Review

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Long COVID: current research and future directions

Rongling Zhang[1,2], Xiaoying Gu[3], Hui Zhang[1], Yuming Guo[4], Bin Cao[1,2,5,*]

[1] National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China;
[2]Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100730, China;
[3]National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Clinical Research and Data Management, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China;
[4]Senior Department of Infectious Diseases, the Fifth Medical Center of Chinese People's Liberation Army (PLA) General Hospital, National Clinical Research Center for Infectious Diseases, Beijing 100039, China;
[5]Tsinghua University-Peking University Joint Center for Life Sciences, Beijing 100084, China.

Abstract

Long coronavirus disease (COVID) is defined as the continuation or development of new symptoms three months after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and that last for at least two months, with no other explanation for their cause. This disease includes various clinical manifestations that affect multiple organ systems, such as complications in respiratory, cardiovascular, neurological, and musculoskeletal systems. The most commonly reported symptoms include fatigue, cognitive dysfunction, dyspnea, and chest pain; however, the prevalence and severity of these symptoms vary greatly among individuals. The underlying mechanisms of long COVID are complex and multifaceted, encompassing viral persistence, immune system dysfunction, mitochondrial abnormalities, endothelial impairment, and alterations in the microbiome. Further, long COVID has imposed a significant burden on individuals, healthcare systems, and the economy by impairing an individual's quality of life and functional capacity, thereby increasing costs and demand for care and rehabilitation services. This review summarizes the definition, phenotypes, mechanisms, and current treatment advancements of long COVID and highlights specific research directions for future investigation.

Keywords: SARS-CoV-2; COVID-19; Long COVID; Mechanism; Long term health

Long coronavirus disease (COVID), also known as post-COVID-19 condition or post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC), is a persistent and complex condition that follows acute COVID-19 illness.[1] It is characterized by a wide range of symptoms that can last for months or even years after infection. Estimates suggest that 6.6%–10.4% of individuals infected with SARS-CoV-2 continue to experience symptoms such as fatigue, palpitations, cognitive dysfunction, shortness of breath, among others, which can persist for several years. In addition to these symptoms, long-term effects may also impact patients' self-perception, work performance, and social engagement, further contributing to their overall burden.[1–5] A recent study revealed that the higher risk of multiorgan manifestations among infected people compared with non-infected controls gradually declined across three years after infection. There also remains a contribution to disability-adjusted life years (DALY) three years after infection.[6–12] Long COVID not only significantly impacts an individual's daily life but also leads to increased healthcare utilization, thereby resulting in an additional financial burden and even a loss of productivity.[13]

We have made some progress in exploring long COVID, but still lack a clear understanding of the phenotype, mechanism, and treatment of long COVID. Long COVID presents diverse clinical manifestations and complex symptoms, with its underlying biological differences between different phenotypes remaining poorly understood. Although several hypotheses have been proposed to explain the mechanism, the pathogenesis remains largely unexplained. Owing to the lack of well-defined disease phenotypes and biomarkers, as well as the unclear pathogenesis, treatment options are limited.[14–16] In recent years, the scientific community has made great efforts to combat the COVID-19 pandemic, but there is a long way to go for long COVID, which is a huge public health issue at this stage. A comprehensive exploration of long COVID necessitates multidisciplinary and multidimensional research approaches.

This review aims to discuss the issues and challenges associated with long COVID, including but not limited to, the lack of a

Rongling Zhang and Xiaoying Gu contributed equally to this work.
* **Corresponding author:** Bin Cao, E-mail: caobin_ben@163.com

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unified definition, phenotype, mechanism, and future research directions (Figure 1).

1. Definition

In May 2020, many COVID-19 survivors expressed, on popular social media platforms, that they had not fully recovered from the infection. They shared their experiences on social media and referred to it as "long haul," which led to the emergence of the term "long COVID."[17] As global attention on long COVID increased, more terms emerged to describe this condition, such as PASC, post-COVID syndrome, post-acute COVID syndrome, post-COVID condition, long haulers syndrome, and many others.

The primary definitions of long COVID come from the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), and the National Institute for Health and Care Excellence (NICE). Recently, the National Academies of Sciences, Engineering, and Medicine (NASEM) considered relevant limitations such as not placing it among infection-associated chronic conditions and not describing it as a distinct disease state, while accumulating clinical and scientific data to refine the definition of long COVID.[18]

The common aspect across the different versions of the definition of long COVID from the WHO,[19]CDC,[20] and the NICE,[21] is that all emphasize the occurrence of new, recurring, worsening, and persistent symptoms within a certain period after contracting the SARS-CoV-2. This applies to both adults and children (Table 1). However, the time requirements for defining long COVID vary among different institutions. The US CDC definition requires only that symptom be present at least four weeks after an acute COVID-19 episode. The NICE refines this definition by requiring that no alternative diagnosis explains the symptoms and that these persist for over 12 weeks. In contrast, the WHO requires that symptoms persist for at least two months and continue to present three months after being diagnosed with acute COVID-19.

Other countries have developed their own definitions, which are generally similar to WHO's definition, with a few countries adopting it directly. For example, the Spanish Ministry of Health defines post-COVID-19 as multiorgan symptoms such as respiratory or cardiopulmonary, musculoskeletal, and gastrointestinal, that persist or fluctuate after the acute phase of COVID-19, lasting at least three months, and not attributable to other causes.[22] Germany defines it as new symptoms, the worsening of pre-existing symptoms, or the exacerbation of

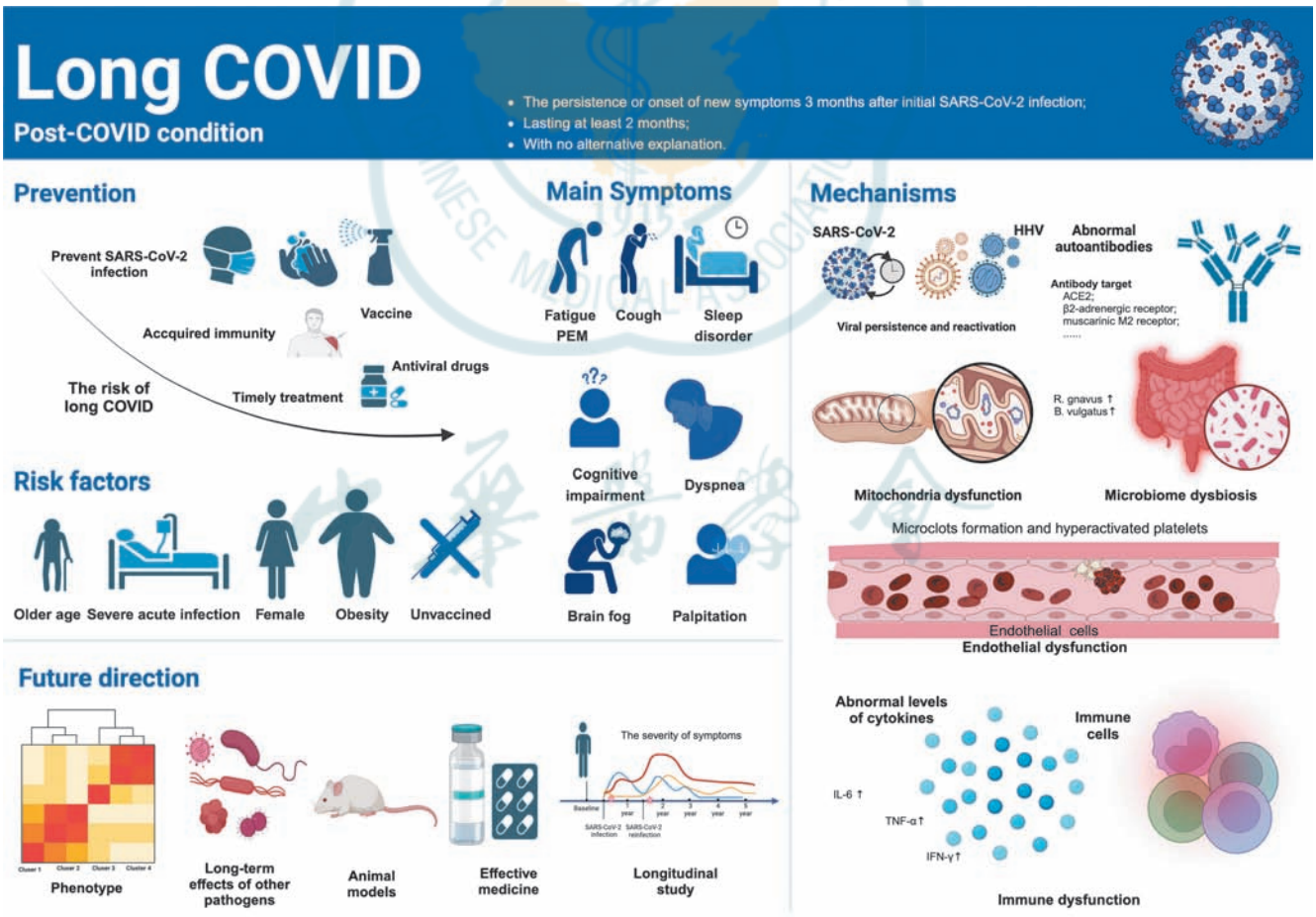

Figure 1: Overview of long COVID: definition, symptoms, mechanisms, and prevention strategies. Long COVID is a heterogeneous condition with various clinical manifestations and diverse underlying mechanisms. Our understanding of long COVID remains limited, and there is currently no effective treatment. Much work remains to be done in the future. COVID: Coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; IFN-γ: Interferon-gamma; PEM: Post-exertional malaise; HHV: Human herpesvirus; TNF: tumor necrosis factor; IL: interleukin; R. gnavus: Ruminococcus gnavus; B. vulgatus: Bacteroides vulgatus. The figure is created in Biorender. The agreement number is IA27TGN8ZF.

Table 1: Long COVID definition criteria

Organization	Name	Definition
WHO	Post-COVID condition/Long COVID	Usually, 3 months from the onset of COVID-19; symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis in individuals with a history of probable or confirmed SARS-CoV-2 infection
CDC	Long COVID	Signs, symptoms, and conditions that continue or develop after initial SARS-CoV-2 infection and last more than 4 weeks
NICE	Ongoing symptomatic COVID-19	Symptoms that are unexplained by an alternative diagnosis and persist for 4–12 weeks after acute COVID-19
	Post-COVID-19 syndrome	Symptoms that are unexplained by an alternative diagnosis and persist for more than 12 weeks after acute COVID-19
NASEM	Long COVID	chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems

COVID: Coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; CDC: US Centers for Disease Control and Prevention; NICE: U.K. National Institute for Health and Care Excellence. NASEM: National Academies of Sciences, Engineering, and Medicine. The definition of long COVID provided by the CDC has change following the release of new definition by NASEM.

underlying conditions.[23] Australia's states and territories, as well as South Africa, generally use the WHO definition.[24]

The NASEM aimed to develop an improved long COVID definition that better reflects patients' needs and incorporates insights from experts across various fields such as feasibility in application, acceptability to affected parties and potential effect for patients.[18] The new definition was described as an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.[25] The NASEM definition was considered simple, easy to understand, and readily communicated, opting to use the term "long COVID" rather than the more specialized term "PASC." The NASEM definition is intentionally inclusive and designed to be readily communicated among patients, family members, caregivers, and others. Additionally, instead of treating long COVID as a diagnosis of exclusion, it acknowledges that other diagnosable conditions—such as interstitial lung disease, postural orthostatic tachycardia syndrome (POTS), and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)—can coexist as distinct disease states. This approach affirms the diversity and complexity of long COVID, thereby enabling an objective and comprehensive description of the condition.[18]

It is important to acknowledge that any definition has its own strengths and limitations, but a unified definition is the foundation for understanding a disease and the basis for related research. It helps to facilitate the research design and execution of the diagnosis, treatment, and management of long COVID, ultimately leading to better prognosis of both long COVID and other IACCs.

2. The phenotypes of long COVID

Long COVID is recognized as heterogeneous, including over 200 symptoms. However, the phenotypes of long COVID are still not clear. Existing studies distinguish disease subtypes of long COVID by symptom clustering, organ systems, and previous disease description.

2.1. Symptoms or organ clustering

Existing studies have identified different subtypes of long COVID through various machine learning methods.[26–28] The major symptoms of long COVID are chest pain, difficulty with breathing, pain when breathing, painful muscles, ageusia or anosmia, tingling extremities, lump in throat, feeling hot and cold alternately, heavy arms or legs, and general tiredness.[29] Zhang leveraged the electronic health record data to identify the four sub-phenotypes: cardiac/renal, respiratory/sleep/anxiety, musculoskeletal/neurologic, and digestive/respiratory.[30] Other similar studies provided similar patterns of classification or clustered them by the number of symptoms.[31] Tanayott developed a PASC symptom assessment based on participant-reported symptoms, categorizing them into four distinct clusters: Cluster 1 was characterized by loss or change in smell or taste; Cluster 2 featured post-exertional malaise (PEM) and fatigue; Cluster 3 included brain fog, PEM, and fatigue; and Cluster 4 was marked by fatigue, PEM, dizziness, brain fog, gastrointestinal symptoms, and palpitations.[2]

Symptoms are a reflection of organ damage. Grouping symptoms according to the corresponding organ or body system is another innovative approach. This method categorizes and maps symptoms to different organ systems based on the heterogeneity of long COVID.[32,33] A systematic review categorized the various symptoms into seven body systems, which can be divided into respiratory, nervous system, cardiovascular, mental health, digestive, skin, and ear, nose and throat system.[34] These organs systems often exhibit persistent symptoms that significantly impact individual health, and understanding the damage to these systems is crucial for elucidating the pathophysiology of long COVID. In particular, the respiratory, nervous, and cardiovascular systems, are not only common sites of long-term effects but also serve as key areas for exploring disease mechanisms and guiding future treatment strategies.[10,35–37]

The relationship between proteomics and metabolomics data with symptom clusters can provide a more comprehensive understanding for different symptom clusters.[26,38] In a recent study, IL-1R2, MATN2, and COLEC12 were found to be associated with cardiopulmonary symptoms, fatigue, and anxiety/depression. Further, MATN2, CSF3, and C1QA levels were found to be elevated in patients with gastrointestinal (GI) symptoms, and C1QA was also elevated in those with cognitive impairment. Other markers of altered neural tissue repair, such as SPON-1 and NFASC, were found to be elevated in patients with cognitive impairment; it was also revealed that elevated SCG3 indicates a disorder of the brain–gut axis and is also elevated

in GI symptoms.[26] Analyzing changes in specific protein and metabolite levels among different symptom clusters may not only be used for early diagnosis but also provide important clues for future exploration of underlying mechanisms.

Mapping symptoms to relevant organ systems enables researchers to design studies and interventions more effectively and target specific biomarkers within systems. This approach provides a new perspective on understanding and managing long COVID.

2.2. Immune feature

Disease progression or recovery from long COVID can be characterized by inflammatory markers. According to a recent study, long COVID can be divided into inflammatory and non-inflammatory clusters.[39] Participants in the inflammatory cluster exhibited persistent inflammation and can be categorized into two major clusters: one characterized by significant IFN-γ and evidence of IFN-γ- and NF-κB-driven inflammation, along with upregulation of various inflammation-driven cytokines, chemokines, receptors, and immune checkpoint proteins. The other cluster also showed evidence of persistent IFN-γ and NF-κB-driven inflammation, but with more pronounced features of neutrophil activation, degranulation, and/or NETosis, along with evidence of ongoing type I IFN signaling.[38] In the inflammatory cluster, IL-6, IL-8, IL-1β, and C-reactive proteins were significantly increased compared to those in the non-inflammatory cluster. High levels of neutrophil activity and active B cell profile were also observed in the inflammatory cluster.[40]

The manifestations of long COVID are highly heterogeneous across individuals. These variations may be associated with different efficacies of treatments or care approaches and clinical outcomes. Understanding the various subtypes could enhance diagnostic accuracy. It can also help healthcare providers develop effective and personalized treatment strategies as well as aids in elucidating the underlying mechanisms of long COVID, thereby facilitating more targeted research efforts. Furthermore, researchers and clinicians can better obtain knowledge of the disease progression and outcomes, ultimately improving patient management and quality of life.

2.3. Comparison of long COVID phenotypes with other conditions

Long COVID shares symptoms with other known conditions, which has led researchers to compare it with diseases such as ME/CFS, POTS, and post-intensive care syndrome (PICS) to better understand its characteristics.[41] Through such comparisons, researchers have been able to identify common features and differences between these diseases and further understand the pathophysiological mechanisms of long COVID. For example, ME/CFS and long COVID both exhibit fatigue, PEM, cognitive deficits, and exercise intolerance,[42] while POTS and long COVID may share heart rate abnormalities and blood pressure regulation problems.[43] PICS also shares similarities with long COVID in terms of chronic inflammation and long-term recovery.[44] These comparative studies not only help to deepen the understanding of long COVID but can also provide new perspectives on diagnosis and treatment. By learning from the management of other diseases, physicians can explore more effective treatments and interventions for long COVID. In addition, these comparative studies may also reveal common biomarkers and potential therapeutic targets, thus promoting integrated research across diseases.

3. The mechanism of long COVID

Existing research has suggested a few possible mechanisms for long COVID, including viral persistence and reactivation, immune dysregulation, microbiome dysbiosis, endothelial dysfunction and mitochondrial dysfunction[45]. These mechanisms do not exist independently; rather, they may interact in a complex manner to cause symptoms. Although some progress has been made in this regard, the exact pathogenesis is still unclear.

3.1. Viral persistence and reactivation

Before the COVID-19 pandemic, there was already some research focusing on patients who experienced long-term fatigue and joint pain due to other viral infections. For example, the chikungunya virus antigens can be detected in the muscle cells of patients, which is a contributing factor to the development of chronic chikungunya arthritis[46]. Similarly, the persistence of the virus itself may be a cause of long COVID.[47–49] SARS-CoV-2 RNA or protein has been identified in tissues several months after onset of the disease, and recent research has revealed that it can be detected in peripheral blood.[50] Our team conducted a study and found that SARS-CoV-2 viral RNA was detected in tissue samples from patients recovering from mild COVID-19, with median follow-up time being four months after infection. The viral RNA was detected in 10 different solid tissues, plasma, and blood cells. Importantly, recovered patients with detectable viral RNA had higher risk of developing long COVID compared to those in whom viral RNA was undetectable. Similarly, patients with higher viral copy number were more likely to experience long COVID sequelae than those with a low virus copy number.[51] Another study demonstrated that even one year after infection, SARS-CoV-2 spike (S) protein could be detected in 60% of long COVID patients, but not in controls. Moreover, the more the number of organ systems involved in the symptoms, the greater the amount of S protein detected.[52]

Swank's study found that plasma samples from multiple long COVID patients revealed detectable levels of the spike protein, but it was only detectable at two to twelve months after infection, not consistently across all time points.[52] SARS-CoV-2 in the host may be inactive for certain periods of time and resume protein production and/or replication at other times (e.g., when immune control is altered). This phenomenon has been reported in other viral infections as well. Adaken *et al*. reported that the decline was followed by a subsequent rise in plasma levels of neutralizing antibodies in survivors of Ebola virus disease as the "decay-stimulation-decay" pattern. This cyclical recovery of neutralizing antibodies may correspond to periods of more active replication at the Ebola virus host site followed by periods of relative inactivity.[53] In contrast, the current levels of detection may not be able to detect the presence of reservoirs in circulating tissues or sites; it is also possible that proteins bind to antibodies and, thus, prevent recognition by the assay. In addition, the SARS-CoV-2 protein may be trapped and persist in certain immune cells or immune organs, thereby limiting the induction and expression of immune-mediated inflammation in the special region. A state of immunity is reached in which the protein is neither cleared nor detected.

Another possible mechanism contributing to the development of long COVID could be the reactivation of latent viruses due to an altered host immune response during and following acute SARS-CoV-2 infection. Research has revealed that multiple human herpesviruses (HHV) are reactivated in COVID-19 patients.[54] In addition, the Epstein-Barr virus (EBV) is particularly more common in patients with long COVID than in those without long COVID, and HHVs are associated with various symptoms, including headache, myalgia, neurological disorders, and pulmonary disorders.[55–57]

3.2. Immune dysfunction

Immune dysfunction in long COVID patients can manifest as persistent immune activation, immune exhaustion, or the production of autoantibodies. These dysfunctions may contribute to a vicious cycle, potentially triggering or worsening long COVID symptoms.

Compared to those who have not been infected with SARS-CoV-2 and those who have fully recovered, long COVID patients suffer from excessive inflammation, with IL-6, TNF-α, and IL-1β remaining elevated.[1] IL-1β, IL-6, and TNF are mainly secreted by monocytes and macrophages upon inflammatory stimuli. The elevation of IL-1β, IL-6, and TNF may be associated with the persistent presence of viral components or antigens in the body, or with chronic reprogramming of immune cells.[58] Notably, a few months to one year after SARS-CoV-2 infection, the immune system undergoes sustained alterations in the innate immune phenotype and epigenetic programming of hematopoietic stem and progenitor cells (HSPC), thereby leading to the activation of different transcription factors, alterations in the modulation of inflammatory programs, and a sustained increase in myeloid cells. It has been found that severe COVID-19 reprograms hematopoiesis and establishes an epigenetic memory in HSPC as well as in daughter myeloid cells, which persists for up to one year.[59] Inflammatory cytokines drive immune cell dysregulation, thereby contributing to the development of long COVID.

Such prolonged inflammatory responses not only impair recovery but also actively contribute to disease progression by reinforcing a feedback loop of immune signaling and tissue damage. IFN-γ is believed to be the main cytokine associated with long COVID.[39] Benjamin A. Krishna *et al*. identified IFN-γ as a central mediator in interactions between T cells and monocyte-derived macrophages in long COVID patients with pulmonary symptoms, thus contributing to sustained lung inflammation and fibrosis. They observed an increased proportion of monocyte-derived alveolar macrophages (MoAM) and T cells along with a decreased proportion of tissue-resident alveolar macrophages (TRAM), which promoted pro-fibrotic inflammatory pathways in the lungs. Therefore, anti-IFN-γ suppressed the inflammatory pathway of MoAM and led to a decrease in pro-pulmonary fibrosis features, which could be a possible direction for future therapy.[60] Excessive inflammation can also affect the nervous system.[61] Chris Greene's study suggested that continued systemic inflammation and a persistent local blood–brain barrier dysfunction is a key feature of the long-term brain fog associated with long COVID. It is characterized by increased blood–brain barrier permeability and elevated S100β. Compared with recovered individuals, brain fog patients had increased levels of plasma transforming growth factor-β (TGF-β), which correlated with abnormal blood–brain barrier permeability and significantly correlated with structural changes in the brain, thereby suggesting that TGF-β may play an important role in neuroinflammation and structural changes in the brain.[62]

Immune exhaustion may be another feature for long COVID. Kalin studied blood samples from 27 people with long COVID and 16 people who fully recovered, all collected 8 months after their initial COVID-19 infection. They used various techniques, including CyTOF (a type of immune cell analysis), RNA sequencing, and antibody testing, to compare the immune system between the two groups. The research found that patients with long COVID had increased frequencies of CD4+ T cells poised to migrate to inflamed tissues and exhausted SARS-CoV-2-specific CD8+ T cells and higher levels of SARS-CoV-2 antibodies. Further, SARS-CoV-2-specific CD8+ T cells, but not total CD8+ T cells, more frequently expressed the exhaustion markers PD-1 and CTLA4, which is consistent with ongoing stimulation by viral antigens.[63] Klein also found that the median relative percentage of circulating CD4+ central memory cells was significantly lower in the long COVID group and expressed PD-1 and Tim-3.[57]

The production of multiple auto-associated antibodies observed in long COVID patients has been reported by several studies.[57,64–67] Autoantibodies against ACE2, β2-adrenergic receptor, muscarinic M2 receptor, G-protein-coupled receptor antibodies, as well as antinuclear antibodies, antiphospholipid antibodies, and other auto-associated antibodies have been reported in patients with long COVID. SARS-CoV-2 infection was associated with increased risk for incident autoimmune inflammatory rheumatic diseases compared with matched patients without SARS-CoV-2 infection.[68] Not only is there an increase in prevalence, but antibody titers are also strongly correlated with symptoms. These antibodies are closely related to the symptoms of patients with chronic coronary symptoms, with antinuclear antibodies persisting for up to one year after infection and associated with fatigue, cough, and dyspnea.[69] Elevated antibody titers also increase the risk of cognitive impairment.[70] Further, G protein-coupled receptors, alpha-adrenergic, and beta-adrenergic receptors are associated with a variety of autonomic dysfunctions, including POTS, constipation, and paralytic bowel obstruction. Certain autoantibodies cause clear harm; just like certain autoimmune diseases, they target a specific tissue and play a primary role in triggering illness.[71] Recently, Iwasaki and Jeroen den Dunnen isolated antibodies from the blood of long COVID patients and transferred them to healthy mice to see if they would cause similar symptoms or lead to immune abnormalities[72,73]. The mice that received the antibodies developed different symptoms and exhibited behavioral changes. They showed a decrease in their mechanical sensory threshold and displayed a trend toward muscle weakness as well as increased thermal sensitivity when subjected to heat stimulation. This may be related to the fact that specific autoantibodies bind to certain sites, which, in turn, trigger specific symptoms. These studies could strengthen the direct link between diseases and autoantibodies.

The exact extent to which immune disorders affect long COVID symptoms is still not fully understood. However, owing to recent advances in multi-omics technology, researchers can gain valuable insights at both the cellular and molecular levels, thereby leading to a deeper understanding of how these immune abnormalities affect the course and symptomatic manifestations of long COVID. According to the blood transcriptomic analyses,

212 genes were identified to be differentially expressed between individuals with long COVID and controls. Several viral RNAs were upregulated: nucleocapsid, ORF7a, ORF3a, Mpro, and host RNAs (ACE2/TMPRSS2 receptors, DPP4/FURIN proteases). Alterations in metabolites may be closely related to symptoms.[74] Viral infection and type I interferon-driven inflammation lead to reduced serotonin. The reduction of peripheral serotonin impedes vagal activity, which impairs hippocampal responses and memory.[75] Our team's research reveals four different recovery patterns by proteomic. The majority of immune response pathways can return to baseline level two years after infection. However, pathways related to neuron generation and differentiation revealed persistent suppression within two years, with slower recovery rates, and fail to return to normal. Multidimensional immunophenotyping and unbiased machine learning methods were able to better identify biological features associated with long COVID.[76,77]

3.3. Mitochondrial dysfunction

Mitochondrial dysfunction is believed to be one of the key mechanisms contributing to the persistence of symptoms in patients with long COVID. Studies have revealed that this dysfunction may lead to decreased energy production, increased oxidative stress, and sustained activation of inflammatory responses, which can trigger a variety of long-term symptoms, including chronic fatigue, cognitive impairment, and exercise intolerance.[78] Mitochondrial respiration and bioenergetics, as well as mitochondria-related gene expression, are abnormal in patients with long COVID.[79,80] These abnormalities suggest impaired mitochondrial energy production, which may underlie symptoms of fatigue and muscle weakness.[81] Simultaneously, disruption of electron transfer promotes the production of reactive oxygen species, thereby leading to oxidative stress, which further causes structural damage to cells. Elevated levels of circulating biomarkers associated with oxidative stress and mitochondrial damage—such as F2-isoprostane, malondialdehyde, and reduced levels of antioxidants such as coenzyme Q10—are observed in long COVID patients; these biomarkers point to oxidative stress as a contributing factor to mitochondrial dysfunction in long COVID.[82]

3.4. Endothelial dysfunction

Abnormal coagulation is a potential risk factor for COVID-19, and elevated D-dimer has also been observed in patients with long COVID, which increases the risk of thromboembolic disease. Amyloid deposits were found in plasma samples from long COVID, thereby revealing the possibility of micro-thrombosis.[83] Angiogenic markers, such as angiopoietin-1 and P-selectin, demonstrate high accuracy in identifying individuals with long COVID.[84] Carlo's research indicated enhanced complement activation and thrombus inflammation in long COVID cases. Both classical and alternative complement pathways are implicated in long COVID.[84] Specifically, C5bC6 levels were elevated during the acute phase and at the six-month follow-up in long COVID patients, while C7 complex levels were reduced. Furthermore, markers of tissue damage—including von Willebrand factor (vWF) and its regulatory component ADAMTS13—were detected, thus indicating extensive vascular injury.[84]

3.5. Microbiome dysbiosis

Current evidence has fully demonstrated that the microbiota in COVID-19 patients undergoes significant alterations. These changes are associated with the onset or severity of the disease and play a critical role in the pathogenesis of long COVID. Furthermore, they have clinical utility in predicting and diagnosing for long COVID.[85] Comparing different stages (acute phase, recovery phase, and post-recovery), it was found that the gut microbiota exhibits dynamic changes. Alpha and beta diversity values were significantly different in patients who have recovered from COVID-19 compared to uninfected controls at three months after discharge.[86] Recovered patients who did not develop long COVID show a gradual restoration of gut microbiota within six months to one year.[87,88] Further, the gut microbiome of long COVID patients was characterized by higher levels of Ruminococcus gnavus and Bacteroides vulgatus and lower levels of Faecalibacterium prausnitzii. Persistent respiratory symptoms were correlated with opportunistic gut pathogens, and neuropsychiatric symptoms and fatigue were correlated with nosocomial gut pathogens, including Clostridium innocuum and Actinomyces naeslundii after six months of infection.[87] Long COVID patients had obvious gut microbiota dysbiosis, including significantly reduced bacterial diversities and lower relative abundance of short-chain fatty acids (SCFAs)-producing salutary symbionts in one year.[88] Thus, not only is the gut microbiome affected, but the oral microbiome is also altered in long COVID patients. Haran found that the abundance of bacteria from the genera Prevotella and Veillonella was higher.[85] Deyu Zhang *et al.* also discovered ectopic colonization of gut microbes in the oral cavity of long COVID patients with gastrointestinal symptoms, including 27 commonly differentially abundant genera within the phylum Proteobacteria. Dysbiosis of the gut microbiome can also be associated with the toxic metabolite 5-sulfoxymethylfurfural.[89]

4. Current state of treatment

It is undeniable that current treatment options for long COVID remain rather limited. Currently, the treatment being explored mainly focuses on antiviral therapy, inhibition of inflammation, improvement of mitochondrial function, and regulation of microbiome dysbiosis.[90–93] Although very few studies have shown positive results, the treatment is still unable to fully respond to the needs of long COVID people with different subtypes.

Encouragingly, the exploration of long COVID treatment has taken a step forward, and the number of related studies has increased significantly. As of January 15, 2025, a search for "long COVID" on the ClinicalTrials.gov website returned 548 studies, of which 160 are completed and 346 are interventional. Ongoing interventional studies encompass various approaches, including drug interventions (including antiviral drug, herbal medicine, monoclonal antibody etc.), rehabilitation, dietary supplements, physical therapy, acupuncture, psychological support, and electronic software support. The main intervention clinical trials are presented in Table 2.

Further, antiviral treatments include Paxlovid, Larazotide, Ensitrelvir, and Truvada/Selzentry, with lingering virus as the major target.[94] The STOP-PASC randomized clinical trial is the first to test Paxlovid for treating long COVID.[91] Although this

Table 2: The major possible effective intervention clinical trial for long COVID

Intervention	Enrollment	Start date	End date	Registry
Antiviral drugs				
Nirmatrelvir/ritonavir	100	2023-04-14	2024-08-27	NCT05668091
	400	2024-01-31	2024-03-31	NCT05823896
	900	2023-07-26	2025-10	NCT05595369
	168	2022-11-08	2023-09-12	NCT05576662
Ensitrelvir	40	2024-04-09	2025-12-31	NCT06161688
Truvada/Selzentry	90	2024-06	2026-01	NCT06511063
AER002	30	2023-08-01	2025-07-31	NCT05877508
LAU-7b	270	2023-11-20	2024-08-31	NCT05999435
Larazotide	48	2023-05-31	2026-03-31	NCT05747534
Immunomodulatory therapy				
IVIG	45	2023-07-10	2025-12-15	NCT05350774
	200	2024-03-11	2026-03	NCT06305793
Baricitinib	550	2024-06-15	2029-12-30	NCT05858515
MSCs	80	2023-02-15	2025-02-15	NCT05808400
	76	2023-09-01	2026-08-31	NCT06492798
BC007	119	2023-06-16	2024-11-30	NCT05911009
Methylprednisolone	418	2023-10-01	2025-03-31	NCT05986422
Symptom Management				
Ivabradine	180	2024-03-11	2026-03	NCT06305806
	250	2023-06-14	2024-09-01	NCT05481177
Ivabradine/IVIG	380	2024-03-11	2026-03	NCT06305780
SIM01	448	2021-06-25	2025-12-31	NCT04950803
Metformin	16	2024-04	2024-10	NCT06147050
Fluvoxamine/Metformin	1500	2023-10-18	2025-05-18	NCT06128967
Fluvoxamine	300	2023-05-15	2025-05-15	NCT05874037

The table lists the main interventional treatments for long COVID found on ClinicalTrials.gov, excluding rehabilitation therapies such as physical rehabilitation, dietary therapy, and exercise. COVID: Coronavirus disease; IVIG: Intravenous Immunoglobulin; MSCs: Mesenchymal stem cells.

study did not show positive results, more detailed consideration—including but not limited to the selection of study population, dosage and timing of drug administration—and more appropriate clinical endpoints are still needed for more comprehensively demonstrating the effectiveness of an antiviral drug for long COVID. Another strategy involves delivering monoclonal antibodies designed to bind to and eliminate the lingering virus. AER002 (neutralizes SARS-CoV-2) and BC007 (neutralizes functional autoantibodies) are potential medicines for long COVID. AER002 (P2G3) is a long-acting fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) selected from the plasma of COVID-19 convalescent and vaccinated patients, with potential for treating COVID-19. It can neutralize Alpha, Beta, Delta (B.1), and Omicron (BA.1, BA.1.1, BA.2, BA.4, BA.4.6, BA.5) variants (but not BQ.1.1, XBB.1, and XBB.1.5). Moreover, it may neutralize the non-replicating S-protein, which could be the reason for its potential use in treating long COVID.[95]

Mesenchymal stem cells (MSCs) possess immunomodulatory and anti-inflammatory properties. The use of MSCs to treat COVID-19 patients has shown to be safe and effective.[96–98] Since more evidence is revealing that long COVID may be caused by persistent inflammation, the proposed anti-inflammatory of stem cell-based therapies is reasonable. In addition, clinical trials involving stem cells are currently underway.

Some long COVID trials are targeting immune dysfunction, such as the immune-modulating drug for rheumatoid arthritis baricitinib. Baricitinib, a Januse Kinase 1 (JAK 1) and 2 (JAK 2) inhibitor, is the first immunomodulator found to reduce mortality in COVID-19 patients. The effective of baricitinib for long COVID is unclear. But Sun *et al*.'s research has identified that baricitinib may merit consideration for treating long COVID.[61,99]

Functional autoantibodies (fAABs) are detectable in blood tests in long COVID patients. Researchers transferred antibodies from patients with long COVID into healthy mice; this resulted in symptoms such as heightened pain sensation and dizziness.[72,73] Further BC007 targeted harmful fAABs implicated in a range of autoimmune conditions to treat long COVID.[100]

Many researchers have studied the alleviation of neuropsychiatric symptoms associated with long COVID through interventions such as transcranial direct current stimulation (tDCS) (NCT05780450, NCT05092516), acupuncture (NCT06633666, NCT06476496, NCT05890508, NCT05212688), vagus nerve stimulation (NCT05918965), and stellate ganglion block (NCT06055270). Furthermore, numerous studies focus on rehabilitation exercises (NCT06492577, NCT06404047, NCT05855356) and psychological support (NCT06045338) to address the broad spectrum of long COVID-related symptoms.

In addition, nutritional supplementation strategies—including vitamin D supplementation (NCT05633472), VSL#3® (NCT05874089), ImmuneRecov (NCT06166030), Immulina™ (NCT05524532), nicotinamide riboside (NCT05703074), and nitrite supplementation (NCT05618574)—are being investigated for their potential to alleviate long COVID symptoms.

Moreover, nutritional supplementation is a convenient and sustainable treatment method. In an RCT study in which vitamin D was administered to long COVID patients experiencing fatigue or neuropsychiatric symptoms revealed that the vitamin helped to reduce fatigue, alleviate anxiety, and improve cognitive symptoms.[101] However, a systematic review of vitamin treatments for long COVID indicates that the effects of vitamins on treating long COVID require further clarification.[102] This aspect may require more reliable clinical trials for verification.

5. Directions for future research

Compared to other diseases, it is reassuring to see that researchers worldwide have made significant progress in such a short time, from recognizing the disease to understanding it. However, our understanding of long COVID remains unclear and requires further investigation.

5.1. Prevention of long COVID

Undoubtedly, the best way to prevent long COVID is to prevent SARS-CoV-2 infection and reinfection. Primary prevention measures—including practicing good hygiene and taking steps for cleaner air, particularly in schools and healthcare settings—can reduce the risk of infection. It is also advisable to wear masks in enclosed areas, particularly in healthcare environments, to further mitigate risk. Other social distancing measures such as teleworking can also contribute to lowering transmission rates. These combined efforts are essential to reducing both the immediate and long-term impacts of COVID-19. Moreover, vaccination remains a cornerstone of primary prevention, effectively preventing long COVID and reducing the risk of severe outcomes.[103] Secondary prevention through robust testing and epidemiological surveillance remains vital. Identifying symptoms early and conducting timely tests is essential to promptly confirm whether they are related to COVID-19. This level of prevention helps in the early detection of COVID-19 cases, thereby enabling timely intervention.

Further, tertiary prevention involves antiviral treatment. Administering antivirals during the acute phase serves as a significant preventive measure, potentially reducing the risk of long COVID.[14,15] However, it is important to note that the emergence of new variants of the virus may necessitate a reevaluation of their impact on the development and management of COVID-19.

Based on current evidence, the implications of long COVID should be taken into account in future public health clinical practices and vaccine policies. Enhancing indoor air quality, developing vaccines that remain effective against SARS-CoV-2 mutations, and ensuring the early use of antivirals will all be crucial for preventing long COVID.

5.2. Identifying high-risk populations and mechanisms in long COVID

Long COVID is a complex and heterogeneous condition. Identifying its potential risk factors and the populations at risk is essential for early detection and intervention. Previous studies have suggested that the female sex, older age, more severe and acute infection, obesity, and unvaccinated COVID-19 patients have a higher risk of long COVID.[104] Understanding these high-risk groups can provide valuable insights for investigating the potential mechanisms underlying the disease. For example, gender differences play a significant role in both the severity of the acute phase and the development of long COVID. While men experience more severe infection and higher mortality during the acute phase, women have a higher likelihood of developing long COVID.[105,106] These differences reflect variations in innate and adaptive immunity. In male patients with long COVID, TGFβ1 levels are elevated during the acute infection phase, whereas this is not the case for females.[107] Obesity, a metabolic proinflammatory state, is another key risk factor. It shares several characteristics with long COVID, promotes persistent inflammation, and contributes to the persistence of symptoms.[108] Integrating these risk factors into the exploration of long COVID mechanisms could enhance our understanding and, thus, provide both deeper insights and greater practical relevance to why certain populations are more vulnerable to developing the condition.

5.3. The prevalence of long COVID

Long COVID not only impacts individuals' lives but also affects healthcare systems and public health policies. By synthesizing existing evidence, Ziyad *et al*. estimated the global prevalence of long COVID, finding that by the end of 2023, the cumulative incidence globally reached approximately 400 million people.[109] A national survey in Scotland reported the prevalence rates of 6.6%, 6.5%, and 10.4% at 6 months, 12 months, and 18 months, respectively.[110] According to the latest CDC data, an estimated 6.9% of noninstitutionalized adults in the US who have previously contracted SARS-CoV-2 experience long COVID.[111] In addition to national surveys, several meta-analyses have clarified the prevalence of long COVID across different time points, symptoms, and regions.[112–114] However, due to the lack of standardized population-based collection methods, interpreting long COVID prevalence remains a cautious endeavor.

During the COVID-19 pandemic, numerous evolutions of SARS-CoV-2 were observed. The Omicron variant of SARS-CoV-2 is associated with less risk of long COVID than the Delta and pre-Delta variants. The authors noted that the reduction in the cumulative risk of PASC transitioning from the pre-Delta and Delta eras to the Omicron era is attributable to two main factors: effects related to the pandemic era and vaccination.[103] In the pandemic era, as the virus evolves, there is a trend towards enhanced transmission and sustained immune escape, while generally reducing the severity of the disease, thereby affecting the prevalence of long COVID.[115] A meta-analysis of primary studies involving 620 221 participants estimated that two doses of vaccine reduces the risk of long COVID by 36.9% and three doses reduces the risk by 68.7%.[116] The incidence of long COVID varies among different variants, and while these differences are closely related to the widespread use of vaccines, the unique and complex effects of each variant on long COVID cannot be overlooked.

Future research needs to establish standardized definitions and explore the prevalence of long COVID across different symptoms and patient populations, considering factors such as demographic characteristics, comorbidities, and vaccination status. This will provide a solid foundation for the management of long COVID patients and the development of public health policies in the future. Additionally, drawing from the research experience on long COVID, we can explore the similarities and differences with other post-acute infection syndromes (influenza,

respiratory syncytial virus infections, and pathogens not limited to the virus). Establishing a comprehensive framework that integrates findings from multiple post-acute infection syndromes will not only enhance our ability to effectively address long COVID but also strengthen our overall response to similar health crises in the future.

5.4. The long COVID phenotype and mechanisms

Long COVID is a heterogeneous disease, with various phenotypes that can be classified based on clinical symptoms (number and severity) and immune status (inflammatory or non-inflammatory). It has shown significant overlaps among clusters, thereby suggesting that long COVID may be a complex post-viral illness affecting multiple systems. This can manifest as single-organ involvement or multi-organ involvement. Moreover, the symptoms may be associated with multiple mechanisms. For instance, fatigue—a prevalent symptom of long COVID—can result from mitochondrial dysfunction impairing energy production or endothelial dysfunction leading to tissue hypoxia.[24] Future research should strive to comprehensively explore and harmonize the relationship among the different mechanisms and long COVID phenotypes, clarify the pathophysiological characteristics of distinct patient populations, and investigate the interactions among different mechanisms. Thus, continued in-depth studies on immune dysregulation, tissue damage, and the characteristics of susceptible populations are crucial. Additionally, utilizing advanced imaging techniques, novel blood tests, molecular diagnostics, and omics approaches will enhance our understanding of the pathogenesis of long COVID. The effective biomarkers of different phenotypes will help clarify differences and provide more accurate and objective diagnostic criteria and treatment options. Further, combining multi-omics approaches with machine learning for in-depth molecular and phenotypic analysis will be beneficial.[27,57,64,117] Such efforts will also provide valuable and objective evidence for future clinical trials.

5.5. Long COVID in animal models

Animal models simulate human disease processes to explore pathophysiological mechanisms and test potential treatments. Current primary models include the golden hamster model and the K18-hACE2 mouse model. The golden hamster model provides valuable insights into sustained lung, kidney, and olfactory damage.[118,119] The K18-hACE2 mouse model serves as a critical tool for studying lung fibrosis and neurological damage associated with SARS-CoV-2 infection.[120,121] But given the current progress in animal models and the inherent differences between species, it is crucial to select the appropriate model based on specific research objectives. One of the main challenges in developing effective animal models is the lack of objective criteria to assess the success of model establishment, thus making it difficult to standardize and evaluate results across studies. Future research needs to carefully select appropriate animal models and establish objective and effective evaluation criteria to ensure that the models accurately reflect the pathological characteristics of long COVID. The exploration of new models will provide essential support for advancing the in-depth study of long COVID pathogenesis and the screening of potential therapeutic options.

5.6. Longitudinal perspectives on long COVID

Both COVID-19 and long COVID are emerging diseases, and we must acknowledge that our understanding of these conditions remains rather limited. We are also uncertain regarding the long-term health trajectories of individuals infected with SARS-CoV-2. Therefore, understanding the evolving patterns of various long COVID symptoms, their potential consequences, and the risk of secondary diseases is crucial. Longitudinal studies can also explore the balance between tissue damage and repair and the associated pathways in long COVID patients. For example, it is important to investigate the significance of pulmonary inflammation and tissue fibrosis in patients with pulmonary manifestations of long COVID. In addition, researchers can provide new insights into lung injury and repair by examining the cellular and systemic immune status through longitudinal studies to determine changes in biomarkers and signaling pathways, which can also inform the selection of medications and the timing of treatment.

6. Conclusion

The persistent global health challenge of recurrent infection waves has given rise to long COVID, a novel post-viral syndrome affecting millions worldwide. While global research efforts have yielded significant advances within a remarkably short timeframe, critical knowledge gaps persist in three key domains: phenotype, pathogenic mechanisms, and therapeutic development. Given the societal impact of long COVID, which affects millions of healthcare systems globally, there is an urgent need for collaboration and concerted efforts to unravel the mysteries of long COVID. In-depth research into long COVID is crucial, as it not only enhances patient management and rehabilitation, improving their quality of life, but also deepens our understanding of chronic conditions linked to infectious diseases. This comprehensive knowledge aids in developing strategic responses that are vital for tackling future pandemics effectively, ensuring better preparedness and potentially mitigating impacts on public health systems worldwide.

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Author Contributions

Bin Cao was responsible for the idea of the work. Rongling Zhang, Xiaoying Gu, Hui Zhang and Yuming Guo did the literature search and wrote the initial version of the manuscript.

Yuming Guo and Bin Cao revised the manuscript and edited the manuscript throughout. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None.

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