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BEYOND ACUTE INFECTION: A REVIEW OF VIRAL PERSISTENCE AND IMMUNE DYSREGULATION AS THE PATHOPHYSIOLOGICAL NEXUS OF LONG COVID PHENOTYPES

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ABSTRACT

Long COVID, or Post-Acute Sequelae of SARS-CoV-2 infection (PASC), represents a significant global health challenge affecting millions worldwide. This review synthesizes recent mechanistic evidence to propose that the pathophysiological nexus of Long COVID's diverse clinical phenotypes lies in the interplay between SARS-CoV-2 viral persistence and subsequent chronic immune dysregulation. Moving beyond hypotheses of residual acute damage, we detail the evidence for viral components, particularly the Spike protein, persisting in tissue reservoirs like the gut, nervous system, and vasculature for months post-infection. This persistent antigen serves as a continuous trigger for a self-perpetuating cycle of immune dysfunction, characterized by chronic inflammation, T-cell exhaustion, autoantibody production, and mast cell activation. A central downstream consequence is a systemic microvascular coagulopathy, driven by the formation of fibrin amyloid microclots that resist fibrinolysis, leading to tissue hypoxia and bioenergetic failure through mitochondrial dysfunction. This mechanistic pathway—from viral persistence to immune dysregulation and microvascular damage—explains the multi-system symptomatology, including fatigue, cognitive impairment, and cardiovascular complications. We conclude that this biological framework validates Long COVID as a distinct disease entity, mandates a shift towards biomarker-driven diagnosis, and provides a rationale for targeted, combination therapies addressing viral persistence, immune dysregulation, and microclotting to mitigate this growing burden of chronic disease.

Keywords: *Long COVID, PASC, viral persistence, immune dysregulation, pathophysiology, microclots*

1. Introduction: Contextualizing the Global Burden of Long COVID

1.1 Definition of Long COVID / PASC

Long COVID, formally termed Post-Acute Sequelae of SARS-CoV-2 infection (PASC), represents a global health challenge characterized by the continuation or emergence of new symptoms following initial SARS-CoV-2 infection (Gusev & Sarapultsev, 2024). The World Health Organization (WHO) defines this condition as occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually within three months from the onset, with symptoms lasting at least two months that cannot be explained by an alternative diagnosis and generally impact everyday functioning (Soriano et al., 2022). The clinical presentation is complex, with reports describing more than 200 possible symptoms across nearly every organ system. The most frequently reported manifestations globally include debilitating fatigue, dyspnea (shortness of

breath), and cognitive impairment, often referred to as "brain fog" (Soriano et al., 2022).

1.2 Duration and Diagnostic Considerations

Early attempts to define the syndrome included criteria based on symptom persistence beyond three weeks, but these have since evolved to reflect the chronic nature of the illness (Shah et al., 2021). Most current definitions require symptoms to persist beyond four weeks, or commonly, beyond twelve weeks after acute infection. Longitudinal studies show that symptoms associated with post-viral fatigue syndrome (PVFS) following COVID-19 can endure for prolonged periods, reaching or exceeding 1.5 years post-infection (Abilbayeva et al., 2023). The primary clinical challenge remains the lack of a universally accepted, full-spectrum diagnostic criterion, which significantly complicates global epidemiological surveillance and the recruitment of standardized cohorts for clinical trials (Shah et al., 2021).

1.3 Global Epidemiological Burden

The scale of the crisis is immense, with global epidemiological estimates suggesting that between 10% and 35% of individuals who survive acute COVID-19 proceed to develop Long COVID (Soriano et al., 2022). Although some evidence indicates a higher reported prevalence in High-Income Countries (HICs), the total burden in terms of affected individuals is massive worldwide (Zakeri et al., 2024). The functional and clinical impact of LC is potentially more severe in Low- and Middle-Income Countries (LMICs). This disparity stems from higher rates of pre-existing health conditions in these regions, coupled with inadequate healthcare infrastructure and a lack of established support systems, leading to a disproportionately severe impact on daily functioning (Zakeri et al., 2024).

1.4 Socioeconomic and Clinical Consequences

The persistence of LC symptoms places continuous, increasing pressure on global healthcare infrastructures (Khouja et al., 2024). The chronic nature of the illness, particularly in populations of working age, translates into massive economic loss due to disability and reduced productivity. Data specifically from the South Asian region highlights the prevalence of core symptoms, with muscle problems, fatigue, and cognitive issues being highly frequent, encountered in 14.7% of surveyed individuals (Khan et al., 2024). The cumulative impact of this chronic disability in resource-constrained environments represents a non-communicable disease burden born from a communicable crisis.

1.5 Current Controversies

The early stages of the pandemic were marked by debates regarding the origin of persistent symptoms, specifically whether they were driven by psychological factors or identifiable biological pathology (Moen et al., 2025; Pretorius et al., 2023). This enduring controversy underscores the urgent need for a rigorous, objective review of the mechanistic evidence. Establishing a clear biological basis is crucial to validate Long COVID as a distinct disease entity and to justify investment in targeted, biologically guided therapies.

1.6 Aim of this Review

This review aims to synthesize recent mechanistic evidence linking SARS-CoV-2 viral persistence with downstream immune dysregulation as the core pathophysiological nexus explaining the diverse clinical phenotypes observed in Long COVID.

2. Methodology: A Global Semi-Systematic Review Approach

This review article employed a semi-systematic literature search strategy designed to ensure comprehensive coverage of mechanistic and global clinical evidence.

Search Strategy and Inclusion Criteria

The search spanned the major bibliographic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search timeframe was restricted to peer-reviewed publications between 2020 and 2025 to capture the most current data. Boolean strategies were utilized, combining keywords such as "Long COVID" AND "Viral persistence" AND "Immune dysregulation," and alternating "PASC" with OR operators for terms like "Autoimmunity" OR "Microvascular injury." Inclusion criteria prioritized peer-reviewed articles reporting primary mechanistic data, encompassing clinical cohorts, molecular

analyses, autopsy studies, biomarker identification, and advanced imaging techniques. A concerted effort was made to incorporate international datasets, specifically seeking out published evidence, case series, and epidemiological patterns from underrepresented regions, including South Asia (e.g., Pakistan, India, Bangladesh, Sri Lanka, Nepal) and the Middle East (GCC countries). Exclusion criteria were applied to preprints, non-peer-reviewed sources, and isolated case reports that lacked detailed mechanistic or longitudinal data, ensuring a high level of evidence quality.

3. Conceptual Framework of Long COVID Pathogenesis

3.1 Traditional Post-Viral Fatigue Syndrome Models

Long COVID shares significant clinical and pathological overlap with historically recognized post-viral syndromes. Notably, the phenotype associated with severe, protracted fatigue in Long COVID closely resembles Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Both LC and ME/CFS are characterized by a profile of exhausted antiviral immune response, suggesting a common inability to fully resolve the primary viral assault.

3.2 Limitations of Early Acute-Damage Hypotheses

Early hypotheses for post-COVID complications focused primarily on the direct damage inflicted by the acute infection, such as severe pulmonary fibrosis or scarring resulting from intensive care hospitalization. However, these models fail to explain the incidence of LC in individuals who experienced mild or asymptomatic acute infections. Furthermore, they do not account for the highly specific, ongoing pathology—such as multisystem microvascular damage—that characterizes the chronic phase, necessitating a shift in pathogenic understanding.

3.3 Shift toward "Chronic Infection + Immune Dysfunction" Paradigm

The conceptual framework for LC has shifted toward a model of continuous pathophysiological activity. Long COVID is now viewed as a sustained state of tissue proinflammatory stress. This stress is fundamentally rooted in the persistent presence of viral antigens, which initiates a relentless cascade of immune dysfunction (Moen et al., 2025; Pretorius et al., 2023). This paradigm moves the focus from residual physical injury to an ongoing, active pathogenic process driven by the persistent presence of the viral trigger, leading to chronic inflammation and cellular stress (McMillan et al., 2024).

3.4 Comparison with Chronic Illnesses (EBV, CMV, HIV, chikungunya, Zika)

Many chronic diseases, particularly those caused by herpesviruses, are characterized by persistent immune evasion and reactivation. A critical observation in LC patients experiencing PVFS is the high rate of concurrent latent viral reactivation; specifically, Epstein–Barr virus (EBV) reactivation was identified in almost half (48%) of individuals presenting with post-COVID PVFS (Abilbayeva et al., 2023). The co-occurrence of EBV reactivation with post-COVID PVFS suggests that SARS-CoV-2 persistence operates as a profound immune disruptor. The enduring presence of SARS-CoV-2 antigen is not only directly immunopathological but also appears to induce functional impairment in the immune system, often manifesting as T-cell exhaustion (Korobova et al., 2025). This exhaustion compromises the host's ability to maintain control over common latent herpesviruses like EBV and Cytomegalovirus (CMV). The subsequent reactivation of these secondary pathogens likely contributes additively or synergistically to the overall burden of chronic inflammation and debilitating fatigue experienced by LC patients. Consequently, diagnostic evaluations for LC often integrate assessments for common herpesvirus reactivation markers, while potential therapeutic strategies might involve combining interventions targeting SARS-CoV-2 persistence with those aimed at immune restoration or suppression of latent viral activity.

4. Evidence of SARS-CoV-2 Viral Persistence in Host Tissues

The detection of persistent SARS-CoV-2 components in extrapulmonary tissues is foundational to the current pathogenic framework of Long COVID.

4.1 Detection in Tissue Sites

Viral components have been identified across numerous anatomical sites well after the resolution of acute illness:

- Gastrointestinal Tract: Studies on patients with inflammatory bowel disease (IBD) showed persistent SARS-CoV-2 nucleocapsid protein and viral transcripts within the gut epithelium and CD8+ T cells, persisting for months post-acute infection. This presence was observed in the majority of patients and was independent of initial disease severity or immunosuppressive therapy, but strongly associated with reporting post-acute COVID-19 symptoms (Zuo et al., 2022).
- Central Nervous System (CNS): Post-mortem examinations of patients deceased from COVID-19 revealed severe neuroinflammation, characterized by microgliosis and astrogliosis, particularly localized near the olfactory bulb, which is hypothesized to be responsible for persistent anosmia and other neurocognitive deficits (Matschke et al., 2020). Viral antigen or nucleic acid persistence is implicated in driving chronic CNS dysfunction, either through direct neuroinvasion or via the gut-brain axis (GBA) pathway influenced by gut dysbiosis (McMillan et al., 2024).
- Vasculature and Lymphatics: Persistent viral RNA fragments and specific proteins, such as the SARS-CoV-2 Spike (S1) protein, have been documented in the blood of LC patients for up to a year (Gusev & Sarapultsev, 2024). The S protein was also transiently detected in draining lymph nodes after vaccination, highlighting the potential for viral components to circulate and accumulate in immune compartments (Vogels et al., 2023).

4.2 Diagnostic and Detection Techniques

Confirming viral persistence requires a combination of highly sensitive and specific techniques. Molecular methods include quantitative polymerase chain reaction (qPCR) for viral transcripts (RNA) and genome sequencing. Protein visualization relies on immunofluorescence, immunohistochemistry, and advanced proteomics platforms (Zuo et al., 2022; Chen et al., 2023). Antibody-based detection in tissues, while providing robust localization data, necessitates careful assay qualification to ensure high specificity and sensitivity, minimizing the risk of misinterpreting the relationship between viral components and PASC (Chen et al., 2023).

4.3 Persistent Viral Proteins vs. Replication-Competent Virus

A key distinction in the pathogenesis of LC is between the persistence of viral antigens and the presence of replication-competent virus. The predominant finding in Long COVID is the sustained presence of viral debris (RNA fragments or proteins), especially the Spike S1 protein, which continuously stimulates the host immune system (Gusev & Sarapultsev, 2024; Moen et al., 2025; Pretorius et al., 2023). While prolonged shedding of viable, replication-competent virus has been observed in acute patients with severe or immunocompromised states (van Kampen et al., 2021), the recovery of live virus from extrapulmonary tissue in the chronic phase is exceedingly rare. However, the detection of subgenomic RNA (sgRNA)—a marker of recent replication—in tissues like the heart suggests that low-level, localized replication may persist in certain severe cases. The evidence points toward the persistent Spike S1 fragment itself acting as the primary pathogenic trigger in chronic disease. The S1 protein is known to directly induce the formation of pathological fibrin amyloid microclots in plasma samples (Pretorius et al., 2023). Given that this fragment retains its potent inflammatory and pro-coagulant properties irrespective of viral infectivity, the therapeutic priority extends beyond merely inhibiting viral replication. It must also encompass strategies aimed at clearing the persistent, inflammatory S1 protein (e.g., through targeted clearance mechanisms or specific binding agents) to effectively interrupt the pathological cycle of chronic inflammation and coagulopathy.

4.4 Duration of Persistence

The duration of viral persistence, as measured by antigen detection, is substantial, often extending many months after the initial infection (Zuo et al., 2022). These persistent antigens serve as the necessary stimulus to maintain the chronic inflammatory state that defines LC.

Table 1: Key Studies Demonstrating SARS-CoV-2 Viral Persistence in Long COVID

Study Reference	Tissue Sampled	Method	Viral Component Detected	Duration Post-Infection	Key Result/Association
(Zuo et al., 2022)	Gut Mucosa (Small & Large Intestine)	qPCR, Immunofluorescence	Nucleocapsid protein, 4 Viral Transcripts	Months (Post-Acute)	Antigens persisted in 24/46 patients; associated with PASC symptoms.
(Gusev & Sarapultsev, 2024)	Blood/Plasma, Lymphatics	Proteomics, RNA Detection	Viral RNA fragments, Spike Protein (S1)	Up to 1 Year	Viral components found in blood; persistent antigenemia confirmed.
(Matschke et al., 2020)	CNS (Post-Mortem)	Histopathology	Microgliosis, Astrogliosis	Acute/Subacute	CNS inflammation in olfactory bulb and parenchyma indicates viral-associated injury.

5. Mechanistic Synthesis: Viral Persistence → Immune Dysregulation

The persistent presence of viral antigen serves as the central hub connecting SARS-CoV-2 infection to the multi-layered immune and vascular dysfunction seen in Long COVID.

5.1 Chronic Inflammation & Cytokine Storm Continuation

Long COVID is characterized by chronic, low-grade systemic inflammation. Elevated cytokine levels persist in both peripheral blood and the central nervous system, driving the diverse symptomatology. This chronic inflammatory state contributes directly to endothelial dysfunction, neuroinflammation, and immune cell exhaustion (Korobova et al., 2025).

5.2 Immune Exhaustion (CD4+, CD8+, NK Cell Alterations)

Failure to clear the persistent antigen leads to chronic overstimulation of the immune system, resulting in T-cell exhaustion. This is marked by persistent abnormalities in T-cell subsets, including a loss of cytotoxicity, depletion of memory T cells, and T regulatory cell alterations (Korobova et al., 2025). The dysfunctional immune environment, particularly a bias toward Th2 or Th17 responses, promotes the initiation of autoimmune processes (Korobova et al., 2025). T-cell exhaustion represents a critical pathogenic mechanism, as the inability of T cells to regain functional competency allows viral components to persist indefinitely (Korobova et al., 2025).

5.3 Autoantibody Formation & Molecular Mimicry

The combination of chronic inflammation and sustained antigenic stimulation, alongside T-cell dysregulation, frequently leads to a loss of immune tolerance and the subsequent emergence of new-onset autoantibodies (Moen et al., 2025; Pretorius et al., 2023; Korobova et al., 2025). These autoantibodies can target host tissues and receptors, potentially exacerbating symptoms. Emerging research identifies autoantibodies targeting various host proteins, including membrane-bound proteins highly expressed on immune cells (e.g., TMED10), requiring further investigation to confirm their causative role in LC pathophysiology (Cervia-Hasler et al., 2024).

5.4 Mast-Cell Activation Syndromes

A persistent inflammatory state in Long COVID leads to an activated condition of mast cells, characterized by abnormal granulation and excessive release of inflammatory mediators. Clinical observations confirm that many

patients with LC suffer from a syndrome clinically indistinguishable from Mast Cell Activation Syndrome (MCAS) (Weinstock et al., 2023). Because MCAS links chronic inflammatory triggers to many systemic, often fluctuating symptoms (such as neurological, gastrointestinal, and autonomic issues), its recognition is highly clinically valuable (Weinstock et al., 2023). The early diagnosis and management of MCAS allows for therapeutic intervention using readily available pharmacological agents, such as histamine H1 and H2 blockers and mast cell stabilizers. These treatments can manage mast cell-mediated hyperinflammation, potentially providing significant symptomatic relief and improving the long-term quality of life for LC patients, particularly in resource-constrained settings where specialized therapies are often inaccessible.

5.5 Endothelial Damage, Microthrombi & Hypoxia

Persistent viral antigens contribute directly to endothelial damage (McMillan et al., 2024). A defining objective feature of Long COVID is a chronic, non-resolving coagulopathy characterized by the presence of fibrin amyloid microclots in the plasma (Pretorius et al., 2023; Pretorius et al., 2022). These abnormal microclots are highly resistant to natural fibrinolysis, hindering their breakdown (Pretorius et al., 2023; Pretorius et al., 2022). Functionally, these microclots physically block microcapillaries, leading to impaired oxygen exchange and localized tissue hypoxia throughout the body (Pretorius et al., 2022; Pretorius et al., 2023). The microclots also entrap numerous inflammatory molecules, including alpha 2-antiplasmin and platelet factor 4 (PF4) (Pretorius et al., 2023). This systematic mechanism of impaired tissue oxygenation due to microclotting is hypothesized to be a key driver of the multisystem symptoms, particularly the debilitating fatigue and post-exertional malaise (PEM) observed in LC.

5.6 Mitochondrial Dysfunction and Metabolic Shift

The tissue hypoxia induced by microclots, combined with chronic inflammatory signaling, creates a sustained bioenergetic defect in LC patients (Macnaughtan et al., 2025). Peripheral blood mononuclear cells (PBMCs) from LC subjects exhibit a distinctive, exceptional change in adenosine triphosphate (ATP) synthase function, where the enzyme contributes to maintaining mitochondrial membrane potential rather than exclusively generating ATP, suggesting it runs both forward and reverse reactions (Macnaughtan et al., 2025). This metabolic defect, evidenced by decreased fat oxidation and increased lactate production even during minimal exertion (Macnaughtan et al., 2025), signifies a systemic shift toward glycolysis (the Warburg effect), driven by a chronic, non-resolving metabolic imbalance (Nunn et al., 2022). This mitochondrial dysfunction strongly correlates with clinical phenotype, indicating a causal relationship with functional limitations and fatigue (Macnaughtan et al., 2025).

5.7 Disruption of Microbiome & Gut Permeability

The gastrointestinal tract, a site of viral persistence (Zuo et al., 2022), frequently suffers from microbial dysbiosis following SARS-CoV-2 infection. This is typically marked by a reduction in beneficial short-chain fatty acid (SCFA)-producing bacteria, such as Bifidobacterium and Lactobacillus (Sokołowska et al., 2023). This dysbiosis severely weakens the intestinal barrier function, leading to increased gut permeability (Sokołowska et al., 2023). The resulting microbial translocation into the systemic circulation further exacerbates the systemic inflammatory cycle, creating a vicious feedback loop between gut pathology and generalized inflammation (McMillan et al., 2024; Sun et al., 2024) (Figure 1).

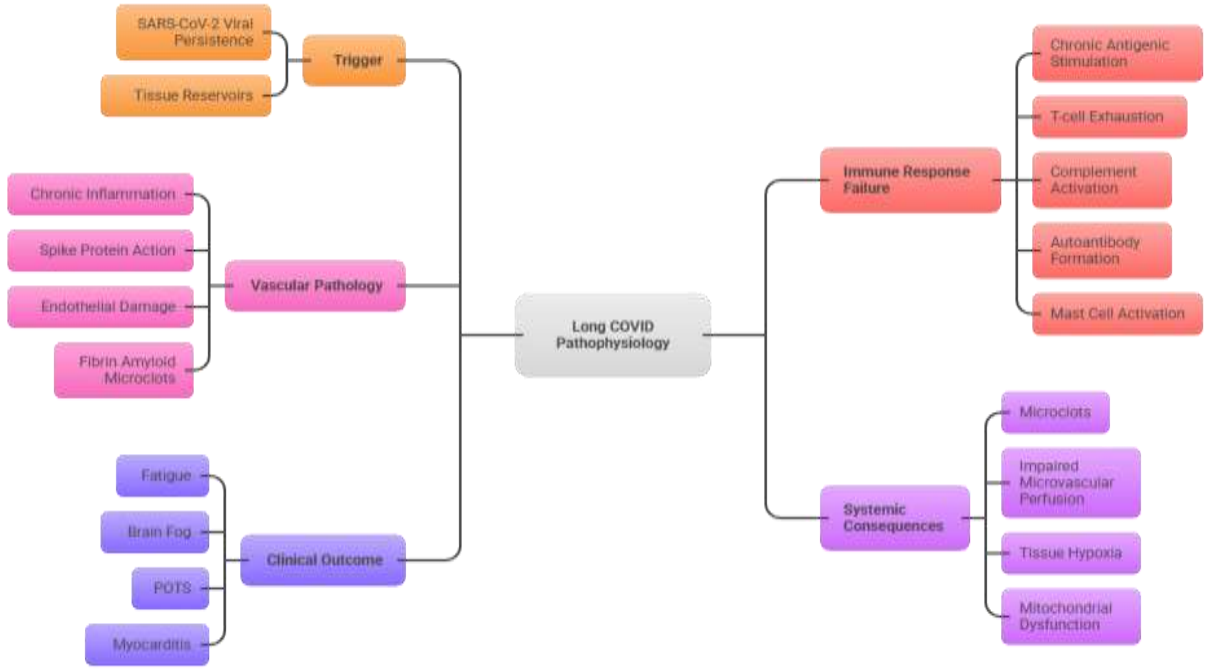

Figure 1: Mechanistic Pathway Diagram A visual pathway illustrating the interconnected elements of LC pathogenesis:

6. Clinical Phenotypes and Organ-Specific Manifestations

6.1 Neurological & Cognitive

Neurological symptoms, encompassing severe "brain fog," memory deficits, and chronic headaches, correlate with persistent neuroinflammation confirmed by autopsy findings of microgliosis and astrogliosis (Matschke et al., 2020). A significant subset of patients develops Autonomic Nervous System (ANS) dysfunction, frequently manifesting as Postural Orthostatic Tachycardia Syndrome (POTS), characterized by a labile heart rate and blood pressure response to activity, which contributes substantially to cognitive symptoms and effort intolerance (Zuin et al., 2022).

6.2 Cardiovascular & Microvascular

Cardiovascular manifestations are frequently caused by prolonged inflammation, which results in structural and functional changes (Krljanac et al., 2025; Zuin et al., 2022). Common symptoms include palpitations, effort intolerance, and chest tightness (Krljanac et al., 2025; Zuin et al., 2022). Advanced multimodality imaging, such as cardiac magnetic resonance imaging (CMR) and echocardiography, is essential for detecting specific pathologies like chronic myocarditis, pericarditis, and signs of early-stage heart failure or pre-ischemic states (Krljanac et al., 2025; Zuin et al., 2022). These chronic structural changes stem from the widespread microvascular injury and coagulopathy driven by the persistent viral antigen.

6.7 Pediatric vs. Adult Differences

Long COVID is a recognized condition in children and adolescents, known as pediatric PASC, presenting with persistent fatigue, headaches, gastrointestinal disturbances, and psychological distress, often leading to school absenteeism (Esposito et al., 2023). While children generally experience milder acute infections, potentially due to a more aggressive and efficient early innate immune response (Type I and II Interferon response) that limits acute systemic disease (Luo et al., 2024), they are not immune to chronic sequelae. The fact that children still develop LC, despite their robust innate clearance mechanisms, suggests that the underlying pathophysiology of antigen persistence and subsequent immune exhaustion, once established, operates similarly in both adults and pediatric cohorts, independent of initial disease severity. Long-term outcomes for pediatric LC, including the risk of chronic conditions like POTS and reduced exercise

tolerance, remain uncertain (Esposito et al., 2023).

Table 2: Long COVID Phenotypes, Hallmark Symptoms, and Proposed Pathophysiological Mechanisms

Organ System/Phenotype	Hallmark Symptom	Primary Mechanistic Driver	Key Evidence/Biomarker Link
Neurological/Cognitive	Brain Fog, Memory Deficit	CNS Inflammation, Autonomic Dysfunction, GBA disruption	Microgliosis (Matschke et al., 2020), Elevated Cytokines (Korobova et al., 2025), POTS (Zuin et al., 2022)
Cardiovascular/Dysautonomia	Palpitations, Effort Intolerance	Microvascular Injury, Chronic Myocarditis, ANS dysfunction	PET/MRI Inflammation (Trivieri et al., 2025), Chronic Inflammation (Krljanac et al., 2025; Zuin et al., 2022)
Systemic/Metabolic	Debilitating Fatigue, PEM	Tissue Hypoxia, Mitochondrial Dysfunction, Bioenergetic Failure	Fibrin Amyloid Microclots (Pretorius et al., 2023; Pretorius et al., 2022), Atypical ATP Synthase (Macnaughtan et al., 2025)
Gastrointestinal	Chronic Diarrhea, Abdominal Pain	Gut Viral Antigen Persistence, Dysbiosis, Barrier Dysfunction	Persistent N protein (Zuo et al., 2022), Increased Permeability (Sun et al., 2024)

7. Biomarkers, Imaging & Diagnostic Approaches

The shift from symptomatic diagnosis to objective, biomarker-driven validation is crucial for managing the heterogeneity of LC.

7.1 Viral RNA/Protein Detection

Direct detection of persistent viral components, such as the Spike S1 protein or viral RNA in plasma, provides tangible evidence of the antigenic trigger sustaining the pathological process (Gusev & Sarapultsev, 2024; Moen et al., 2025; Pretorius et al., 2023).

7.2 Inflammatory Immune Signatures

High-throughput proteomic technologies, such as the SomaScan platform, have been instrumental in identifying persistent systemic inflammatory signatures in LC patients. A key finding is chronic complement activation, particularly of the alternative pathway. Elevated levels of split products like Ba and C3d have been consistently associated with the development of LC at six months post-infection (Cervia-Hasler et al., 2024).

7.4 Endothelial and Coagulation Markers

Markers related to microvascular pathology offer functional diagnostic potential. The quantification of fibrin amyloid microclots and the entrapment of fibrinolysis inhibitors like alpha 2-antiplasmin (α2AP) within these clots are currently used as experimental functional biomarkers for fibrinolytic resistance and microvascular distress (Pretorius et al., 2023; Pretorius et al., 2022).

7.5 Neuroimaging and Cardiac Imaging

Advanced multimodality imaging provides objective visualization of the underlying pathology. Cardiopulmonary Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI) has successfully identified persistent signs of inflammation in the heart and lungs of Long COVID patients (Trivieri et al., 2025). Critically, these abnormal findings are not just correlative; they are linked to an increased likelihood of developing future cardiac and pulmonary diseases (Trivieri et al., 2025). This objective, visual confirmation of hidden inflammatory processes necessitates a fundamental change in the clinical approach to

LC. The presence of measurable, structural disease mandates active surveillance and early, preventive interventions rather than passive symptomatic management, especially to mitigate long-term morbidity such as heart failure and pulmonary hypertension (Trivieri et al., 2025).

7.6 Multi-omic and AI-driven Predictive Models

The future of LC diagnostics lies in integrating longitudinal multi-omic data (proteomics, metabolomics, and immune phenotyping) to overcome clinical heterogeneity. AI-driven predictive models will be essential for distinguishing between various LC sub-phenotypes (e.g., vascular vs. autoimmune dominant) and guiding phenotype-specific treatment selection (Cervia-Hasler et al., 2024).

Table 3: Clinical and Experimental Biomarkers of Long COVID Pathogenesis

Biomarker Category	Example Biomarker	Pathophysiological Link	Clinical Utility/Status
Viral Trigger	SARS-CoV-2 Spike S1 Protein	Continuous Antigenic Stimulation	Experimental/Translational (Gusev & Sarapultsev, 2024)
Immune Activation	Complement Split Products (Ba, $C3d$)	Chronic Complement Activation (Alternative Pathway)	Translational/Diagnostic Potential (Cervia-Hasler et al., 2024)
Vascular Pathology	Fibrin Amyloid Microclots	Endothelial Damage, Tissue Hypoxia	Experimental/Functional Diagnostic (Pretorius et al., 2023; Pretorius et al., 2022)
T-Cell Integrity	$CD8^+$Exhaustion Markers	Immune Dysregulation, Loss of Tolerance	Research/Correlative (Korobova et al., 2025)
Secondary Infection	EBV VCA IgG Reactivation	Immune Exhaustion, Secondary Trigger	Clinical/Correlative (Abilbayeva et al., 2023)

8. Therapeutic Strategies and Emerging Interventions

The mechanistic understanding of LC drives the exploration of targeted therapeutic strategies.

8.1 Antivirals

Antivirals, such as remdesivir and nirmatrelvir/ritonavir (NMV-r, or Paxlovid), are primarily effective in mitigating acute COVID-19 severity (IDSA, 2023). However, their role in resolving established chronic infection and LC symptoms remains under evaluation. Recent retrospective cohort studies show that NMV-r use in the acute phase was not associated with a reduced overall risk of developing Long COVID, though it showed heterogeneous effects on specific symptoms. This suggests that therapeutic strategies aimed at clearing chronic, sequestered antigen may require direct-acting antivirals or host-directed antivirals that target cellular processes independent of viral mutation, rather than relying solely on acute replication inhibitors (Robinson et al., 2022).

8.2 Immunomodulators

Immunomodulatory agents target the persistent inflammation and immune dysfunction. Agents under investigation include low-dose naltrexone (LDN) and intravenous immunoglobulins (IVIg), which address chronic immune exhaustion and autoimmune components (Fernandez-de-las-Peñas et al., 2023). Furthermore, Phase 2–4 Randomized Controlled Trials (RCTs) are examining novel immunomodulators such as Anakinra, Ibudilast, and Infliximab (Fernandez-de-las-Peñas et al., 2023).

8.3 Anti-thrombotic & Endothelial Therapies

Given the central role of microclot formation, anti-thrombotic and endothelial-targeting therapies are critical. These include anti-platelet and anti-coagulation agents. For patients with severe coagulopathy, specialized experimental interventions such as therapeutic apheresis have been explored (Fernandez-de-las-Peñas et al., 2023).

8.4 Mitochondrial & Metabolic Therapies

To address the documented bioenergetic deficit and metabolic shift toward glycolysis, interventions focusing on enhancing mitochondrial function are being investigated. These strategies include nutritional supplements (e.g., omega-3 fatty acids, L-arginine) and lifestyle interventions designed to mimic beneficial metabolic stressors, such as calorie restriction or optimized physical activity, aiming to "tip" the metabolically imbalanced state back toward resolution (Nunn et al., 2022; Fernandez-de-las-Peñas et al., 2023).

8.7 Precision & Phenotype-Based Medicine Approach

The heterogeneity of Long COVID necessitates a move toward precision medicine. Combination therapy, incorporating both antiviral agents (to suppress persistence) and immunomodulatory drugs (to restore function and reduce inflammation), is considered the most effective path forward (Robinson et al., 2022). Treatment selection must be guided by objective biomarkers; for example, patients identified with MCAS-dominant phenotypes benefit from targeted mast cell stabilizers and antihistamines.

9. Knowledge Gaps, Challenges & Future Research Directions

9.1 Difficulty in Obtaining Tissue Biopsies

A major challenge in LC research is the ethical and practical difficulty of obtaining chronic tissue biopsies from the key reservoirs where viral antigen is believed to persist (e.g., CNS, gut, lymph nodes) (Zuo et al., 2022). Direct quantification of viral burden in these chronic reservoirs is crucial for definitively proving the persistence hypothesis and validating clearance therapies.

9.2 Heterogeneity in Clinical Phenotype Categorization

The broad, overlapping spectrum of symptoms hinders the design of standardized, clean clinical trials. Future research must prioritize the use of high-dimensional multi-omic data and computational modeling to objectively categorize distinct, underlying biological phenotypes, which can then be used to stratify patient populations for trials (Cervia-Hasler et al., 2024).

9.3 South Asian Clinical and Research Landscape: Challenges and Opportunities

Long COVID presents a particularly formidable challenge in Low- and Middle-Income Countries (LMICs). While the symptomatology and impact on functioning are similar to those in HICs, the overall burden is compounded by pervasive healthcare infrastructure limitations (Zakeri et al., 2024). Health systems in South Asia (including India, Pakistan, and Bangladesh) were severely strained during the acute phase of the pandemic, evidenced by critical shortages of PPE and tragically high mortality rates among frontline healthcare workers (Islam et al., 2020; Razu et al., 2021). This systemic weakness in acute care directly translates into profound limitations in managing chronic, complex conditions like LC. LC represents a massive pool of chronic disability impacting the working-age population. The structural limitations within LMIC health systems—such as inadequate intensive care facilities, fragmented care, and logistical issues (Razu et al., 2021)—mean that the subsequent economic and functional consequences of LC will be disproportionately amplified compared to HICs, where comprehensive support systems may exist (Zakeri et al., 2024). Furthermore, access to advanced diagnostics, such as PET/MRI (Trivieri et al., 2025) or high-throughput proteomics (Cervia-Hasler et al., 2024), is severely limited or non-existent in many LMIC settings. To address this global disparity, health policy and research strategies must prioritize accessible, scalable solutions. This requires pivoting global health investment toward chronic disease infrastructure in LMICs, focusing on low-cost diagnostic algorithms. For instance, diagnostic pathways could integrate clinical scoring with accessible serological markers (e.g., EBV reactivation markers (Abilbayeva et al., 2023)) and simple lab panels to guide treatment. Furthermore, scalable multidisciplinary rehabilitation and low-cost pharmacological interventions (like readily available antihistamines for MCAS-dominant phenotypes) must be deployed equitably to mitigate the widespread disability (Zakeri et al., 2024).

10. Conclusion

The cumulative evidence strongly supports a biological foundation for Long COVID, moving the condition definitively beyond controversies regarding psychological origins. The core pathophysiology is mediated by the persistent presence of SARS-CoV-2 viral components, particularly the inflammatory Spike protein, sequestered in various tissue reservoirs. This persistent antigenemia drives a sustained state of immune dysregulation, characterized by chronic complement activation, T-cell exhaustion, autoimmunity, and, crucially, a systemic microvascular coagulopathy leading to tissue hypoxia and bioenergetic failure. This understanding allows for a transition from generalized symptomatic care to targeted, mechanism-guided treatment. The recognition of specific pathogenic pathways—such as MCAS, mitochondrial dysfunction, and fibrin amyloid microclot formation—enables the development and deployment of precision therapies, ranging from targeted immunomodulators to anti-thrombotic agents. Finally, a commitment to global health equity is paramount, requiring multi-disciplinary and precision-guided strategies that are adaptable and accessible to resource-constrained health systems worldwide to address the massive, long-term disability burden of Long COVID.

Authors Contribution

SY: Conceptualized the study, Data Collection, Structural arrangement

B: Literature Selection, Literature Search, Proofreading

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