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Reviews

# Long COVID: Current Status, Challenges and Future Directions

DIO:https://dx.doi.org/10.71373/ELJT3204
Submitted 4 October 2024
Accepted 20 October 2024
Published 1 November 2024

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**Long COVID refers to the persistent symptoms and health issues experienced by patients following infection with the SARS-CoV-2. As the pandemic continues, research into Long COVID has gradually become a focal point for the global medical community. Current studies suggest that the pathogenesis of Long COVID may be closely related to factors such as immune response, inflammatory reactions, neurological damage, and microvascular lesions. The clinical manifestations are diverse and include, but are not limited to, fatigue, dyspnea, cognitive impairment, and mental health issues. Epidemiological studies show that there are significant differences in the incidence of Long COVID among different populations, and its effects can be long-lasting, severely affecting patients' quality of life. Currently, diagnostic methods for Long COVID are still under exploration, with common assessment tools involving clinical interviews and questionnaires. In terms of treatment strategies, while no specific treatments exist yet, a comprehensive management approach including symptom relief, rehabilitation training, and psychological support has shown some efficacy. By analyzing the latest research findings, this paper aims to provide references for clinical practice and future research, promoting further understanding and response to Long COVID.**

## Introduction

At the end of 2019, the novel coronavirus (SARS-CoV-2) outbreak erupted and rapidly swept across the globe, inflicting a significant impact on human health and socio-economics. Although the current COVID-19 pandemic situation is generally stable, and the social harm and burden have eased compared to before, more evidence has emerged as the pandemic progresses that some patients still experience a range of long-term symptoms even after their nucleic acid tests turn negative following infection with the coronavirus. This condition is referred to as "Long COVID." According to incomplete statistics from the World Health Organization (WHO), it is predicted that there are cumulatively 400 million people worldwide suffering from Long COVID, causing at least $1 trillion in economic losses annually, which is approximately 1% of the global economic income. Long COVID is not a specific disease but a complex clinical syndrome characterized by diverse symptoms lasting for an extended period, severely affecting the quality of life of patients and placing a heavy burden on public health systems. Therefore, Long COVID has become one of the hot topics in current medical research. Studying Long COVID is crucial for understanding the long-term effects of the coronavirus. Research indicates that Long COVID not only affects individuals' physical health but may also lead to mental health issues such as anxiety and depression[1].Currently, research is being conducted globally to explore the epidemiological characteristics, risk factors, and impact of Long COVID on different populations. The results of these studies will provide important evidence for policymakers to develop effective interventions and improve the quality of life for patients.

Although the peak of the COVID-19 pandemic has passed, its impact on people has not disappeared. Particularly, Long COVID has brought a huge burden to public health, and humanity's battle against the coronavirus may well be a "protracted war." To address the challenges of Long COVID, ambitious and coordinated global research and policy strategies are required. Therefore, it is necessary to further study and clarify the mechanisms underlying Long COVID and propose targeted treatment and long-term management plans.

## Definition of Long COVID

Long COVID, as a professional term, was first introduced in 2020 to describe the phenomenon where various symptoms persist for weeks or months after a SARS-CoV-2 infection[2]. The specific definition varies among different research institutions and countries. The World Health Organization (WHO) defines Long COVID as symptoms or new symptoms that persist for at least two months following three months of SARS-CoV-2 infection that cannot be explained by other diagnoses[3]. The Centers for Disease Control and Prevention (CDC) in the United States adopts a definition where symptoms or health problems persist for more than four weeks after a SARS-CoV-2 infection with no detectable replicating virus[4].Additionally, the National Institute for Health and Care Excellence (NICE) in the UK proposes an alternative definition that covers all symptoms unrelated to SARS-CoV-2 infection occurring after acute infection, distinguishing different time points: ongoing COVID-19 symptoms (4-12 weeks later) and COVID-19 syndrome (more

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than 12 weeks later)[5]. On July 31, 2024, the National Academies of Sciences, Engineering, and Medicine (NASEM) in the United States introduced a new definition: Long COVID is an infection-related chronic condition occurring after SARS-CoV-2 infection, lasting for at least three months with a continuous, relapsing, and remitting or progressive disease course, affecting one or more organ systems. It emphasizes consistency in adults and children, documentation in the literature, and treatment[6].

Despite the differing definitions of Long COVID, it is generally believed that its core characteristics include: 1. Symptoms that appear weeks or months after a SARS-CoV-2 infection. 2. These symptoms persist for at least two months. 3. The symptoms cannot be explained by other diagnoses. These definitional differences reflect the varying understanding and focus of different organizations on Long COVID, and also demonstrate the complexity and variability of this field. The evolution of the term Long COVID has gone through a process from early variability to gradual standardization. Initially, due to limited understanding of the long-term effects of SARS-CoV-2 infection, many different terms were used to describe this phenomenon. For example, "post-acute sequelae of SARS-CoV-2 infection (PASC)," "post-acute COVID-19 syndrome," and "long-haul COVID" were all terms used in the early stages. As research has progressed and understanding has increased, these terms have gradually been replaced by "long COVID" and "post-COVID-19 condition," which have been widely recognized and used in the academic and healthcare communities. Long COVID is a relatively new field of research, and the evolution of its terminology reflects the deepening understanding of this phenomenon.

# Epidemiological Characteristics of Long COVID

## Incidence and Epidemiological Data

The incidence of Long COVID varies by region, population characteristics, and study design. According to an observational cohort study involving over 2 million adults, the prevalence of Long COVID is significantly higher in older populations compared to younger groups[7]. Other studies have shown that the symptoms of Long COVID manifest with different frequencies among various groups; for instance, women and patients with underlying diseases are more likely to experience Long COVID symptoms[8]. These epidemiological data provide a crucial foundation for understanding the impact of Long COVID on different populations.

## Risk Factor Analysis

Research indicates that risk factors for Long COVID include age, gender, underlying diseases, and the severity of acute phase illness[9]. For example, young women and patients with cardiovascular diseases or diabetes have a higher incidence of Long COVID. Additionally, socio-economic factors may also influence the occurrence of Long COVID, such as patients from low-income and marginalized communities being more susceptible to its effects[10]. Understanding these risk factors helps identify high-risk groups and provide them with better medical support.

## Incidence Among Different Populations

The incidence of Long COVID shows significant variation across different populations. Studies have found that children and adolescents have a relatively lower rate of Long COVID symptoms after infection with the coronavirus, though some still experience persistent symptoms[11]. In older populations, Long COVID symptoms are more common and usually more severe[12]. Moreover, certain occupational groups, such as healthcare workers exposed to high-risk environments, also have a significantly increased incidence of Long COVID[13]. These findings underscore the importance of developing personalized intervention measures for different populations.

# Clinical Manifestations of Long COVID

Long COVID exhibits high heterogeneity in its clinical manifestations, with over 200 symptoms currently attributed to it. The most common complaints include dyspnea, fatigue, brain fog, olfactory dysfunction, hair loss, and sleep disorders, among others[14]. Fatigue is considered the most prevalent symptom, with many studies indicating that approximately 50% to 80% of Long COVID patients still experience varying degrees of fatigue after infection[11, 13]. Dyspnea is also a commonly reported symptom among Long COVID patients, with related research finding that about 30% to 40% of patients still feel breathless or have shortness of breath after the acute phase[12, 15]. Additionally, symptoms such as chest pain and joint pain often accompany these, affecting patients' daily lives and potentially leading to long-term health issues[10, 16]. Therefore, assessment and management of these common symptoms are particularly important. Based on a two-year follow-up study conducted in China, we found that a certain proportion of patients still had Long COVID symptoms two years after infection with the original strain of the coronavirus, and the prevalence of each symptom changed over time[14]. Some studies suggest that Long COVID can manifest as four different syndromes, including post-intensive care syndrome, post-viral fatigue syndrome, and long haul COVID syndrome, among others. This further emphasizes the high heterogeneity and diversity of Long COVID symptoms[17]. Long COVID represents a series of long-term health impacts following the acute phase of coronavirus infection; it is a complex multi-system disease affecting nearly every organ system and can lead to severe disability. Figure 1 summarizes the main symptoms and pathologies, organ function abnormalities, etc., involved in each system reported in current studies [18-22]. Considering these systemic symptoms comprehensively helps develop more hol

istic management strategies for Long COVID.

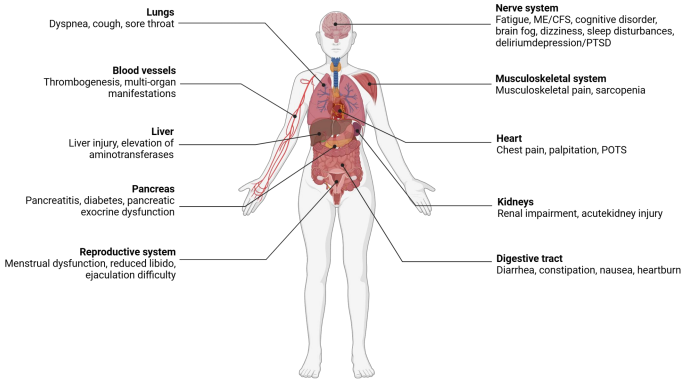


**Figure 1 Multi-organ complications of COVID-19 and long COVID**

## Potential Mechanisms of Long COVID

The pathogenesis of Long COVID remains unclear, but it is currently believed to involve multiple mechanisms (Figure 2), including alterations in the immune system, persistent presence of the virus, dysbiosis of the microbiome, mitochondrial dysfunction and metabolic abnormalities, neuronal and myelin sheath disturbances, as well as vascular microthrombosis and endothelial dysfunction. These are multi-systemic pathophysiological changes.

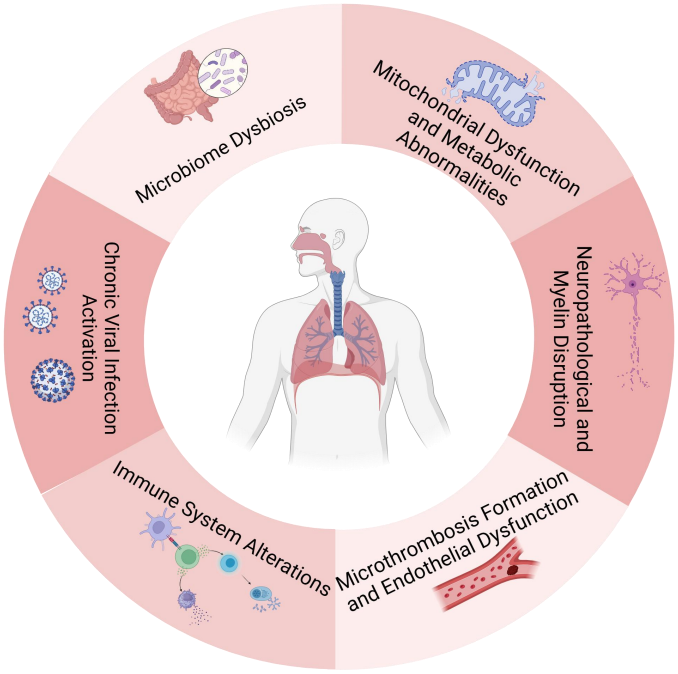


**Figure 2 Hypothesized mechanisms of long COVID pathogenesis**

## Immune System Alterations

Long COVID represents a set of symptoms and health issues that persist after infection with the coronavirus and is closely related to changes in the immune system. Research has shown that COVID-19 infection significantly affects the human immune system, leading to various changes in immune responses. Firstly, patients with Long COVID often exhibit immune dysregulation, including T cell exhaustion and a decrease in CD4+ central memory cells[23]. This change in immune status may prevent the body from effectively controlling immune responses, thereby triggering autoimmune reactions and attacking multiple organs such as the brain, heart, lungs, and kidneys. Secondly, the immune system of Long COVID patients remains in a highly vigilant state for an extended period, with COVID-specific adaptive immune responses lasting for many months, and neutralizing antibody titers and T cell responses can last up to 12 months[24]. Additionally, the coronavirus may induce cross-reactions with host self-antigens, leading to the production of autoantibodies[25]. Several studies[26, 27] have found elevated levels of autoantibodies against various tissues, organs, and immune regulatory factors in Long COVID patients. In more than 85% of patients, anti-COVID-19 IgG antibodies were detected, positively correlated with the levels of autoantibodies, and anti-interferon-lambda IgG antibodies were associated with the persistence of respiratory symptoms in Long COVID. The potential autoimmunity is related to the humoral response to SARS-CoV-2[28]. Complement activation is also one of the important mechanisms behind Long COVID[29]. When the complement system becomes uncontrolled, it can lead to cellular and vascular damage, which may underlie some of the characteristics of long-term COVID illnesses. Furthermore, studies have noted low levels of protective antibodies and high levels of autoantibodies in Long COVID patients, suggesting increased susceptibility to reinfection[30]. Meanwhile, the coronavirus can hijack all classes of immune cells through widely expressed integrins and can even target helper T cells (CD4+), further depleting the immune system[31]. In-depth immunophenotypic analysis has revealed significant disturbances in the gene expression of innate immune cells (such as NK cells, low-density neutrophils, and CXCR3+ monocytes) and adaptive immune cells (such as Th cells, Tfh cells, and regulatory T cells) in Long COVID patients[32]. When immune cells are stimulated by antigens for an extended period, they can become dysfunctional or exhausted. Studies have found that in severe COVID-19 patients, the absolute numbers of antiviral lymphocytes such as cytotoxic T lymphocytes (CTL) and natural killer cells (NK) are significantly reduced and functionally exhausted[33]. During COVID-19 infection, many immune inhibitory receptors on lymphoid and myeloid cells are upregulated[33]. This immune suppression and immune cell exhaustion can promote COVID-19 infection, leading to post-COVID sequelae. After systemic inflammatory response syndrome, some balanced compensatory anti-inflammatory mechanisms will be activated to restore immune homeostasis. On the other hand, there is still a possibility that SARS-CoV-2 could integrate into the host genome, which might lead to cancer. These mechanisms have also been proven to be related to tumorigenesis and metastasis[34]. Overall, the occurrence of Long COVID is closely related to complex changes in the immune system, including immune dysregulation, sustained high alert status, autoimmune reactions, and abnormal activation of the complement system. These changes not only affect the patient's short-term recovery process but may also lead to long-term health issues.

## Chronic Viral Infection Activation

Studies have indicated that even after symptoms disappear, the virus may still persist in the body for a long time and impact health. Additionally, individuals with specific genetic mutations are more likely to suffer from Long COVID. The reactivation of certain chronic viruses, such as EBV, CMV, and HIV, may be a potential factor in the development of Long COVID[35]. Chronic viral infections can lie dormant within the host for extended periods and reactivate under certain conditions. This reactivation may lead the immune system to overreact to these viruses, triggering or exacerbating symptoms of Long COVID[36]. EBV is more active in COVID-19 patients and is associated with various symptoms, including fatigue and brain fog[26, 37]. Serological evidence of EBV reactivation is independently associated with fatigue and neurocognitive dysfunction [38]. Furthermore, the reactivation of EBV and other herpesviruses (such as HSV-1) overlaps with symptoms in patients with ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome), further supporting the potential role of EBV in Long COVID symptoms[36, 39]. The impact of chronic viral co-infections on the development of Long COVID varies and requires further assessment.

The persistence or reactivation of SARS-CoV-2 itself is also considered a significant factor in Long COVID. Viral persistence refers to the continued existence of the virus in certain parts of the body after acute infection, potentially leading to subsequent symptoms. Studies have found that the genetic material of the novel coronavirus can still be detected in some patients with Long COVID, suggesting that the virus may persist in some tissues and even reactivate[40]. This phenomenon may be related to the virus's latent mechanism, where some viruses may exist at a low level in the body, not completely cleared, and reactivate when the body's immunity declines[41, 42]. This mechanism may explain why some patients still experience recurrent symptoms similar to the acute infection months later[43]. The latest research refers to these novel coronaviruses that persist in human tissues as "reservoirs." This viral "reservoir" has the ability to replicate and transcribe, translating viral RNA and proteins into the bloodstream, affecting host immune and inflammatory responses, and triggering symptoms in various systems of "Long COVID."[44]

## Microbiome Dysbiosis:

Research has found that there are significant changes in the gut microbiomes of patients with long COVID, and this dysbiosis may be associated with the persistence of the disease. Studies indicate that gut bacterial imbalances in patients with COVID-19 are linked to a variety of post-COVID conditions. Patients with long COVID exhibit abnormalities in their gut microbiota, characterized by a noticeable decrease in beneficial bacteria and an increase in potentially harmful bacteria. Conversely, individuals without post-COVID symptoms have a more diverse and varied gut microbiota, similar to those who have never been infected[45]. It has been reported that altered gut microbiome composition remains closely associated with persistent symptoms in COVID-19 patients up to six months after the clearance of SARS-CoV-2. This suggests that changes in the gut microbiome may persist during the recovery process and affect the patient's long-term health status[46]. Compared to healthy controls, patients showed significantly reduced bacterial diversity and increased relative abundance of opportunistic pathogens, along with decreased relative abundance of beneficial symbionts[47]. This dysbiosis may exacerbate the severity of COVID-19 by influencing the host's immune response and inflammation. Changes in the gut microbiome due to SARS-CoV-2 infection may further contribute to the severity of COVID-19 by affecting the host's immune response and inflammation[48, 49]. Causal relationships between the gut microbiome and COVID-19 have been supported by Mendelian randomization studies, indicating that specific microbial communities are associated with susceptibility to, hospitalization for, and the severity of COVID-19[50, 51]. The gut microbiota of patients with long COVID differs from that of healthy individuals, with long-lasting changes and significant differences in microbial distribution. Potential mechanisms affecting the occurrence and progression of long COVID involve the gut-lung axis (GLA), the gut-brain axis (GBA), potential pathogenic bacteria, and microbial metabolites. Prevention and treatment methods based on the gut microbiome for long COVID primarily include probiotics, prebiotics, and fecal microbiota transplantation (FMT). Clarifying the role of the gut microbiome in the pathogenesis of long COVID may aid in early diagnosis and the identification of new biomarkers[52]. Multiple studies have shown that the gut microbiomes of COVID-19 patients undergo significant changes, including a reduction in beneficial symbiotic bacteria and an increase in opportunistic pathogens[47, 53, 54]. These changes in the gut microbiome of COVID-19 patients are linked to the occurrence of long-term complications known as Post-Acute COVID-19 Syndrome (PACS). In patients with long COVID, characteristics of the gut microbiome include high levels of Ruminococcus gnavus and Bacteroides vulgatus, and low levels of Faecalibacterium prausnitzii[46]. Since metabolites produced by the microbiome serve as regulators of host immunity, metabolism, and hormonal signaling, they can activate the immune system and suppress pathogens. Therefore, dysbiosis may trigger a series of pathological processes[55]. Supplementing with probiotics and prebiotics can effectively regulate the gut microbiota, enhance gut barrier function, reduce pathogen invasion, and mitigate lung inflammation and damage through the gut-lung axis[56].

## Mitochondrial Dysfunction and Metabolic Abnormalities:

These factors are considered important causes leading to symptoms such as fatigue in patients with long COVID. Mitochondrial dysfunction and metabolic abnormalities play a crucial

role in the mechanism of long COVID. Mitochondria are the cell's power plants, primarily generating ATP through oxidative phosphorylation (oxphos) to provide energy. SARS-CoV-2 infection directly affects mitochondrial function, leading to suppressed gene expression and causing dysfunction in mitochondrial energy production, while also activating immune responses[57]. This energy insufficiency results in symptoms such as weakness and fatigue in patients[58]. Recently, a team from Children's Hospital of Philadelphia (CHOP) collaborating with the international COVID-19 research group (COV-IRT) discovered that SARS-CoV-2 adversely impacts mitochondrial genes, leading to multi-organ dysfunction beyond the lungs. This study provides strong evidence that we should no longer view COVID-19 merely as an upper respiratory tract disease but rather as a systemic illness affecting multiple organs[57]. SARS-CoV-2 infection can disrupt mitochondrial gene expression, resulting in impaired mitochondrial function in the host. This long-term impairment of mitochondrial function may lead to serious post-COVID conditions, such as organ failure. SARS-CoV-2 infection affects mitochondrial gene expression and function through multiple mechanisms, including direct interference with gene expression regulation via viral proteins[59], and indirectly by altering the host's translational efficiency[60] and immune responses, impacting mitochondrial-related biological processes. Peripheral blood mononuclear cells (PBMCs) from COVID-19 patients display characteristics of mitochondrial dysfunction, metabolic alterations, and elevated levels of mitochondrial factors. Different subgroups of T-cells exhibit mitochondrial dysfunction and increased risk of death[33]. Thus, mitochondrial dysfunction leads to an imbalance in immune homeostasis and metabolic reprogramming of infected cells, which may contribute to post-COVID conditions. These changes suggest that mitochondrial dysfunction plays a critical role in the progression of COVID-19, particularly in driving disease severity and prognosis[61]. In long COVID patients following SARS-CoV-2 infection, there are alterations in the mitochondrial membrane potential of peripheral blood leukocytes, indicating mitochondrial functional abnormalities[14]. These changes not only affect energy generation in muscle cells but can also lead to multi-organ dysfunction.

## Neuropathological and Myelin Disruption

The specific mechanisms of neuropathological and myelin disruption following COVID-19 infection involve direct viral invasion, immune-mediated inflammatory responses, and possible disruption of the blood-brain barrier. These mechanisms collectively result in widespread neurological damage, including cognitive decline and sensory disturbances[62-64]. SARS-CoV-2 can directly invade the nervous system, a fact confirmed by the presence of the virus in neural cells. Research indicates that SARS-CoV-2 can enter the central nervous system (CNS) through neuronal spread or via the bloodstream, affecting neural cells[63]. Moreover, the virus may also directly invade the brain through pathways such as the olfactory nerve or trigeminal nerve[65]. One study showed that among non-severely ill survivors of mild-to-moderate COVID-19, the incidence of objective cognitive impairment was 40%[66]. Patients recovering from mild cases of COVID-19 may experience cognitive impairments, such as "brain fog," which includes symptoms like slow thinking and difficulty concentrating[67]. Research shows that five months post-discharge, 42.1% of patients had processing speed deficits, 26.3% exhibited delayed verbal recall deficits, and 21% had both processing speed and verbal memory deficits[68]. Additionally, COVID-19 may cause damage to key areas of the brain, such as the hippocampus and anterior cingulate cortex, which could be one of the underlying mechanisms for cognitive decline[69]. German scientists found through experiments with mice that after SARS-CoV-2 infection, protein structures within brain neurons undergo changes similar to those seen in diseases like Alzheimer’s and Parkinson’s, involving the accumulation of misfolded proteins. This protein buildup could explain the attention and memory disorders observed in patients with long COVID[70]. Furthermore, SARS-CoV-2 infection can trigger widespread inflammatory responses, including non-specific neuroinflammation and anti-neuronal autoimmune dysregulation. These inflammatory responses may disrupt the blood-brain barrier, leading to significant metabolic changes in neurons and surrounding cells, and inducing inflammation in cortical neurons[71]. Low levels of viral RNA were detected in the brains of a few acutely ill patients, suggesting possible direct or indirect effects of the virus on the nervous system[72]. Additionally, studies have indicated that CNS damage post-SARS-CoV-2 infection may be related to factors such as glutamate reuptake in astrocytes, NMDA receptors and transporters (EAAT2), ROS signaling, NF-κB signal-triggered astrocyte proliferation, KNDy neurons, and the hypothalamic network involving Kiss1 (the GPR54 receptor ligand)[64]. It is recommended that comprehensive cognitive assessments be conducted for survivors of COVID-19 upon admission and discharge, and screening tools such as the Montreal Cognitive Assessment (MoCA) be used to identify and treat cognitive communication skill impairments[73]. Given the impact of COVID-19 on the nervous system, large-scale follow-up studies are necessary.

## Microthrombosis Formation and Endothelial Dysfunction

This may lead to damage and dysfunction in multiple organ systems. SARS-CoV-2 enters vascular endothelial cells by binding to ACE2 receptors through its S protein, and the binding efficiency is further enhanced by activation via TMPRSS2[74, 75]. By infecting vascular endothelial cells, SARS-CoV-2 triggers a series of pathophysiological reactions leading to microthrombosis formation and endothelial dysfunction. Researchers at Hannover Medical School in Germany found the presence of microthrombi in tissue samples from deceased COVID-19 patients and observed an increase in capillary branches to maintain oxygen-rich blood flow[76]. The exact origin of these microthrombi is not fully understood; however, Pretorius and Kell believe that the spike protein used by SARS-CoV-2 to enter cells could be a contributing factor in patients with long

COVID. They found that adding spike proteins to the plasma of healthy volunteers in the laboratory was sufficient to induce the formation of these abnormal clots[77]. A study by Academician Zhong Nanshan and Professor Wang Jian's team at Guangzhou Lab revealed that abnormal expression and activation of the store-operated calcium channel SOCC and mechanosensitive ion channel Piezo1 play a critical role in SARS-CoV-2 spike protein-induced pulmonary vascular endothelial injury and vascular remodeling, providing new mechanisms and targets for prevention and treatment of pulmonary vascular diseases caused by SARS-CoV-2[78].

Multiple studies have shown that the spike protein of SARS-CoV-2 can significantly downregulate the level of ACE2 receptors on host cells and thereby inhibit mitochondrial function[79, 80]. This downregulation directly affects the dysfunction of vascular endothelial cells. Infected endothelial cells release large amounts of inflammatory cytokines, which are associated with the "cytokine storm" in COVID-19 and can further promote endothelial dysfunction. SARS-CoV-2 infection activates the endothelial-to-mesenchymal transition (EndMT) process, causing endothelial cells to lose their specificity and gain mesenchymal characteristics, ultimately leading to thrombosis and fibrotic damage[81]. Studies have shown that patients with long COVID harbor a unique form of microthrombi—amyloid fibrin microclots (fibrinaloids)—which can obstruct capillaries, restrict red blood cell passage and gas exchange, thereby causing a range of symptoms[82]. There is a close relationship between microthrombosis formation and endothelial cell injury. Endothelial cell injury can lead to microthrombosis, and microthrombosis can cause further damage to endothelial cells. Elevated levels of various endothelial markers such as CD31, VEGFR-2, ICAM-1, VCAM-1, E-selectin, P-selectin, and vWF have been observed in the lung tissues and circulatory systems of COVID-19 patients, supporting the importance of pulmonary endothelial cells in local and systemic pathophysiology[83]. The specific process of endothelial cell injury following SARS-CoV-2 infection involves binding to ACE2 receptors, downregulation of ACE2 receptors, endothelial cell dysfunction, inflammatory activation, and mitochondrial remodeling. These processes collectively promote the formation of microthrombi, exacerbating disease severity and potentially leading to multi-organ dysfunction and death[84-86]. Endothelial cell dysfunction and inflammatory responses triggered by SARS-CoV-2 infection lead to platelet aggregation and subsequent microvascular thrombosis in the cardiovascular system, which can eventually result in heart failure[84]. Further studies show that SARS-CoV-2 infection can lead to systemic vascular coagulopathy or vascular injury, causing disseminated intravascular coagulation (DIC), especially evident in severely ill patients. In such cases, microthrombi are widely present in small blood vessels, leading to organ failure and multisystem complications[87]. Research indicates that systemic microvascular embolism may be one of the causes of symptoms of long COVID, such as fatigue, muscle pain, and brain fog. The European Society of Cardiology also recommends screening for microthrombi and endothelial dysfunction in patients with long COVID[88]. In clinical practice, it is important to focus on screening and management of these potential complications to enable timely intervention and symptom relief. Overall, according to current research, the causes of post-COVID conditions may be numerous, and these mechanisms may overlap to varying degrees, ultimately contributing to the occurrence and development of post-COVID conditions. Of course, the above possible mechanisms are speculations based on basic or clinical research by researchers, and the true pathogenesis of post-COVID conditions requires further investigation.

## Diagnostic Methods for Long COVID

Currently, the diagnosis of Long COVID mainly relies on clinical manifestations and evidence of previous SARS-CoV-2 infection, without necessarily requiring confirmation of infection through prior polymerase chain reaction or antigen testing results. Nevertheless, due to the diverse and nonspecific nature of Long COVID symptoms, there are currently no specific laboratory tests or biomarkers available for diagnosing Long COVID. Diagnostic methods for Long COVID involve multiple aspects, including laboratory tests, imaging examinations, and clinical symptom assessment.

### Clinical Diagnostic Criteria

Long COVID refers to a series of long-term symptoms experienced by patients after acute COVID-19 infection. According to existing research, the clinical diagnostic criteria for Long COVID typically include persistent symptoms such as fatigue, dyspnea, cognitive impairment, sleep disorders, muscle or joint pain, etc., lasting at least four weeks after infection[89]. Additionally, patients may experience neurological symptoms such as headaches, loss of taste or smell, which can persist for months or even longer after the acute phase[90]. To better identify patients with Long COVID, clinicians need to consider a patient's medical history, symptom presentation, and potential influencing factors such as comorbidities, age, and gender[91]. Currently, there are no unified international diagnostic standards, but guidelines from different countries are gradually moving towards establishing systematic assessment tools to assist clinicians in making accurate diagnoses[92].

### Laboratory Tests and Imaging Evaluation

In the diagnosis of Long COVID, laboratory tests and imaging evaluations play an essential auxiliary role. Laboratory tests help rule out other potential diseases and assess the patient's overall health status. For example, blood tests can detect inflammatory markers, immune function, and nutritional status, which may correlate with the severity of Long COVID symptoms[93]. Studies have shown that elevated levels of interleuki

n-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) may serve as potential diagnostic biomarkers for Long COVID. Patients with neurological symptoms of Long COVID exhibit higher levels of neurofilament light chains and glial fibrillary acidic protein, whereas those with pulmonary symptoms have higher levels of transforming growth factor beta[94]. Compared to COVID-19 survivors without Post-Acute Sequelae of SARS-CoV-2 Infection (PACS), survivors with PACS exhibit higher levels of CRP (standardized mean difference [SMD] = 0.20; 95% CI: 0.02-0.39), D-dimer (SMD = 0.27; 95% CI: 0.09-0.46), and lactate dehydrogenase (LDH) (SMD = 0.30; 95% CI: 0.02-0.66). Sensitivity analysis also showed that lymphocyte counts (SMD = 0.30; 95% CI: 0.12-0.48) and IL-6 (SMD = 0.30; 95% CI: 0.12-0.49) were significantly higher in PACS cases than in non-PACS cases[95]. Chinese research teams have identified 23 protein biomarkers associated with Long COVID for the first time. These biomarkers help identify high-risk populations for Long COVID early and provide targets for the development of new interventions[96]. In a multicenter study analyzing the differences in biomarkers between Long COVID patients, those infected but without sequelae (recovery control), and those not infected with COVID-19 (healthy control), it was found that Long COVID patients exhibit abnormal T-cell activity, reactivation of several latent viruses (including Epstein-Barr virus and other herpesviruses), and a significant decrease in cortisol levels. Machine learning analysis models could distinguish Long COVID patients from others with 94% accuracy[97]. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were shortened, fibrinogen (FIB) levels were elevated, platelet count (PLT) was increased, and the proportion of elevated D-dimer (D-D) was 20% in Long COVID patients; inflammatory markers were normal in over 90% of patients. This suggests that despite inflammatory markers being largely normal, abnormal coagulation function persists, which may be an important mechanism behind the persistent symptoms in Long COVID patients[98, 99]. Furthermore, imaging evaluations such as chest CT scans can be used to assess long-term lung damage, particularly in the context of acute COVID-19 infection, where some patients may develop complications such as pulmonary fibrosis[100]. Neuroimaging exams, such as MRI, can help identify neurological damage associated with Long COVID[101]. Combining these examination results, doctors can gain a more comprehensive understanding of the patient's health status and formulate personalized treatment plans.

## Other Auxiliary Diagnostic Tools

In addition to clinical diagnostic criteria and laboratory tests, other auxiliary diagnostic tools are also significant in assessing Long COVID. For example, physiological function tests can evaluate a patient's exercise tolerance and lung function, which is crucial for understanding the patient's daily living capabilities and recovery status[102]. Psychological assessment is also essential as many Long COVID patients report mental health issues such as anxiety and depression; psychological assessment can help identify and manage these issues[103]. Besides, symptom monitoring tools such as questionnaires can effectively collect information on symptom changes and quality of life in patients, assisting doctors in making more precise evaluations[104]. In summary, the diagnosis of Long COVID requires a combination of various methods to ensure a comprehensive assessment of the patient's health status.

# Treatment Strategies for Long COVID

Long COVID refers to the persistent symptoms experienced by some COVID-19 patients after acute infection, affecting their quality of life and daily functioning. Treatment strategies for Long COVID are increasingly garnering attention, primarily focusing on symptomatic treatment and supportive care, advancements in pharmacological therapy, and rehabilitation treatments alongside lifestyle interventions. Typically, treating Long COVID requires a multidisciplinary approach involving internists, pulmonologists, cardiologists, neurologists, rehabilitation specialists, and psychologists.

## Symptomatic Treatment and Supportive Care

Symptomatic treatment forms the cornerstone of managing Long COVID, aiming to alleviate a variety of symptoms such as fatigue, dyspnea, and cognitive impairments. Supportive care encompasses psychological support, nutritional guidance, and adjustments to lifestyle, helping patients better cope with prolonged symptoms. Research indicates that individualized symptomatic treatment can significantly improve the quality of life for patients. For instance, addressing fatigue symptoms involves recommending a balanced regimen of moderate exercise and rest, which helps restore physical strength and improves mental state[105]. Additionally, psychological support is crucial for patients with Long COVID, as many may suffer from anxiety and depression following acute infection, necessitating professional psychological intervention and support[106].

## New Developments in Pharmacological Therapy

In terms of pharmacological therapy, researchers are exploring the efficacy of various medications in treating symptoms of Long COVID. Recent studies suggest that certain anti-inflammatory drugs and immunomodulators may be effective in alleviating symptoms associated with Long COVID. For example, inhaled corticosteroids have been proposed for use in improving chronic cough and dyspnea related to respiratory symptoms[107]. Furthermore, antiviral drugs are also under investigation, although there is currently no definitive evidence of their effectiveness in treating Long COVID, their potential applications remain noteworthy[108]. Overall, research into p

harmacological treatments is ongoing, and more therapeutic options may be proposed in the future.

### Rehabilitation Treatments and Lifestyle Interventions

Rehabilitation treatments are an indispensable component of managing Long COVID, aimed at restoring function and enhancing quality of life through structured rehabilitation programs. Research demonstrates that physical therapy and exercise interventions can effectively improve the physical and mental states of patients with Long COVID[105]. For example, aerobic exercises and strength training are widely recommended for Long COVID patients, as they can strengthen cardiorespiratory capacity and muscular strength. Additionally, lifestyle interventions such as healthy eating habits and regular sleep schedules have proven to positively impact Long COVID symptoms. Adjusting lifestyle not only enhances physical health but also promotes mental well-being, thus better equipping patients to deal with long-term symptoms[109]. Close collaboration between patients and professional rehabilitation teams is key to achieving optimal outcomes during the rehabilitation process.

## Research Challenges

The mechanisms behind long COVID are not yet well understood and require further investigation. Multiple proposed mechanisms still lack sufficient evidence, and the specific mechanisms underlying different symptoms or organ damage need more in-depth study. Secondly, there is a lack of specific diagnostic methods; diagnosis primarily relies on symptom presentation, which can lead to misdiagnosis or missed diagnoses. There is a need to develop more accurate diagnostic methods to identify and treat patients with long COVID early. Thirdly, treatment protocols for long COVID lack evidence-based medical support, and treatment options and drug choices are limited. More clinical trials are needed to evaluate the efficacy and safety of different treatment approaches. Fourthly, the epidemiological characteristics, risk factors, and natural course of long COVID require further research. Larger-scale, multicenter studies are necessary to better understand the epidemiological characteristics and influencing factors of long COVID. Lastly, the long-term impact of long COVID on children and adolescents needs attention. Currently, there is little research on long COVID in children and adolescents, and further investigation into its pathogenesis, clinical manifestations, and treatment strategies is needed.

## Future Research Directions

### The impact of different variants of the novel coronavirus on long COVID

It is necessary to study the pathogenicity and immune escape mechanisms of different variants and their impact on long COVID.

### Characteristics of long COVID in asymptomatic and mild cases

Attention should be given to the incidence and clinical manifestations of long COVID in asymptomatic and mildly infected individuals, as well as differences compared to severe cases.

### Interactions between different symptoms of long COVID.

It is necessary to study the mechanisms of interaction between different symptoms and their impact on patient prognosis.

### Genetic studies of long COVID

It is necessary to study the genetic susceptibility to long COVID and the relationship between relevant genes and disease progression.

### Application of advanced technologies such as artificial intelligence, deep sequencing, and machine learning in long COVID research.

These technologies can be used for large-scale data analysis and prediction, as well as the development of new diagnostic and therapeutic tools.

### Development of personalized treatment plans for long COVID

Treatment should be individualized based on the specific circumstances of each patient to improve treatment outcomes and quality of life.

## Conclusion

Long COVID is a complex clinical syndrome that faces many challenges in terms of understanding its pathogenesis, diagno

sis, treatment, and management. Through interdisciplinary and cross-regional cooperation, conducting in-depth research on long COVID will help us better understand its pathogenesis, epidemiological characteristics, and clinical manifestations, providing scientific basis for clinical practice and policy-making, ultimately reducing the harm caused by long COVID to patients and society.

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**Author Contributions**: The authors contributed equally to all aspects of the arti cle. All authors have read and agreed to the published version of the manuscript.
**Conflicts of Interest:** The authors declare no conflict of interest.