden on healthcare systems, economies, and labor markets [8].

Millions of individuals are unable to return to work at full capacity, contributing to workforce shortages and economic disruption. Healthcare systems must adapt to meet the needs of patients requiring long-term, multidisciplinary care. Social safety nets and workplace accommodations will play critical roles in mitigating the broader impact. Furthermore, Long COVID amplifies existing health inequities, disproportionately affecting marginalized populations who face barriers to healthcare access, financial instability, and increased exposure to the virus due to occupational and environmental factors.

The scientific community is mobilizing to address these challenges, but the task is formidable. Understanding the pathophysiology of Long COVID requires integration across multiple disciplines virology, immunology, vascular biology, neurology, psychiatry, and systems biology. The search for effective treatments will necessitate innovative clinical trial designs that account for the heterogeneity of symptoms and mechanisms. Patient advocacy groups have also played a crucial role in shaping the research agenda, emphasizing the importance of lived experiences and highlighting symptoms that may otherwise be overlooked [9].

In this context, the purpose of this paper is twofold: first, to provide a comprehensive analysis of the pathophysiological mechanisms thought to underlie Long COVID, and second, to evaluate current and

emerging management strategies. By synthesizing the latest evidence, this work aims to contribute to the development of a coherent framework for understanding and addressing Long COVID. While much remains uncertain, the rapid progress in research offers hope that targeted, effective interventions will emerge. Ultimately, addressing Long COVID is not only a medical necessity but also a societal imperative. As the acute phase of the pandemic subsides, the long-term sequelae will define the next chapter in our global response to COVID-19.

In summary, Long COVID embodies the complexities of a post-viral syndrome at unprecedented scale. It challenges existing paradigms of infectious disease, immunity, and chronic illness, while simultaneously demanding novel approaches to clinical care and health policy. A deeper understanding of its mechanisms and management strategies will be essential for reducing its long-term impact on individuals, healthcare systems, and societies worldwide [10].

Pathophysiological Mechanisms

Persistent Viral Reservoirs

Evidence suggests that SARS-CoV-2 RNA and proteins may persist in tissues such as the gut, CNS, and lymphoid organs. Residual viral antigens can maintain a state of chronic immune activation, promoting inflammation and tissue injury.

Immune Dysregulation

Many patients with Long COVID display altered immune profiles, including elevated pro-inflammatory cytokines (IL-6, TNF-α), aberrant T-cell activation, and impaired interferon responses. These mechanisms overlap with autoimmune processes, and autoantibodies against G-protein coupled receptors and endothelial antigens have been identified in some patients [11].

Endothelial Dysfunction and Microvascular Injury: SARS-CoV-2 has strong tropism for endothelial cells via ACE2 receptors, leading to endotheliitis and microvascular thrombosis. Long COVID patients often present with endothelial dysfunction, reduced nitric oxide bioavailability, and micro clot formation, which may underlie persistent fatigue, exercise intolerance, and neurological sequelae.

Dysautonomia and Neurological Involvement: A significant proportion of patients develop postural orthostatic tachycardia syndrome (POTS), neuropathic pain, or cognitive impairment. These may result from autonomic nervous system imbalance, neuroinflammation, or microvascular compromise of the central nervous system [12].

Mitochondrial Dysfunction and Metabolic Derangements: Persistent systemic inflammation impairs mitochondrial function, leading to reduced ATP production and altered oxidative metabolism. This mechanism explains the hallmark symptom of post-exertional malaise in Long COVID, paralleling findings in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Psychosocial and Epigenetic Factors: Chronic stress, trauma, and socioeconomic vulnerability contribute to symptom persistence and exacerbation. Moreover, epigenetic modifications induced by viral infection may alter immune and metabolic pathways, sustaining chronicity.

Clinical Manifestations

Long COVID manifests heterogeneously across organ systems:

- ✓ **Respiratory:** dyspnea, reduced lung diffusion capacity, pulmonary fibrosis in some cases.
- ✓ **Neurological:** cognitive dysfunction, sleep disturbances, anosmia, Dysautonomia.
- ✓ **Cardiovascular:** palpitations, myocarditis sequelae, arrhythmias, micro thrombotic events.
- ✓ **Musculoskeletal:** myalgia, arthralgia, chronic fatigue.
- ✓ **Psychiatric:** anxiety, depression, post-traumatic stress.

Management Strategies

Symptom-Based Clinical Management

- ✓ **Fatigue & Exercise Intolerance:** pacing and energy conservation techniques, graded rehabilitation programs with caution to avoid post-exertional symptom exacerbation.
- ✓ **Respiratory Symptoms:** pulmonary rehabilitation, breathing exercises, inhaled corticosteroids when indicated [13].
- ✓ **Cardiovascular & Autonomic Dysfunction:** beta-blockers, ivabradine, volume expansion, and salt supplementation for POTS-like symptoms.
- ✓ **Neurocognitive Symptoms:** cognitive rehabilitation, occupational therapy, and pharmacologic interventions under study (e.g., stimulants, low-dose naltrexone).

Pharmacological Interventions

Anti-inflammatory & Immunomodulatory Therapies: ongoing trials explore corticosteroids, colchicine, and biologics targeting IL-6 or TNF-α.

Anticoagulant & Antiplatelet Strategies: low-dose anticoagulation may benefit patients with evidence of micro clot pathology.

Antiviral Therapy: Pavlova and other antivirals are being tested for their potential in clearing persistent viral reservoirs.

Multidisciplinary and Holistic Approaches

Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), represents one of the most significant and enduring challenges of the pandemic era. While the acute phase of COVID-19 drew immediate attention due to its high morbidity and mortality, the long-term burden of persistent symptoms is only now being fully appreciated. The condition is marked by heterogeneity in presentation, duration, and severity, making it a complex clinical and scientific problem. A comprehensive conclusion must therefore reflect both the biological complexity and the broader societal implications of Long COVID [14].

From a mechanistic perspective, the evidence indicates that Long COVID is driven by a confluence of overlapping factors rather than a single causal pathway. Persistent viral reservoirs in tissue, immune dysregulation with sustained cytokine release, endothelial and microvascular dysfunction, mitochondrial impairment, and autonomic nervous system imbalance appear to contribute to the clinical phenotype. These biological insights not only explain the multisystem involvement but also highlight why patients experience such varied symptoms ranging from fatigue and "brain fog" to cardiovascular instability and psychiatric disturbances. Importantly, Long COVID shares similarities with other post-viral syndromes, such as ME/CFS, while also demonstrating unique features related to SARS-CoV-2's endothelial and vascular tropism.

In terms of management, no universal therapy has yet emerged, and current strategies rely primarily on a multidisciplinary and holistic framework. Symptom-based care remains the cornerstone of treatment, with approaches including pacing and energy conservation for fatigue, pulmonary rehabilitation for respiratory complaints, pharmacological treatment for dysautonomia, and cognitive rehabilitation for neurocognitive impairments. Integrative care models involving pulmonologists, cardiologists, neurologists, psychiatrists, immunologists, and rehabilitation specialists are increasingly recognized as essential. Emerging pharmacologic interventions such as immunomodulatory, antivirals aimed at clearing viral reservoirs, and anticoagulants to address microvascular pathology offer hope but remain under investigation. Nutritional and mitochondrial support therapies also show potential, though evidence is still preliminary [15].

One of the most striking lessons of Long COVID is the necessity of bridging biomedical treatment with psychosocial support. Patients frequently encounter disbelief, stigma, and a lack of recognition within healthcare systems, which exacerbates suffering. Mental health care, workplace accommodations, and patient-centered rehabilitation programs must therefore form integral parts of management. Equally critical is the recognition of health inequities: Long COVID disproportionately impacts vulnerable and marginalized populations, amplifying preexisting social and economic disparities. Addressing this inequity requires systemic changes in healthcare delivery, access, and policy.

The socioeconomic implications of Long COVID are profound. With millions worldwide experiencing prolonged illness, workforce participation has declined, productivity has been disrupted, and healthcare systems face unprecedented demand for long-term care. This reality underscores the need for policymakers to treat Long COVID not just as a medical condition but as a public health and economic issue. Investments in rehabilitation infrastructure, disability support systems, and long-term monitoring programs are crucial. Failure to address these dimensions' risks entrenching the pandemic's legacy into a chronic societal burden [16].

Looking forward, several research priorities must guide the global response. First, consensus on diagnostic criteria is urgently needed to improve clinical recognition and standardize research efforts. Second, biomarker discovery should be prioritized to stratify patients into subgroups, enabling personalized interventions. Third, longitudinal cohort studies are essential to clarify the natural history of Long COVID, identifying predictors of recovery versus chronicity. Fourth, innovative clinical trial designs must account for the heterogeneity of symptoms and mechanisms, ensuring that promising treatments are tested across different patient subtypes. Finally, collaboration between clinicians, researchers, policymakers, and patient advocacy groups will be key to sustaining momentum and ensuring that research aligns with patient needs.

Despite the uncertainties, progress has been made. The rapid mobilization of the scientific community has led to growing insights into the immunological, vascular, and neurological underpinnings of Long COVID. The recognition of its overlap with other post-viral syndromes opens avenues for shared research and therapeutic strategies. Moreover, patient advocacy movements have played a transformative role in driving awareness and shaping research agendas, ensuring that lived experiences inform scientific inquiry [1].

Ultimately, Long COVID serves as a reminder of the long shadow pandemics can cast. It challenges conventional boundaries between infectious disease and chronic illness, highlighting the need for adaptive healthcare systems capable of responding to emerging syndromes. Addressing Long COVID

requires more than symptom management it demands a rethinking of how societies support individuals with chronic, poorly understood conditions. By integrating biomedical, psychosocial, and policy approaches, it is possible to mitigate its burden and foster resilience in the face of ongoing uncertainty.

In conclusion, Long COVID is not merely a medical curiosity but a multidimensional phenomenon with far-reaching implications. Its pathophysiology underscores the interconnectedness of viral persistence, immune dysregulation, vascular injury, and metabolic dysfunction, while its clinical impact reflects the vulnerabilities of both individuals and societies. Multidisciplinary and holistic approaches are essential to managing its complexity, but lasting solutions will depend on sustained research, equitable healthcare delivery, and global cooperation. As the world transitions out of the acute crisis of COVID-19, Long COVID will remain a defining challenge of the post-pandemic era one that requires vision, compassion, and scientific innovation to overcome [17].

Emerging and Experimental Approaches

- ✓ **Plasmapheresis & Apheresis:** aimed at removing autoantibodies and micro clots.
- ✓ **Mitochondrial Support Therapies:** supplementation with CoQ10, NAD+, and antioxidants under investigation.
- ✓ **Immunotherapy:** targeted biologics for autoimmunity-driven subgroups.

Challenges and Future Directions

Research on Long COVID remains in early stages, with heterogeneity in definitions, diagnostic criteria, and outcome measures. Biomarker discovery, patient stratification, and personalized medicine approaches are crucial. Large-scale longitudinal studies are needed to distinguish transient post-viral syndromes from chronic, progressive disease. Moreover, the socioeconomic and public health impacts of Long COVID necessitate investment in rehabilitation infrastructure and workplace accommodations [18].

Discussion

Post-acute sequelae of SARS-CoV-2 infection (PASC), commonly known as Long COVID, represents a complex, multisystem syndrome characterized by diverse biological mechanisms. This complexity makes it difficult to identify a single causal pathway or a universal therapeutic approach. In this discussion, the main pathophysiological mechanisms are summarized, followed by a comparative review of selected studies, supported with tables highlighting similarities, differences, and research gaps.

Summary of Key Mechanisms: Systematic reviews and mechanistic studies point to several overlapping contributors: (1) persistent viral reservoirs or antigens driving chronic inflammation, (2) immune dysregulation and production of autoantibodies, (3) endothelial damage and microvascular pathology, particularly fibrinaloid micro clots, (4) mitochondrial dysfunction leading to impaired energy metabolism, and (5) neurological involvement and dysautonomia. Evidence suggests that these mechanisms often coexist, producing distinct clinical subgroups rather than a single phenotype.

Microclots and Coagulation Pathophysiology: Work from Pretorius, Kell, and others has highlighted the potential role of amyloid-like fibrinaloid microclots and fibrinogen abnormalities in driving fatigue, impaired microcirculation, and reduced tissue oxygen delivery. This line of inquiry has generated considerable interest, offering a novel explanatory model. However, critics emphasize the need for standardized assays and independent replication before establishing causality [19].

Autoantibodies and Immune Dysregulation: Multiple studies and systematic reviews report functional autoantibodies particularly against G-protein coupled receptors (GPCRs) and renin-angiotensin system components in subsets of Long COVID patients. While causality is not firmly established, these findings raise the possibility that certain patients may benefit from immune-modulatory approaches or pathogenetic removal strategies (e.g., apheresis). Reproducibility across different research centers, however, remains incomplete.

Pharmacological Interventions Prevention vs. Treatment: Observational evidence suggests that early administration of viral replication inhibitors such as nirmatrelvir/ritonavir may reduce the risk of developing Long COVID, with large cohort studies supporting this claim. In contrast, trials of the same drugs as treatment for chronic Long COVID have produced mixed results. For example, a Stanford RCT testing a 15-day Pavlova regimen in chronic patients showed no significant benefit compared to placebo. This discrepancy suggests that antivirals may be more effective in prevention during the acute phase than as curative therapy for established chronic disease. Timing, treatment duration, and patient stratification may be key determinants of efficacy [20].

Overlap with ME/CFS and Implications for Rehabilitation: Many Long COVID features such as persistent fatigue, post-exertional malaise, and cognitive impairment mirror those of other post-infectious syndromes, particularly myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This overlap creates both opportunities

and challenges. On one hand, ME/CFS research offers valuable rehabilitation insights that may be adapted for Long COVID care. On the other, the ME/CFS experience highlights the risks of poorly tailored interventions; rehabilitation strategies must be individualized and carefully monitored to avoid exacerbating symptoms.

Table 1. Mechanistic and Review Studies

Study Type	Key Findings	Strengths/Limitations
Comprehensive review	Multimechanistic nature; call for clinical subtyping	Broad synthesis but largely observational evidence
Lab/Review	Role of fibrinaloid micro clots in pathogenesis	Hypothesis-generating; needs replication and assay standardization
Immunological review	Integrated immune pathway model	Useful conceptual framework; limited causal validation

Table 2. Therapeutic and Preventive Evidence

Study	Year	Intervention	Population/Design	Long COVID Outcomes
Xie et al., JAMA Int Med	2023	Nirmatrelvir (acute phase)	Large cohort, high-risk patients	Significant reduction in PASC incidence
Wang et al.	2024	Pavlova (real-world)	Large population dataset	HR ~0.74 reduction; outcomes influenced by clinical variables
Stanford RCT	2024	Pavlova 15 days (chronic LC)	RCT (n≈155)	No significant benefit vs. placebo; short-course ineffective in chronic cases

Implications for Research and Clinical Care: Several priorities emerge from this comparative analysis:

1. Standardized definitions and biomarker discovery are urgently needed to stratify patient subgroups.
2. Clinical trials must incorporate timing, duration, and stratification to optimize intervention efficacy.
3. Independent replication of micro clot and autoantibody findings across multi-center cohorts is necessary to validate mechanistic claims.
4. Multidisciplinary, evidence-informed care models should be implemented, addressing both physical symptoms and psychosocial burden.

Current evidence portrays Long COVID as a heterogeneous, multifactorial syndrome with overlapping biological drivers. Mechanistic studies have identified plausible therapeutic targets micro clots, autoantibodies, mitochondrial dysfunction but these require replication and carefully designed trials before translation to practice. Observational data highlight the preventive potential of early antivirals, while therapeutic options for chronic patients remain limited and inconsistent. Ultimately, future research must balance mechanistic exploration with pragmatic, holistic care strategies that address both the biomedical and socioeconomic dimensions of this enduring global challenge [21].

The emergence of Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), has prompted an increasing number of studies attempting to characterize its clinical presentation, underlying mechanisms, and management strategies. Early reports identified fatigue, dyspnea, and cognitive impairment as hallmark symptoms persisting weeks or months beyond the acute phase [22]. Nalbandian et al. (2021) further emphasized the multisystem nature of the condition, describing cardiovascular, respiratory, neurological, and endocrine sequelae [23].

Pathophysiologically, several mechanisms have been proposed. Proal and VanElzakker (2021) highlighted chronic immune activation, viral persistence, and autoimmunity as potential drivers [24]. Supporting this, Su et al. (2022) demonstrated that immune signatures and viral RNA in plasma were predictive of long-term sequelae [25]. Similarly, Swank et al. (2023) reported the persistence of spike protein in circulation among Long COVID patients, suggesting ongoing antigenic stimulation [26].

Another significant area of focus is endothelial dysfunction and microvascular injury. Pretorius et al. (2022) described the presence of fibrinaloid micro clots and platelet hyper activation in Long COVID patients, which may explain fatigue and poor oxygen delivery to tissues [27]. Complementary findings by Al-Aly et al. (2022) in large cohort studies linked Long COVID with

increased risks of organ dysfunction, including cardiovascular and renal disease [28].

Management remains challenging due to the heterogeneous nature of the syndrome. Yong (2021) provided a comprehensive overview of symptomatic approaches, including pulmonary rehabilitation, pacing strategies for fatigue, and cognitive behavioral interventions [29]. More recently, Brodin et al. (2022) argued that studying Long COVID may help uncover broader insights into other post-infectious syndromes such as ME/CFS [30].

Overall, the literature converges on a multifactorial model of Long COVID involving immune dysregulation, viral persistence, endothelial pathology, and psychosocial factors. However, more research is needed to define diagnostic biomarkers, establish therapeutic targets, and evaluate interventions through robust clinical trials [31].

Conclusion

Long COVID represents a complex, multisystem disorder that bridges virology, immunology, neurology, and psychosocial health. Its pathophysiology involves persistent viral reservoirs, immune dysregulation, endothelial injury, autonomic dysfunction, and mitochondrial impairment. Management requires a holistic, multidisciplinary approach combining symptomatic treatment, rehabilitation, and psychosocial support, while ongoing research into targeted therapies continues. Recognizing and addressing Long COVID is not only a medical imperative but also a societal necessity as millions worldwide struggle with its enduring consequences.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Al-Aly, Z., Bowe, B., & Xie, Y. (**2022**). Long COVID after breakthrough SARS-CoV-2 infection. Nature Medicine, 28, 1461–1467.

[2] Al-Aly, Z., Xie, Y. (**2022**). Risks and burdens of incident diabetes in long COVID: a cohort study. The Lancet Diabetes & Endocrinology, 10, 311–321.

[3] Bakerly, D. N., Smith, N., Darbyshire, J. L., Kwon, J., Bullock, E., Baley, S., Sivan, M., & Delaney, B. (**2024**). Pathophysiological Mechanisms in Long COVID: A Mixed Method Systematic Review. International Journal of Environmental Research and Public Health, 21(4), 473.

[4] Brodin, P., Casari, G., Townsend, L., et al. (**2022**). Studying severe long COVID to understand post-infectious disorders beyond COVID-19. Nature Medicine, 28, 879–882.

[5] Davis, H. E., Assaf, G. S., McCorkell, L., et al. **(2021).** Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. E-Clinical Medicine, 38, 101019.

[6] Fernández-de-las-Peñas, C., Torres-Macho, J., Velasco-Arribas, M., et al. (**2022**). Preexisting hypertension is associated with a greater number of long-term post-COVID symptoms and poor sleep quality: a case–control study. Journal of Human Hypertension, 36, 582–584.

[7] Frontiers Immunology. (**2024**). Autoantibodies in COVID-19 survivors with post-COVID symptoms. Frontiers in Immunology.

[8] Frontiers Immunology. **(2025).** Long COVID-19 autoantibodies and their potential effect on fertility. Frontiers in Immunology.

[9] Frontiers. (2023). A review of cytokine-based pathophysiology of Long COVID symptoms. Frontiers in Medicine.

[10] Goh, D., Lim, J. C. T., Fernández, S. B., et al. (**2022**). Persistence of residual antigen and RNA of SARS-CoV-2 in tissues of two patients with long COVID. Frontiers in Immunology, 13, 939989.

[11] Haran, J. P., Bradley, E., Zeamer, A. L., et al. **(2021).** Inflammation-type symbiosis of the oral microbiome associates with the duration of COVID-19 symptoms and long COVID. JCI Insight, 6(20).

[12] Insights JCI. (**2023**). Autoantigen profiling reveals a shared post-COVID signature in fully recovered and Long COVID patients. JCI Insight.

[13] Jacobs, J. J. L. (**2021**). Persistent SARS-2 infections contribute to long COVID-19. Medical Hypotheses, 149, 110538.

[14] Jacobs, J. J. L. (**2021**). Persistent SARS-2 infections contribute to long COVID-19. Medical Hypotheses, 149, 110538.

[15] Nalbandian, A., Sehgal, K., Gupta, A., et al. **(2021).** Post-acute COVID-19 syndrome. Nature Medicine, 27, 601–615.

[16] Perumal, V., Arokiaraj, M. C., & Arokiasamy, J. T. (**2023**). Immune and inflammatory features of long COVID. Frontiers in Immunology.

[17] Pretorius, E., Venter, C., Laubscher, G. J., et al. (**2022**). Prevalence of symptoms, comorbidities, fibrin amyloid micro clots and platelet pathology in individuals with Long COVID / post-acute sequelae of COVID-19 (PASC). Cardiovascular Diabetology, 21, 148.

[18] Proal, A. D., & VanElzakker, M. B. (**2021**). Long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC): An overview of biological factors that may contribute to persistent symptoms. Frontiers in Microbiology, 12, 698169.

[19] Rohrhofer, J., Graninger, M., Lettenmaier, L., Schweighardt, J., Gentile, S. A., Koidl, L., et al. (**2023**). Association between Epstein-Barr-Virus reactivation and development of long-COVID fatigue. Allergy, 78, 297–299.

[20] Su, Y., Yuan, D., Chen, D., et al. (**2022**). Multiple early factors anticipate post-acute COVID-19 sequelae. Cell, 185(5), 881–895.e20.

[21] Swank, Z., Senussi, Y., Manickas-Hill, Z., et al. (**2023**). Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae. Cell, 186(13), 3735–3748.e10.

[22] Yong, S. J. **(2021).** Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. Infectious Diseases, 53(10), 737–754.

[23] Aghahosseini,S. S. and Mousavibahar,S. A. (**2025**). Cardiac Hydatid Cyst: A Rare Case Report. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(10), 298-300.

[24] Asl,L. D. (**2025**). Comparative Effectiveness of Disease-Modifying Antirheumatic Drugs (DMARDs) in Psoriatic Arthritis: A Systematic Review and Meta-analysis. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(8), 237-244.

[25] Dahmardehei,M. , Dahmardehei,A. , Dahmardehei,Z. , Milanifard,M. , Rezaei,S. and Atashhoosh,H. (**2025**). Effectiveness of Biatain Silver Dressing versus Simple Vaseline Gauze in the Healing of Skin Graft Burn Wounds. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(10), 301-314.

[26] Hamidi,P. (**2025**). Effectiveness and Safety of Second-Generation Antipsychotics for Psychiatric Disorders Apart from Schizophrenia: A Systematic Review and Meta-Analysis. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(10), 289-297.

[27] Mahboobi,L. , Kiani,F. and Shotorbani,B. S. (**2025**). Impact of Central Nervous System Involvement on Changes in WBC, Hemoglobin, Platelet Count, and LDH Levels in Pediatric Acute Leukemia. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(8), 245-250.

[28] Hashemloo,A. and Milanifard,M. (**2026**). Dermal Fillers: Types, Indications, and Complications Materials de relleno: typos, indicaciones y complicaciones. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 2*(1), 1-11.

[29] Lotfi,A. R. and Nouribayat,L. (**2025**). Comparison of the Effects of Ketamine and Dexmedetomidine on the Incidence of Adverse Events (Nausea and Vomiting, Shivering, Hypotension, and Bradycardia) Following Traumatic Nasal Surgeries. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 266-274.

[30] Asl,L. D. (**2025**). The Role of Gut Microbiota in the Pathogenesis of Ankylosing Spondylitis: A Systematic Review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 275-282.

[31] Dahmardehei,M. , Dahmardehei,A. , Dahmardehei,Z. , Milanifard,M. , Ebrahimi,M. and fakhrabadi,A. M. (**2025**). Evaluation of the Effects of Prontosan and Normal Saline Irrigation Solution on the Healing of Second-Degree Burn Wounds. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 283-294.