

Advances in Research on the Diagnosis and Treatment of Long COVID-19

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Abstract

Since the outbreak of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), hundreds of millions of cases have been reported. Although COVID-19 was initially considered an acute respiratory disease, recent evidence suggests that a complex array of clinical manifestations and potential long-term sequelae—such as persistent fatigue, diarrhea, dyspnea, limited exercise tolerance, endocrine abnormalities, taste and smell dysfunction, and depression—may affect all COVID-19 patients, regardless of disease severity. These manifestations, collectively referred to as Long COVID, encompass over 200 symptoms affecting multiple systems. The pathogenesis of Long COVID remains unclear, and diagnosis typically relies on symptoms not attributable to any other disease, alongside blood tests and imaging. However, current diagnostic and treatment approaches are inadequate. Some related drugs have entered clinical trials, and symptom-based interventions are in place, but there is a lack of effective integration of research findings on Long COVID diagnosis and interventions. This article summarizes the current diagnostic and therapeutic strategies for Long COVID, proposing effective remedies and corresponding recommendations.

Keywords

Long COVID; Post-Acute Sequelae of COVID-19; COVID-19; Diagnosis; Clinical Features; Treatment Measures; Management Strategies; Exercise Therapy; Nutrients; Traditional Chinese Medicine; Acupuncture; Review

Introduction

Since the COVID-19 pandemic began in 2019, over 770 million COVID-19 cases and more than 6.9 million deaths have been recorded [1]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, enters host cells by binding to the angiotensin-converting enzyme 2 (ACE2) [2]. Subsequently, SARS-CoV-2 replicates and causes damage to multiple organs and tissues, leading to a complex array of clinical manifestations and potential long-term sequelae [3].

Long COVID, also referred to as persistent symptomatic COVID-19 and Post-Acute Sequelae of COVID-19 (PASC), is defined as COVID-19 symptoms lasting 4 to 12 weeks or post-acute sequelae lasting more than 12 weeks that cannot be attributed to any other disease. It is a multisystem disease that can occur regardless of the initial severity of the illness. Conservative estimates suggest a global prevalence of Long COVID at 43%, with rates of 51% in Asia, 44% in Europe, and 31% in North America. The global prevalence rates at 30, 60, 90, and 120 days post-infection are estimated at 37%, 25%, 32%, and 49%, respectively. Risk factors may include female gender, type 2 diabetes, the presence of underlying pathogens, specific autoantibodies, connective tissue disease, attention-deficit hyperactivity

disorder (ADHD), chronic urticaria, allergic rhinitis, a history of smoking, and obesity, although one-third of Long COVID patients have no identifiable pre-existing conditions. Long COVID encompasses a variety of adverse outcomes, with common new-onset diseases including cardiovascular, thrombotic, and cerebrovascular diseases, type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and autonomic dysfunction, especially postural orthostatic tachycardia syndrome (POTS). Symptoms can persist for years or even a lifetime, posing significant long-term risks to patients' physical, psychological, and social activities. A survey found that 44% of Long COVID patients had left the workforce, and 51% had reduced their working hours. The decline in quality of life and work capacity among Long COVID patients will have profound implications for social employment and economic development, underscoring the public health significance of Long COVID [4].

Early detection and diagnosis are crucial for effective treatment and improved prognosis. Long COVID treatment is often symptomatic and based on the affected systems. Several studies have shown that exercise can be an effective way to promote physical and mental health and treat certain diseases. Additionally, research on the use of nutrient supplementation, Traditional Chinese Medicine (TCM), and acupuncture for treating Long COVID is ongoing, though the evidence is fragmented and needs systematic review and synthesis. This article summarizes and reviews the latest research findings on Long COVID diagnosis and treatment measures to provide new insights for clinical treatment.

1. Literature Search Strategy

We conducted searches in PubMed, MEDLINE, China National Knowledge Infrastructure (CNKI), VIP Database, and other databases for original articles or reviews in Chinese and English that explore potential links between Long COVID and its diagnosis or treatment, up to March 2024. Chinese search terms included "长新冠" (Long COVID), "治疗" (treatment), "中药" (traditional Chinese medicine), and "针灸" (acupuncture). English search terms included "Long COVID," "Acute sequelae of COVID-19," "PASC," "diagnose," "Treatment," "measures," "management strategy," and "Marker." Inclusion criteria were literature discussing the diagnosis, treatment, management strategies, and clinical manifestations of Long COVID. Exclusion criteria were literature unrelated to the topic, of poor quality, or unavailable in full text. A total of 53 articles were included.

2. Clinical Manifestations and Diagnosis of Long COVID

Although COVID-19 was initially considered a respiratory disease, SARS-CoV-2 can damage multiple organ systems. This damage in various tissues is mainly attributed to immune-mediated responses and inflammation rather than direct viral infection. Multiple studies have revealed multi-organ damage associated with COVID-19. A prospective study on low-risk individuals focused on the heart, lungs, liver, kidneys, pancreas, and spleen, finding that 70% of 201 patients had at least one organ affected, and 29% had multiple organ damage. In a follow-up study of 536 participants over one year, 59% had single organ damage, and 27% had multiple organ damage. Subtle changes in hematological parameters related to Long COVID have been observed. Studies indicate that reduced lymphocyte counts are common in Long COVID, while most people's red blood cell counts return to normal. Changes in red blood cell morphology were noted in patients four and eight months after discharge, including decreased size and deformability of red blood cells in hospitalized and recovering COVID-19 patients. Individuals followed for six months with at least one Long COVID symptom had significantly higher mean corpuscular hemoglobin concentration (MCHC) compared to asymptomatic recoveries. Moreover, neutrophil count, BNP, C-reactive protein, IL-6, TNF- α , lactate dehydrogenase, D-dimer, and ferritin levels may be higher in Long COVID patients than in asymptomatic recoveries. Besides hematological changes, we summarized common system symptoms and diagnostic methods.

2.1 Cardiovascular System

Research has found that Long COVID patients experience long-term reduced vascular density, particularly affecting small capillaries, 18 months post-infection compared to control groups. Vascular endothelial growth markers ANG1 and P-selectin have shown high sensitivity and specificity in predicting Long COVID. Microclots detected in acute COVID-19 and Long COVID patients may lead to thrombosis and serve as attractive diagnostic and therapeutic targets. Cardiac MRI can assess heart damage in Long COVID patients. Among 100 previously infected patients, a study at 12 months post-infection found that 58% still had heart damage. Additionally, echocardiography and electrocardiography can evaluate arrhythmias. A widened QRS complex on ECG suggests heart damage.

2.2 Nervous and Cognitive Systems

Neurological and cognitive symptoms of Long COVID include sensory and motor symptoms, memory loss, cognitive impairment, paresthesia, dizziness, and balance problems, which typically impact daily life activities. One study found that 16% of patients experienced these symptoms 2 months post-infection, and 26% experienced them 12 months post-infection. Activation of the kynurenine pathway, particularly the presence of metabolites such as quinolinic acid, 3-hydroxyanthranilic acid, and kynurenine, has been linked to cognitive impairment in Long COVID. Auditory vestibular manifestations in Long COVID patients include tinnitus, hearing loss, and vertigo. Cognitive impairment in some patients may go unrecognized and can result from anxiety and depression, assessable through psychological evaluation scales. A report on over 1.3 million COVID-19 patients showed that psychological health issues such as anxiety and depression could normalize over time, but the risk of cognitive impairment (brain fog), seizures, dementia, psychosis, and other neurocognitive conditions persists for at least two years. These conditions may involve neuroinflammation and cerebrospinal fluid abnormalities. While liquid biopsy has been observed to have diagnostic potential for Long COVID, most evidence is based on preliminary studies with limited sample sizes. Imaging of microclots and corneal microscopy to identify small fiber neuropathy are potential diagnostic tools.

Moreover, some Long COVID patients exhibit retinal hemorrhage, cotton wool spots, retinal vein occlusion, corneal small nerve fiber loss, increased dendritic cell density, significant changes in pupillary light response, and retinal microcirculation impairment. These can be diagnosed with auxiliary examinations such as fundus fluorescein angiography, ocular OCT, or ocular ultrasound.

3. Changes in Long COVID Treatment

Managing the chronic health conditions triggered by Long COVID can be challenging due to their complexity, meaning they involve multiple components or pathogenic pathways that may lead to disease. Additionally, not all pathways operate simultaneously in all individuals, resulting in heterogeneity in the presentation of chronic health conditions. Personalized and precision medicine are emerging therapeutic approaches that can address the complexity and heterogeneity of chronic diseases and may be useful for Long COVID.

3.1 Respiratory System Treatment Measures

To better manage symptoms such as dyspnea and cough associated with Long COVID, a multidisciplinary approach is recommended. For managing dyspnea, self-management strategies, including avoiding pollutants, quitting smoking, and regular exercise, can alleviate exacerbated symptoms. Previous studies have shown that inspiratory muscle training and music-based respiratory training can improve chest symptoms and dyspnea and should be recommended for Long COVID patients. One study found that administration of umbilical cord mesenchymal stem cells (UC-MSCs) in COVID-19 patients resulted in significant improvement in symptoms and lung lesions one-year post-infection compared to the control group. The COVID-Rehab study proposed a cardiopulmonary rehabilitation program, which includes a supervised personalized exercise regimen (aerobic exercise, muscle strengthening, and breathing exercises) for treating Long COVID patients. Except for UC-MSC administration, these methods are simple, feasible, and can be applied in clinical practice in China.

3.2 Nervous System Treatment Measures

For neurological symptoms caused by Long COVID, the use of H1 and H2 antihistamines has been proposed to alleviate symptoms, though cognitive decline associated with H1 receptor blockers should be monitored. Additionally, transcranial magnetic stimulation (TMS) has shown significant improvement in fatigue, cognitive function, and depressive symptoms. For anosmia induced by COVID-19, Hummel proposed olfactory training to improve the olfactory function of affected patients. This training involves the use of four odorants (rose, eucalyptus, lemon, clove), with patients focusing on each odorant for approximately 10 seconds, twice daily, in the morning and evening. This method is simple to implement and has no side effects. Due to the unique regenerative capacity of olfactory epithelial cells, patients showed improved sensitivity to odors after 12 weeks of continuous training.

3.3 Psychological Health Interventions

Cognitive Behavioral Therapy (CBT) is recommended as a frontline psychological treatment in clinical practice. It primarily aims to change negative thinking and behavioral habits through dialogue. Studies have shown that the CBT intervention group experienced a greater reduction in depression, anxiety, stress, and DASS-21 total scores compared

to the control group, highlighting the effectiveness of CBT in improving patients' mental health. XiaoE, a CBT-based mental health chatbot, is a feasible and engaging digital therapy that provides accessible, self-guided mental health assistance for young people with depressive symptoms. Compared to the treatment-as-usual (TAU) group, the computerized CBT (cCBT) + TAU group showed significant reductions in Hamilton Depression Scale (HAM-D17), Hamilton Anxiety Scale (HAM-A), Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), and Athens Insomnia Scale (AIS) scores (all $P < 0.001$). These studies demonstrate the importance of CBT in alleviating psychological distress in Long COVID patients, making it applicable for treating anxiety, depression, and other psychological issues related to Long COVID.

4. Other Treatments for Long COVID

4.1 Immune Support Therapy

Research indicates that various dietary supplements and natural bioactive foods have been tested for combating Long COVID, with several showing therapeutic potential. These include amino acids, trace elements like iron, selenium, magnesium, bromelain, probiotics (mainly *Bifidobacteria* and *Lactobacillus*), and vitamin D, which play crucial roles in immune regulation, antimicrobial action, and accelerating virus clearance. Additionally, immune modulation can be achieved through intravenous immunoglobulin infusion, though this treatment is less commonly applied to non-hospitalized patients in China.

4.2 Traditional Chinese Medicine and Acupuncture

In China, traditional Chinese medicine (TCM) and acupuncture play significant roles in treating Long COVID. Studies report that Xiaochaihu Tang is one of the recommended TCM prescriptions during the recovery phase of COVID-19. The Shangjiao Xuanbi Tang, composed of loquat leaf, turmeric, belamcanda, bai tong cao, and fermented soy, has been found effective in treating post-COVID symptoms such as throat discomfort, cough, insomnia, and stomach discomfort. The traditional "three-volt plaster" therapy used in winter diseases treated in summer, including plaster, acupuncture, and tonics, has shown significant improvement in post-COVID symptoms. Research by Xu Zhongde and others has demonstrated that applying Xue's Sanyang San with modifications in elderly patients effectively treats heart and lung diseases related to Long COVID, with no cases progressing to severe illness or death.

Furthermore, a platform trial named STIMULATE-ICP has been established to evaluate interventions for Long COVID, such as famotidine and loratadine (antihistamines), rivaroxaban (an anticoagulant), and colchicine (an immunomodulator). Various other interventions, including remdesivir (NCT04978259), nirmatrelvir-ritonavir (NCT05595369), metformin (NCT04510194), ibudilast/pentoxifylline (NCT05513560), heparin (NCT05204550), leronlimab (NCT04678830), montelukast (NCT04695704), apixaban/atorvastatin (NCT04801940), infliximab/imatinib (NCT05220280), and vortioxetine (NCT05047952), are also being explored for Long COVID treatment.

5. Summary and Outlook

Long COVID affects various systems and organs throughout the body, presenting a wide range of complex symptoms, with fatigue, cough, sore throat, concentration issues, anxiety, muscle pain, joint pain, and loss of smell is common. Clinical studies have shown that various treatments can alleviate these symptoms, including symptom-based medication, rehabilitation training, psychological support, cognitive-behavioral therapy, nutritional supplements, exercise programs, and stem cell therapy. Despite the existence of intractable features, these could be crucial considerations in patient clinical management and clear research targets. As the exact mechanisms of Long COVID are still under investigation and no drugs are approved for Long COVID treatment, although hundreds of clinical trials have been registered, few have been widely implemented in clinical practice. The foreseeable healthcare demand for post-COVID-19 sequelae will continue to grow due to the global pandemic. However, current diagnostic and treatment strategies remain inadequate. Addressing these challenges necessitates integrating existing laboratory tests, appropriate health education, outpatient infrastructure, and rigorously designed clinical trials. Long-term follow-up on the efficacy and recovery of Long COVID patients is essential to identify potential organ or tissue damage and pathogenic mechanisms, ultimately improving the quality of life for Long COVID patients.

Author Contributions

Huiqi Sun was responsible for the conception and design of the article, collection, and organization of research data, writing and revision of the paper, and quality control of the article. Jiuxi Liu was responsible for reviewing the article and editing the tables.

Conflicts of Interest

There are no conflicts of interest in this article.

References

- [1] WHO coronavirus (COVID-19) dashboard, <https://covid19.who.int> (2023).
- [2] Wang C, Wang Z, Wang G, Lau JY, Zhang K, Li W. (2021). COVID-19 in early 2021: current status and looking forward. *Signal Transduct Target Ther.*, 2021 Mar 8; 6(1):114. doi: 10.1038/s41392-021-00527-1.
- [3] Nalbandian, A., et al. (2021). Post-acute COVID-19 syndrome. *Nat Med.*, 2021 Apr; 27(4): 601-615. Epub 2021 Mar 22. doi: 10.1038/s41591-021-01283-z.
- [4] Su, Y. et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 185, 881-895. e20.
- [5] Castanares-Zapatero, D., Chalon, P., Kohn, L., Dauvrin, M., Detollenaere, J., Maertens de Noordhout, C., ... Van den Heede, K. (2022). Pathophysiology and mechanism of long COVID: a comprehensive review. *Annals of Medicine*, 54(1), 1473-1487. <https://doi.org/10.1080/07853890.2022.2076901>.