

Biochemical and Immunological Insights into Long COVID: Pathophysiology, Biomarkers, and Clinical Management

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Abstract

A complex, multisystemic illness, long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), lasts longer than four weeks following the acute phase of COVID-19. It affects between 10–30% of those who are recovering from infection, regardless of initial disease severity. Characterized by fatigue, cognitive impairment, dyspnea, autonomic dysregulation, and multiple systemic abnormalities, Long COVID poses a significant burden on healthcare systems worldwide. This review explores the current understanding of its biochemical and immunological mechanisms, emerging biomarkers, clinical manifestations, and management strategies.

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1. Introduction

Long COVID encompasses a constellation of persistent symptoms lasting more than four weeks post-SARS-CoV-2 infection (1). It affects multiple organ systems, including neurological, cardiovascular, respiratory, endocrine, and musculoskeletal systems (2). Understanding the biochemical and

immunological underpinnings is crucial for accurate diagnosis, risk stratification, and the development of targeted therapies (3).

Clinically, patients may present with fatigue, cognitive dysfunction, dyspnea, palpitations, and metabolic disturbances (4). The heterogeneous nature of Long COVID has prompted extensive research into immune dysregulation, endothelial dysfunction, persistent viral fragments, and mitochondrial impairment as potential mechanisms (5).

With the consistently low mortality rates observed for SARS-CoV-2 infection, research focus has shifted toward individuals who, despite apparent recovery, continue to experience persistent symptoms. These prolonged clinical effects, collectively referred to as “long-COVID (LC),” encompass a broad and diverse spectrum of post-infectious conditions. Although LC is rarely fatal, it significantly compromises patients’ quality of life(6). When combined with Due of its high frequency, LC significantly raises the pandemic’s overall human costs and health care burden. According to conservative estimates, Approximately 76 million instances of LC occur worldwide, accounting for at least 10% of affected individuals (7).These reviews will not address all of the current biomarkers until May 2023, including their relationship to etiopathogenetic mechanisms, a comprehensive diagnostic work-up, comparisons with acute severe COVID-19, the provision of copious epidemiologic data and risk factors, symptoms, discussions regarding similarities to post-viral illnesses, or treatment perspectives (8,9). In light of the syndrome’s epidemiological and pathogenetic components, we want to examine the available data on the primary LC symptomatology, common laboratory findings, and potential LC biomarkers.

, classify them according to etiopathogenetic mechanisms, and evaluate any potential implications for potential therapeutic interventions.

2. Pathophysiology of Long COVID

The pathophysiology is multifactorial:

2.1 Immune Dysregulation

Persistent elevation of pro-inflammatory cytokines (IL-6, TNF- α , IL-1 β) reflects chronic inflammation (2). Dysregulated T-cell and B-cell responses, including expansion of exhausted T-cells, contribute to ongoing immune activation (4)

2.2 Endothelial Dysfunction and Microthrombosis

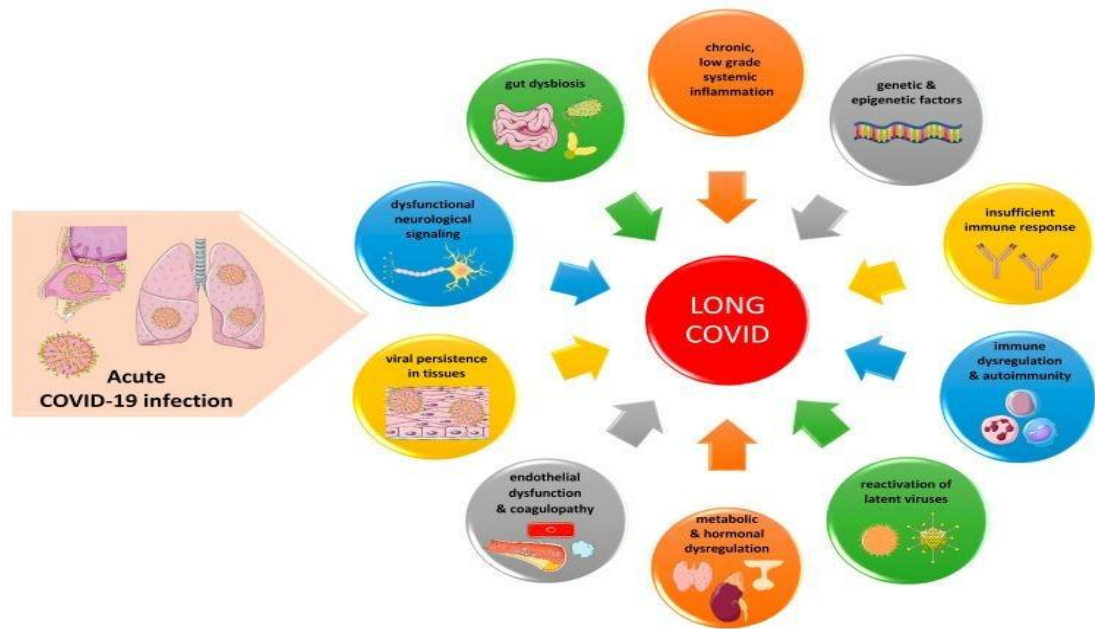
SARS-CoV-2 damages endothelial cells, leading to vascular inflammation and microthrombi formation (5). Markers such as D-dimer, fibrinogen, and von Willebrand factor remain elevated in some patients, indicating a sustained hypercoagulable state.

2.3 Viral Persistence

Residual viral RNA and spike protein fragments have been detected months after acute infection, potentially acting as a chronic antigenic stimulus that perpetuates immune activation (6).

2.4 Mitochondrial Dysfunction and Oxidative Stress

Metabolomic studies demonstrate impaired mitochondrial energy metabolism, elevated lactate levels, and increased oxidative stress markers, which may explain fatigue and muscle weakness in affected individuals (7).



Figure(1) Potential pathophysiological mechanisms involved in the development of long COVID following acute SARS-CoV-2 infection

3. Biochemical and Immunological Biomarkers

3.1 Inflammatory Markers

- C-reactive protein (CRP), IL-6, ferritin, TNF- α
- Soluble IL-2 receptor indicates persistent T-cell activation
- During the acute phase of a viral infection, the immune system triggers the activation of many cells, such as T cells and macrophages, which releases various inflammatory chemicals, such as chemokines and cytokines. One consequence of a SARS-CoV-2 infection is
- "cytokine storm," which is defined by a moderate release of proinflammatory cytokines linked to significant dysregulation of monocytes (8). One of the primary causes of death for COVID-19 patients is acute respiratory distress syndrome (ARDS), which is primarily brought on by the cytokine storm (9) Remarkably, a variety of recurrent LC symptoms could be caused by elevated cytokines, which are generated by an aberrant immune response (10)
- Specifically, increased ferritin and CRP were present in 8% of individuals, while
- Elevations of procalcitonin and IL-6 were found in 4% and 3% of patients, respectively (11). Nevertheless, this was a preliminary only a few publications with a moderate number of participants that examined laboratory abnormalities were included in the meta-analysis. However, a recent meta-analysis of 23 studies (14 prospective and 9 retrospective case control) with 18 meta-analyzed biomarkers revealed that LC survivors had higher levels of leukocytes, lactate dehydrogenase (LDH), D-dimer, and CRP than non-LC controls, though the effect sizes were small (12).

3.2 Coagulation Markers

- ✓ D-dimer, fibrinogen, PAI-1, platelet activation markers

3.3 Cardiac and Musculoskeletal Markers

- ✓ Troponin, NT-proBNP for myocardial involvement

- ✓ Creatine kinase (CK), lactate dehydrogenase (LDH) for muscle injury

3.4 Multi-Omics Signatures

- ✓ Proteomics: dysregulation of complement cascade and coagulation factors
- ✓ Metabolomics: altered amino acid metabolism, dyslipidemia, impaired fatty acid oxidation
- ✓ Transcriptomics: persistent interferon signaling and immune exhaustion signatures

4.4 Biomarkers Reflecting Autoimmunity

Both autoimmunity and antibody polyreactivity, which are generally seen as detrimental, can result after infections. Numerous clinical manifestations associated with COVID-19 exhibit exaggerated and misdirected host immune responses (13). Autoantibody reactivities are substantially higher in COVID-19 patients than in non-infected individuals. These individuals are more likely to have autoantibodies against immunomodulatory proteins, including complement components, cytokines, chemokines, and cell-surface proteins, which may alter immune function and make viral control more challenging [241]. Autoantibodies, particularly those that neutralize type I IFNs, have been implicated in LC and have also been connected to immunological dysregulation, the severity of COVID-19, and mortality (14) as well.

4. Clinical Manifestations

Long COVID is heterogeneous, affecting multiple systems:

- ✓ Fatigue and Post-Exertional Malaise: resembling myalgic encephalomyelitis/chronic fatigue syndrome (15)
- ✓ Cognitive Dysfunction (“Brain Fog”): attention deficits, memory impairment (16)
- ✓ Respiratory Symptoms: dyspnea, reduced lung diffusion, chronic cough (17)
- ✓ Cardiovascular Sequelae: palpitations, tachycardia, myocarditis, POTS (18)
- ✓ Endocrine/Metabolic Effects: new-onset diabetes, thyroid disorders, dyslipidemia (4)
- ✓ Neuropsychiatric Symptoms: anxiety, depression, sleep disturbances (19)

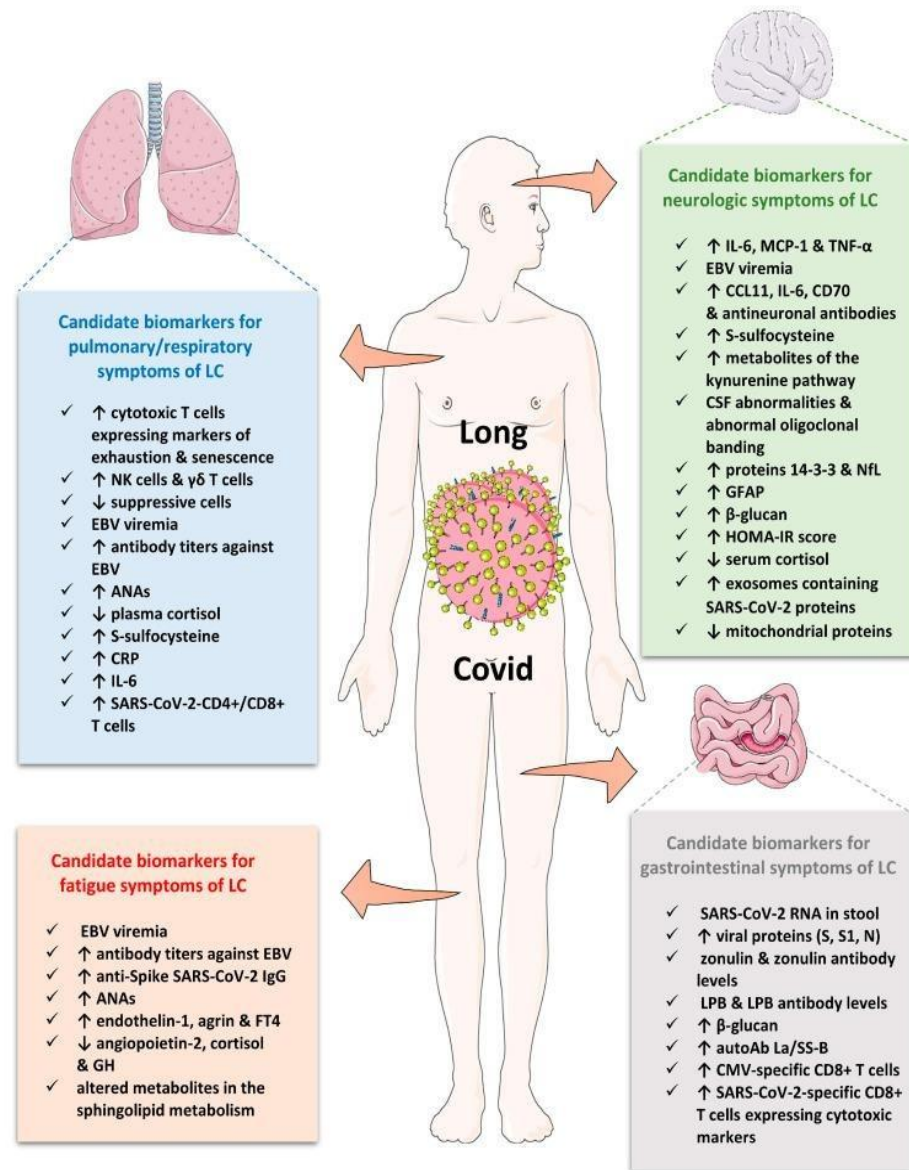
Its non-specific nature and the variety and variability of its clinical presentations complicate the thorough investigation of LC as a homogeneous illness. Rather than being a collection of disordered manifestations that happen independently of one another, the central neurological, cardiorespiratory, systemic/inflammatory, and abdominal clusters are examples of groups or clusters of symptoms that are likely to impact people collectively. Surprisingly, after infection with different strains of SARS-CoV-2, some clusters of symptoms appear to be associated with LC (20).

It is uncertain if the variety of LC symptoms is a feature of the SARS-CoV-2 infection itself, even as researchers and doctors learn more about them. Or how much it mimics previous episodes following respiratory—or other—viral diseases. In conjunction with COVID-19, this illness has been better studied and characterized due to the sheer volume of instances during the past three years. However, they have been linked to previous coronavirus epidemics and chronic post-viral disorders. 60% of SARS survivors reported experiencing chronic fatigue 12 months after their recovery (21) and up to 40% of survivors reported experiencing chronic fatigue approximately 41 months after the initial infection (22).

4.1 Biomarkers Classifying Clinical Manifestations in Long COVID

Since LC is a complicated multisystem disorder that exhibits a variety of clinical presentations, it would be excellent to classify it for the sake of diagnosis, prognosis, and treatment. The following categories comprise Although most of the biomarkers reviewed in this study apply to the whole LC, there are candidate-specific biomarkers for the primary distinguishing clinical aspects of LC: respiratory,

neurologic, gastrointestinal, and general symptoms like weariness and muscle discomfort. Figure 2 displays the main potential biomarkers for the traits that differentiate LC symptoms.



Figure(2) Candidate biomarkers classifying clinical manifestations in long COVID (LC). Abbreviations: ↑, increased; ↓, decreased; ANAs, antinuclear antibodies; CMV, Cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; EBV, Epstein–Barr Virus; GFAP, glial fibrillary acidic protein; GH, growth hormone; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance

5. Clinical Management and Therapeutic Strategies

5.1 Symptom-Based Approach

- ✓ Fatigue: pacing and energy conservation strategies
- ✓ Cognitive dysfunction: cognitive rehabilitation, sleep hygiene
- ✓ Dyspnea: pulmonary rehabilitation

5.2 Pharmacological Interventions

- ✓ Anti-inflammatory agents: low-dose corticosteroids, colchicine
- ✓ Anticoagulation for hypercoagulable patients
- ✓ Antihistamines and mast cell stabilizers for dysautonomia

5.3 Psychosocial Support

Multidisciplinary care with mental health support improves quality of life (15)

5.4 Ongoing Clinical Trials

RCTs are investigating antivirals, immunomodulators, and mitochondrial-targeted therapies (3).

6. Future Directions

- ✓ Standardized diagnostic criteria and validated biomarkers (2)
- ✓ Longitudinal studies to track recovery trajectories (11)
- ✓ AI-integrated multi-omics for personalized medicine (4)
- ✓ Targeted therapies for immune modulation and endothelial repair (5)
- ✓ Because of its high frequency and persistence after an acute infection, LC has a significant influence on society and healthcare. Considering rates of acute infection-related direct
- ✓ related immunity as well as less virulent variants of SARS-CoV-2, the relative significance of long-term effects linked to SARS-CoV-2 infection is becoming more significant.

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