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Review Article

Desktop Primer Regarding the Etiology, Risk Factors, Symptoms, Pathophysiology, Mechanisms, Management, and Treatment for Long COVID

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Abstract

Long COVID is a general term for a complicated multisystemic disease that develops after acute infection with COVID-19, regardless of severity, immediately or after a period of apparent recovery. Long COVID has been shown in studies to affect the entire spectrum of COVID-19 patients, from mild acute illness to the most severe manifestations. Long COVID has a complex etiology that involves viral seeding and persistence in several organs, stimulation, and reactivity to unrelated viruses, autoimmune inflammation, and autoimmunity. Fatigue, dyspnea, irregular heartbeats, cognitive dysfunction, muscular discomfort, attention deficits and headaches, etc., are some of the symptoms. Together with symptoms and problems, Long COVID patients frequently struggle with poor quality of life (QoL), mental health concerns, and work issues. These patients may need multidisciplinary treatment, including long-term symptom monitoring to spot potential problems, rehabilitation programs, psychological health, social care support, immunization, and pharmaceutical and non-pharmacological methods. However, given the wide range of symptoms and issues that people with extended COVID may encounter, a better understanding of the clinical history of the condition is necessary. Improved and integrated care models are essential to support and manage patients with Long COVID-19, and resilient healthcare systems are required to ensure effective responses to future health challenges. Future clinical trials must standardize diagnostic standards, including people with concurrent chronic cardiometabolic diseases, and standardize the results. This review aims to comprehensively review the current literature on Long COVID, including its pathophysiology, risk factors, management, options, challenges, and future perspectives.

Keywords: *Adaptive Autoimmunity; Epstein-Barr Virus; Human Herpesvirus; Isocapnic Buffering; Long COVID Risk Factors; SARS-CoV-2 Infection; Sleeplessness*

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Abbreviations

BCG: Bacillus Calmette-Guérin; CNS: Central Nervous System; EBV: Epstein-Barr Virus; GI: Gastrointestinal; HHV: Human Herpesvirus; ICU: Intensive Care Unit; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; MIS: Multisystemic Inflammatory Syndrome; NIHR: National Institute of Health and Care Research; ONS: UK Office of National Statistics; PACS: Post-Acute COVID-19 Syndrome; POTS: Postural Orthostatic Tachycardia Syndrome; QoL: Quality of Life; TNF: Tumor Necrosis Factor

Introduction

The phenomenon of people who experience prolonged symptoms or difficulties after COVID-19 infection is referred to by the terms "Long COVID", "post-COVID syndrome," "post-acute COVID-19 syndrome," and "post-acute sequelae of SARS-CoV-2 infection" [1].

Long COVID (also known as post-acute COVID-19 syndrome (PACS)) is a multisystemic illness characterized by typically severe symptoms that develop after infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The extended COVID condition develops in people who have a history of probable or proven SARS-CoV-2 infection, generally 3 months after the beginning of COVID-19, with symptoms that persist for at least 2 months and cannot be answered by another diagnosis [1]. People of various ages, including those with moderate or asymptomatic COVID-19 infections, are susceptible to Long COVID. Moreover, individuals with Long COVID have organ involvement and dysfunction in several organ systems [3].

On the other hand, the term "post-COVID-19 sequelae" describes various symptoms and issues that continue even after a person has been cured of their acute COVID-19 sickness [2]. Unfortunately, there are not many studies in this area. Nevertheless, about 90% of COVID-19 survivors have had sequelae, including severe neurological, cardiovascular, renal, or pulmonary signs and general symptoms such as fatigue [4].

Causes of Long COVID

Although the exact mechanism underlying Long COVID is not yet fully understood, there are likely multiple, potentially overlapping causes. Several hypotheses have been proposed regarding its pathogenesis, including the existence of persisting SARS-CoV-2 reservoirs in tissues, immune dysregulation with or without reactivation of underlying pathogens such as Epstein-Barr virus (EBV) and human herpesvirus (HHV-6), immunologic aberrations and inflammatory damage in response to the acute infection, anticipated sequelae of post-critical illness, impacts of SARS-CoV-2 on the microbiota, including the virome, autoimmunity, and priming of the immune system through molecular mimicry, microvascular blood clotting with endothelial dysfunction, and dysfunctional signaling in the brainstem and vagus nerve. Long COVID may also be influenced by persistent viremia and psychological factors. Long COVID may also be affected by persistent viremia and psychological factors. Other potential causes of Long COVID could be an elevated inflammatory state, cerebral alterations, peripheral organ failure, dysfunction, nonspecific hospital effects, critical illness sequelae, post-intensive care syndrome, COVID infection problems, or drugs' undesirable effects [2,5-7].

Prevalence and predictors of Long COVID

Due to different definitions and study techniques, it needs to be clarified what the actual prevalence of Long COVID is. However, according to a conservative estimate, 10% of infected individuals and more than 651 million known cases of COVID-19 worldwide have Long COVID; the actual figure is probably considerably higher due to many unreported cases [8]. Furthermore, some studies predicted that the incidence was 10 - 30% in non-hospitalized patients, 50 - 70% in hospitalized patients, and 10 - 12% of cases among those who received vaccinations [9-12].

Prioritizing at-risk groups and developing treatments depend heavily on identifying Long COVID factors. According to Arjun., *et al*. (2022), hospitalization and the degree of COVID-19 illness are two of the most reliable indicators of Long COVID. A severe illness increases

the probability of enduring lasting symptoms 4 weeks after infection [13]. A systematic review by Iqbal., *et al*. (2021) supports this assertion, as it discovered that hospitalization during the acute infection (odds ratio 2.9, 95% CI 1.3 - 6.9) was the most significant predictor of developing post-COVID syndrome [14].

Another association between Long COVID and the severity of the illness is the presence of many symptoms throughout the acute phase of COVID-19 [15]. For example, according to data from the COVID Symptom Study app, people had a 3.5 times higher probability of getting Long COVID than those who reported fewer symptoms during their first week of illness [16].

The existence of preexisting diseases such as diabetes and hypertension was another critical predictor of Long COVID. Research from India and a comprehensive review discovered a close and robust link between preexisting conditions and Long COVID [17,18]. King's College London researchers examined anonymized data from 1.2 million primary health records throughout the UK and 10 population-based studies with 45,096 individuals. According to the results, those with poor mental health had a 50% higher likelihood of reporting extended COVID, while those with asthma had a 32% higher chance [19].

Age and sex have also been discovered to be the main predictors of Long COVID. According to a more recent study by the UK Office of National Statistics (ONS), Long COVID is more likely to affect people in their midlife [20]. Similarly, research published in the *Lancet* in January 2021 discovered that those over 50 were more likely to continue developing symptoms of COVID-19 [21]. Another study found that females ≥ 20 are more likely than men to experience persistent symptoms such as exhaustion, dyspnea, brain fog, muscular soreness, anxiety, or sadness following their initial COVID-19 infection (10.6% vs. 5.4%) [22].

Discussion

Long COVID risk factors

Although the specific factors contributing to Long COVID's development are still unclear, several potential risk factors have been identified through research. These include gender, with women at higher risk than men, and certain ethnicities, such as Hispanic or Latino heritage. Genetics may also play a role, including variations in the ACE2 gene, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), and the presence of specific autoantibodies (IgM). Other potential risk factors include post-intensive care syndrome, preexisting conditions such as type 2 diabetes, obesity, cardiovascular disease, respiratory disease, hypertension, connective tissue disorders, attention deficit hyperactivity disorder, chronic urticaria, and allergic rhinitis. However, it is worth noting that a third of people with Long COVID have no identified preexisting conditions, and lifestyle may also play a role. The EBV reactivation has also been identified as a potential risk factor for Long COVID [2,3,23,24]. EBV, which infects approximately 90% of the human population and typically remains inactive after infection, was reactivated shortly after SARS-CoV-2 infection, significantly linked to persistent symptoms. This reactivation may be related to the immune response to COVID-19 [16]. Older age is a significant risk factor for the severity of acute COVID-19 infection and the development of Long COVID. The COVID Symptom Study also found that advanced age was associated with a higher risk of Long COVID [25].

Another risk factor is multisystemic inflammatory syndrome (MIS), which can occur during or after COVID-19 illness [24]. Furthermore, socioeconomic risk factors such as lower income and the inability to rest adequately in the first weeks after developing COVID-19 have been identified [26,27]. Before the emergence of SARS-CoV-2, other viral and bacterial infections were known to cause post-infectious illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and there is evidence that Long COVID shares similar mechanistic and phenotypic characteristics with these conditions [28].

Long COVID signs and symptoms

Long COVID is a diverse clinical condition that can persist for several months after the initial infectious phase. A substantial body of research already demonstrates that up to 70% of hospitalized patients and 30% of outpatients continue to have a range of symptoms for

weeks after diagnosis [29]. However, the onset and duration of symptoms can vary between individuals and by type of symptoms (Figure 1) [2,23,30,31].

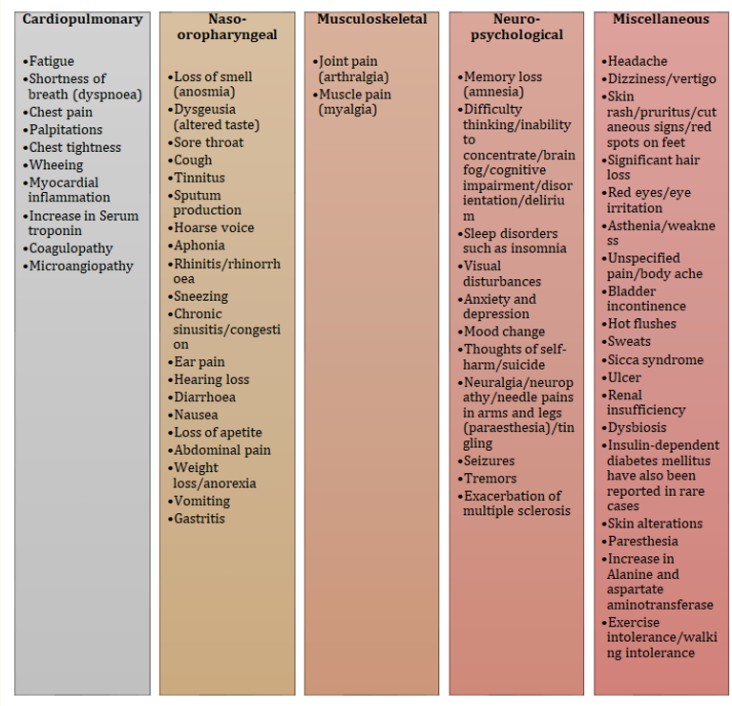

Figure 1: *Signs and symptoms of Long COVID [2,23,30,31]*

Long COVID effects on the quality of life (QoL)

Long COVID symptoms can profoundly impact patients, leading to a decreased QoL. The persistence of symptoms, such as fatigue, can negatively affect various aspects of QoL, including physical function, bodily pain, vitality, emotional health, and social functioning. Studies have shown that compared to a healthy control group, Long COVID patients reported significantly lower quality of life scores in these areas. Specifically, patients experienced marked reduced social functioning, suggesting a lack of interest in normal daily activities due to the disease. Additionally, the social distancing measures required for COVID-19 can compound the negative impact on QoL for patients with Long COVID [30].

Persistent weariness is a prevalent symptom of Long COVID and is frequently described as a side effect following recovery from COVID-19. This circumstance can significantly impact QoL by lowering a person's energy, drive, and focus [32]. "Brain fog" is another symptom that can adversely affect a patient's quality of life. Long-lasting impaired concentration or impaired cognitive skills are signs of brain fog. Also, a lower vocational function is associated with cognitive impairment [33]. Some typical symptoms that can negatively impact patient QoL include cough, chest discomfort, and headaches. Sleep disturbances are another symptom that might have a detrimental impact on QoL [34]. Finally, elevated stress may persist in patients well after the illness has been resolved, and as is well known, stress has a poor impact on QoL [35].

A decreased QoL might make it harder for a patient to work and resume daily life. According to a study by Chopra., *et al*. (2021), 40% of 195 COVID-19 patients who worked before hospitalization could not resume their jobs within 8 weeks after being released due to lingering health problems or loss of work. One-quarter of those who returned to work had to change employment or cut hours due to health problems [36]. According to another study, 38 out of 56 individuals who had previously been hospitalized could not work for 3 months following their stay [37].

People's opinions about the patients in their vicinity may be another unfavorable element that lowers patients with Long COVID's QoL. The lack of precise diagnostic techniques frequently results in the simplification of patient complaints. Individuals with Long COVID may experience increased anxiety and decreased overall QoL due to their surroundings and medical personnel trivializing their symptoms [38].

Long COVID comorbidities and sequelae

Long COVID is accompanied by several comorbidities that may increase the chance of acquiring or worsening the disorder. According to Subramanian., *et al*. (2022), the most prevalent comorbidities related to Long COVID were depression (22.1%), nervousness (20.3%), asthma (20.1%), dermatitis (19.5%), and hay fever (18.1%). Other comorbidities found in the research were arrhythmias (7%), osteoarthritis (10.9%), migraine (11.1%), hypertension (15%), and osteoarthritis [39]. Similar findings were found in a prospective cohort study of 215 individuals, which showed that Long COVID was more common among those with a history of bronchial asthma (94%) compared to 59% of those without it [40]. Moreover, individuals with preexisting type 2 diabetes are at an increased risk of developing Long COVID, as chronic inflammation associated with insulin resistance can lead to a more pronounced immune response during acute SARS-CoV-2 infection and subsequent COVID-19 sequelae [41]. Furthermore, poor mental health is associated with a 50% increase in the risk of developing Long COVID and its relative severity [19].

Fatigue is a common persisting symptom, regardless of the severity of the acute stage of COVID-19. A cross-sectional study revealed that 92.9% of hospitalized and 93.5% of nonhospitalized patients with COVID-19 reported ongoing fatigue 79 days after the onset of the disease. A narrative review suggests that congestion of the glymphatic system and subsequent toxic build-up in the central nervous system (CNS) due to increased resistance to cerebrospinal fluid drainage through the cribriform plate caused by olfactory neuron damage may contribute to post-COVID-19 fatigue [42].

Studies have also revealed that dyspnea is a frequent symptom of COVID-19 infection [43,44]. In one study, 143 patients were evaluated, and 43.4% still had dyspnea 60 days after COVID-19 began [45]. Because COVID-19 is primarily a pulmonary infection, endothelial damage from the multiplication of SARS-CoV-2 inside endothelial cells and a solid immunological and inflammatory response might arise from acute illness [46,47]. After recovering from the acute infection, some people may experience dyspnea due to long-term lung abnormalities. However, most people who experience breathing problems after COVID-19 do not show evidence of long-term or permanent lung damage [48].

People with Long COVID may experience persistent cardiovascular abnormalities that can be burdensome. For example, according to a cohort study by Puntmann., *et al*. (2020), many individuals with COVID-19 showed cardiac involvement, ongoing myocardial inflammation, and elevated serum troponin levels 71 days after diagnosis [49]. Additionally, a large case series reported by Kim., *et al*. (2020) found that chest pain, potentially due to myocarditis, was a common symptom in patients with Long COVID [50].

Research on cognitive performance and impairments in COVID-19 patients points to the possibility of septic encephalopathy, non-immunological consequences including hypotension, hypoxia, and vascular thrombosis, as well as immunological effects such as adaptive autoimmunity, microglial activation, and an unfavorable cytokine profile [51]. Furthermore, COVID-19 patients who were hospitalized

had encephalopathy, cognitive problems, cerebrovascular events or disease, seizures, hypoxic brain injuries, corticospinal tract symptoms, dysexecutive syndrome, altered mental status, and psychiatric problems [52-54]. These results indicate that COVID-19-related neurological symptoms are widespread and varied and may significantly complicate rehabilitation and post-COVID-19 treatment. It is uncertain which individuals are most affected by COVID-19-induced cognitive problems and their duration. Nevertheless, patient reports and published descriptions of Long COVID have reported "brain fog" as a prevalent and severe effect [55-57].

Stroke and headaches are common in those who have recovered from acute COVID-19; according to the UK Office for National Statistics (ONS), 10.1% of all COVID-19 survivors had headaches 5 weeks after recovery [4,58-60]. Excessive systemic inflammation, often referred to as a "cytokine storm," and activation of glial cells pose a significant risk to the brain and may increase the probability of neurological complications, such as encephalitis and stroke [46]. Following COVID-19 infection, symptoms such as hypercoagulability and cardioembolisms, which are caused by virus-related heart damage, can increase the incidence of stroke. Furthermore, COVID-19 has been linked to a higher incidence of neurological diseases, including Guillain- Barré syndrome and neurodegenerative diseases such as Alzheimer's dementia [61-64].

Sleeplessness is also frequently observed after recovering from COVID-19. Numerous studies have shown that sleep disturbances and poor sleep quality are typical after acute illness. [43,65-69].

Furthermore, SARS-CoV-2 may alter the permeability of the blood-brain barrier, allowing peripheral cytokines and other blood-derived chemicals to enter the CNS and exacerbate neuroinflammation [70]. According to Proal., *et al*. (2021), long-term sequelae after COVID-19 may arise in part due to cerebrovascular alterations, systemic inflammation, peripheral organ failure, and direct viral encephalitis [71].

It has been observed that after recovering from COVID-19, there are still taste and smell abnormalities. ONS estimated that the 5-week prevalence of loss of smell and loss of taste is 7.9% and 8.2% of all people with COVID-19, respectively [72]. The SARS-CoV-2 virus may enter perivascularly, stem cells, and olfactory support cells through non-neuronal expression of the ACE2 receptor. This local infection may result in an inflammatory reaction that impairs the ability of olfactory sensory neurons to function. In addition, SARS-CoV-2 can alter communication between nerve cells and the brain, altering the ability to smell by damaging support cells responsible for maintaining local water and ionic equilibrium [73].

COVID-19 infection can cause multiorgan damage in those at low or high risk of severe acute illness. Studies have revealed acute renal impairment in individuals discharged after recovering from COVID-19 [74-76]. For example, Huang., *et al*. (2021) discovered that 35% had impaired kidney function 6 months post-discharge [21].

During acute SARS-CoV-2 infection, individuals with COVID-19 have been observed to experience pancreatitis, with higher levels of serum amylase and lipase in severe cases compared to mild cases. Computed tomography images have shown evidence of pancreatic injury in some cases [77-79]. According to cross-sectional research by Dennis., *et al.* (2020), 141 days after infection, 40% of COVID-19 patients with a low risk of severe illness showed minor pancreatic dysfunction [58].

According to research by Townsend., *et al*. (2021), with a median follow-up of 54 days following discharge, nearly 30% of survivors had high D-dimer levels, and 9.5% had elevated C-reactive protein levels. Also, hospitalized COVID-19 survivors over the age of 50 were more likely to have elevated convalescent D-dimer levels ($p < 0.001$) [80].

Figure 2 outlines the possible mechanisms linking comorbidities to the long-term sequelae of COVID-19 [3].

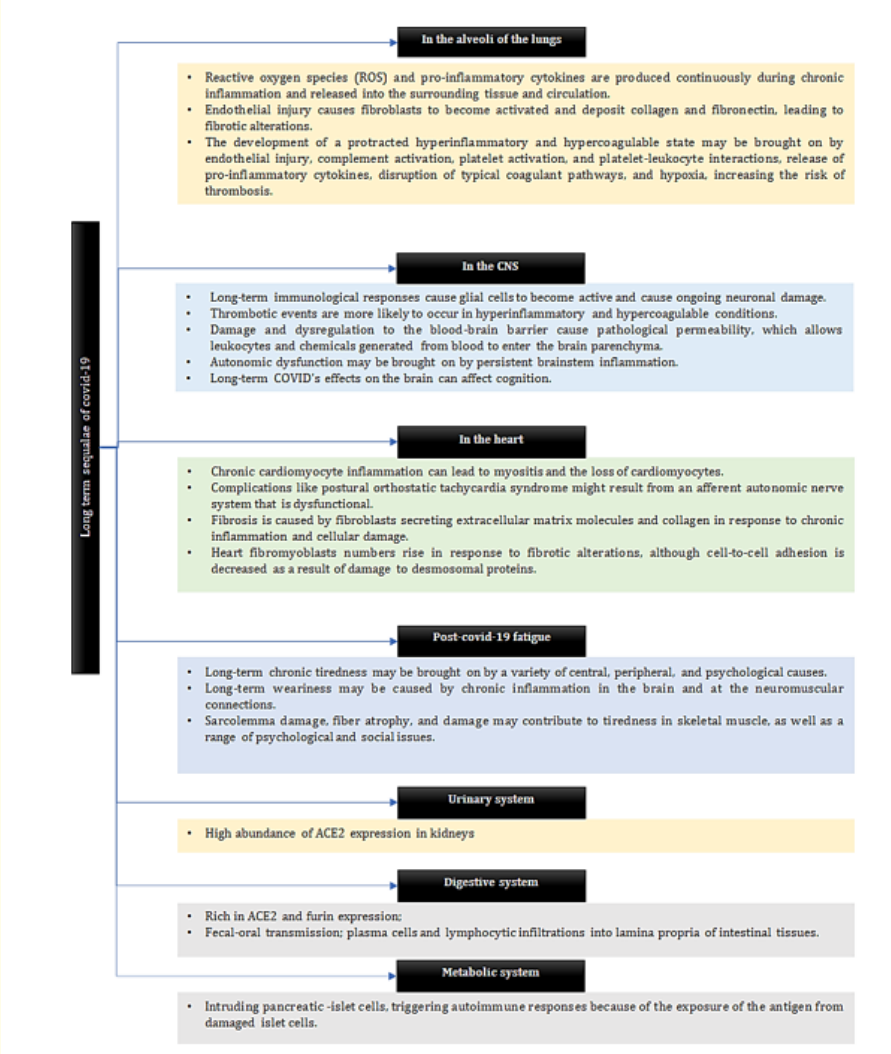

Figure 2: *Possible mechanisms existing between comorbidities and long-term sequelae of COVID-19 [3]*

Specific criteria and tests for Long COVID

Although certain aspects of Long COVID have diagnostic tools (such as tilt table testing for postural orthostatic tachycardia syndrome (POTS) and MRI scans to detect cardiovascular damage), Long COVID diagnostic tools are primarily in development. They include imaging to detect micro clots, corneal microscopy to identify tiny fiber neuropathy, novel fragmentation of the QRS complex on electrocardiograms as symptomatic of cardiac injury, and using hyperpolarized MRI to detect pulmonary gas exchange abnormalities [81-86].

In individuals with a recent SARS-CoV-2 infection, a thorough medical history and clinical examination aid in the diagnosis. A positive antibody test can help establish the diagnosis in people who have Long COVID symptoms but no prior signs of SARS-CoV-2 infection

[7]. Early biomarker research reveals that extracellular vesicles and immunological markers that suggest significant cytotoxicity may be symptoms of Long COVID [87,88]. Systemic inflammatory indicators have been recommended as potential COVID biomarkers. For example, patients with aberrant levels of CRP, procalcitonin, and neutrophil count have been reported to have D-dimer, c-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, and neutrophil count related to persistent symptoms of Long-COVID [89]. Investigation of endothelial function in 30 Long COVID patients revealed a gap between the ET-1 and RHI profiles in Long COVID patients [90]. In addition, compared to healthy controls, the levels of neurodegenerative markers such as amyloid beta, neurofilament light, neurogranin, total tau, and p-T181-tau were higher in Long COVID patients [91]. IgM and IgG3 immunoglobin profiles have been associated with an increased risk of Long COVID, according to Hadjadj., *et al*. (2020). In reality, *β*-cells release IgM and IgG3 in response to interferon stimulation and IL-4 signaling. Ineffective conversion of IgG isotypes may be caused by impaired interferon generation, characterized by elevated interleukin signaling, and affects immune control [92].

Research on biomarkers for ME/CFS, such as electrical impedance blood tests, saliva testing, erythrocyte deformation, sex-specific plasma lipid profiles, and factors relating to isocapnic buffering, may also be useful for Long COVID [93-95].

At the acute stage, SARS-CoV-2 RNA can be found in fecal samples, indicating gastrointestinal (GI) involvement in COVID-19 pathology [96,97]. Recent research has shown that COVID-19 infection alters the diversity and makeup of the gut microbiome [98,99]. Increased levels of cytokines caused by viruses can damage intestinal integrity, making it easier for bacteria and their metabolites to enter the bloodstream. Due to this dysbiosis, the innate immune system responds inappropriately, leading to secondary infections and pulmonary dysfunction [100]. Elevated levels of *Ruminococcus gnavus* and *Bacteroides vulgatus* and reduced levels of *Faecalibacterium prausnitzii* and butyrate-producing bacteria correlated with Long COVID [101]. Such a complex relationship might be used to identify the presence of Long COVID. Figure 3 displays helpful investigational tools for patients with Long COVID-19 Syndrome [102].

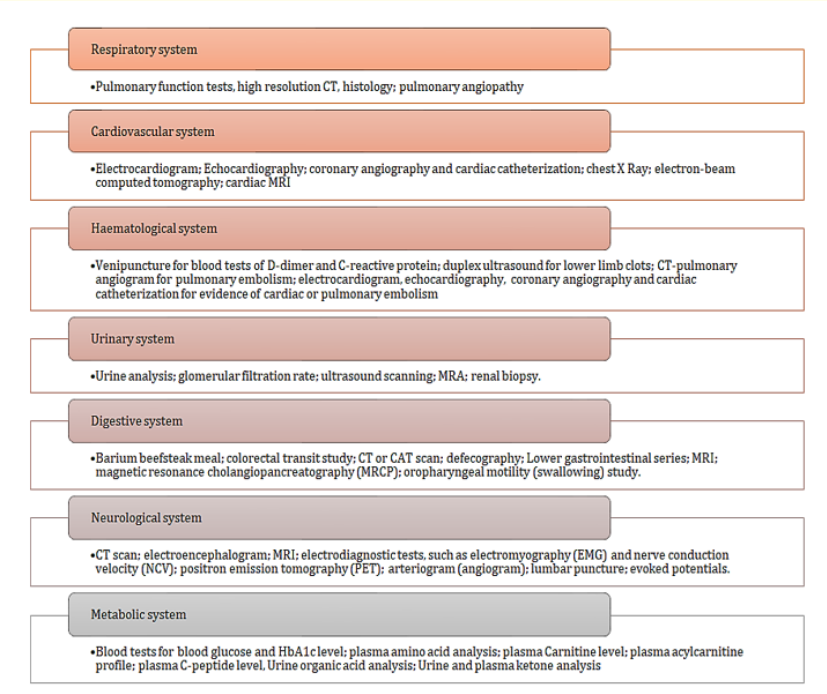

Figure 3: *Investigation tools for patients with Long COVID syndrome [102]*

Discovering and verifying biomarkers for the Long COVID diagnosis are vital; they will help establish the diagnosis and objectively quantify therapy responses.

Management of Long COVID

As the processes behind Long COVID still need to be fully understood, only some treatment options are available. Some nations have created clinical recommendations to help practitioners, although there are still questions about the best ways to treat people with Long COVID [30]. According to the NICE guideline, a clinical examination for Long COVID should begin as soon as 4 weeks following the onset of acute symptoms. Also, the National Institute of Health and Care Research (NIHR) advised prioritizing care for specific populations and assessing Long COVID symptoms [23]. A multidisciplinary approach is necessary to treat people with Long COVID and should include assessment, symptomatic treatment, treatment of underlying problems, physical therapy, occupational therapy, and psychological support [7,30,103].

Mild symptoms such as coughing, discomfort, and myalgia can be treated with paracetamol, cough suppressants, and oral antibiotics. However, if there is an etiology to the symptoms, they must be treated according to conventional practice, such as pulmonary embolism, cerebrovascular accident, or coronary artery disease [7].

Several ME/CFS treatment methods, such as pacing, symptom-specific pharmaceutical alternatives, and non-pharmacological approaches, benefit people with Long COVID [2,25,95,104,105]. Low-dose naltrexone has been used in many diseases, including ME/CFS, and has also shown promise in treating Long COVID [104,106]. H_1 and H_2 antihistamines, often following protocols for mast cell activation syndrome and particularly involving famotidine, alleviate many symptoms, although they are not a cure [107,108]. BC007, another drug, can potentially treat autoimmunity by neutralizing GPCR autoantibodies [109]. Anticoagulant regimens are a potential strategy for managing irregular clotting; in one investigation, all 24 patients undergoing triple anticoagulant medication had symptom remission [110,111]. Apheresis has also shown promise in easing Long COVID; it has been hypothesized to assist in removing micro clots and has been shown to reduce autoantibodies in ME/CFS patients [112,113]. However, its advantages could be more precise, and it is rather pricey. Coenzyme Q10 and d-ribose are 2 substances that have shown promise in treating both Long COVID and ME/CFS and may be worth further investigation [114].

Exploring additional treatment options for Long COVID is warranted based on findings from pilot studies and case reports. For example, a case report documented the resolution of Long COVID symptoms following treatment with the antiviral drug Paxlovid. Furthermore, studies investigating the use of Paxlovid for treating acute COVID-19 have reported a 25% reduction in the incidence of Long COVID. These findings suggest that Paxlovid should be further investigated as a possible treatment and preventive measure for Long COVID [115,116]. Charfeddine., *et al*. (2022) have observed that sulodexide reduced the intensity of symptoms in patients with endothelial dysfunction [117].

Vaccination: Vaccinations have been shown to dramatically lower the frequency of morbidity and mortality associated with COVID-19. Two recent investigations in Israel and the UK examined the incidence of Long COVID symptoms in patients with and without vaccinations. Both studies revealed a high correlation between immunization and reduced Long COVID-related symptoms. Furthermore, one of the studies found that those who have received the vaccine are not more likely than those who have not previously been exposed to the virus to report signs of Long COVID [118,119].

In addition to SARS-CoV-2 immunizations, patients claimed unrelated vaccines might provide protection. Recent influenza vaccination decreased the probability of SARS-CoV-2 infection and the severity of COVID-19, according to research conducted on healthcare workers [120]. The risk of sepsis, stroke, and deep vein thrombosis related to long-term COVID was also significantly reduced by influenza vaccination, and the number of admissions to emergency rooms and intensive care units also decreased, according to a retrospective analysis

[121] by Taghioff., *et al*. (2021). In addition to the recently developed COVID vaccine, the Bacillus Calmette-Guérin (BCG) vaccine against TB provides broad-spectrum immunity from various infectious illnesses [122,123].

In the COVID period, the BCG vaccine has been advocated against the severity of SARS-CoV-2, where it has been demonstrated that BCG immunization has a negative association with COVID-19 mortality [124]. Furthermore, according to a study by Fu., *et al*. (2021), the COVID-19 protection provided by the BCG vaccination was effective in young people but less so in older people [125].

Anti-inflammation treatment: During acute COVID-19 infection, immunological anomalies caused by molecular mimicry cause the formation of autoantibodies, which activate T cells and cause tissue destruction [126]. Therefore, controlling inflammatory responses is essential to treat the clinical consequences and viral manifestations of SARS-CoV2. In patients with acute COVID-19, dexamethasone is frequently used to alleviate inflammation. In an observational trial by Milne., *et al*. (2021), COVID-19 patients who received dexamethasone had a lower risk of Long COVID symptoms at the 8-month follow-up [127]. According to this study, the method used to treat acute COVID may significantly affect patients' well-being.

Repurposing drugs for Long COVID: In many nations, repurposed medications, such as hydroxychloroquine and ivermectin, are common, which might interfere with dexamethasone and vaccines, which are appropriate therapies. Such circumstances may enhance the likelihood of Long COVID development [3].

Antihistamines have been proposed as a potential therapy for COVID-19, with cellular studies indicating that histamine-1 antagonists may reduce COVID-19 infection rates by preventing SARS-CoV-2 from reaching ACE2-expressing cells [128].

The use of antidepressants has been suggested as a potential treatment for Long COVID. It is reported that antidepressant use is associated with a lower risk of intubation or death in COVID-19 patients [129]. Furthermore, a meta-analysis of antidepressant drug treatment for major depressive disorder has revealed that using antidepressants, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, leads to a decrease in peripheral inflammatory markers [130].

During the pandemic, an antiparasitic drug called ivermectin has been offered as a possible therapy for COVID-19. Unfortunately, several nations have turned to the inappropriate use of ivermectin as a COVID-19 control tool due to its accessibility and cost. However, laboratory results have been the primary evidence for using ivermectin in COVID-19 therapy. However, there are substantial methodological limitations in the clinical data used to justify using ivermectin [131].

Since the first COVID-19 epidemic, the anti-malarial drug chloroquine/hydroxychloroquine has been extensively used and investigated [132].

According to preliminary findings, hydroxychloroquine therapy improved viral clearance in individuals infected with COVID-19 compared to usual care [133]. However, as research progressed, the use of hydroxychloroquine became debatable, as there needed to be more well-designed trials and possible media bias [134]. Additional trials in Long COVID are shown in Figure 4 [135-140].

Natural remedies for Long COVID: Figure 5 shows some examples of herbal tinctures, dietary supplements, and food items that can be used as natural remedies to treat Long COVID [141,142].

Physical rehabilitation: Patients with severe acute COVID-19 managed in the intensive care unit (ICU) may experience muscle weakness, deconditioning, myopathies, and neuropathies, the physical manifestations of post-intensive care syndrome. To prevent this syndrome, appropriate rehabilitation is recommended to begin in the ICU as soon as sedation and clinical stability allow [143]. Patient breathing,

Reference	Sample size	Long COVID diagnosis	Comorbidities	Intervention	Comparator	Outcomes	Reference
Charfeddine et al.	290	Diagnosis based on NICE guidelines + endothelial dysfunction	37% had hypertension; 28% had diabetes mellitus	Sulodexide	None	On Day 21, sulodexide significantly reduced chest pain and endothelial dysfunction	135
Stadio et al.	158	Persistent olfactory dysfunction 6 months post-COVID	Excluded subjects with pre-existing olfactory disorders	PEA-LUT + olfactory training	Olfactory training only	PEA-LUT group showed greater improvement in olfactory function	136
Rathi et al.	200	Persistent fatigue 4–87 days after acute COVID	No comorbidities	Systemic and probiotic enzymes	Placebo	Greater improvement in fatigue in the intervention group	137
Jadhav and Jariwala 2	24	Persistent palpitations 7 days post-discharge	No known comorbidities	Ivabradine	Carvedilol	Ivabradine more effective in treating palpitations	138
Sabico et al.	36	Cough and gustatory loss 30 days after acute COVID	55% of participants had hypertension; 51% had diabetes mellitus	High dose vitamin D3	Low dose vitamin D3	Shorter time to recovery for cough and ageusia among individuals who received high dose vitamin D	139
Dhooria et al.	130	Persistent dyspnea or resting hypoxemia or exertional desaturation; and diffuse lung parenchymal changes 3–7 weeks after acute COVID	73% had at least one comorbidity (not specified)	High dose prednisolone (starting dose: 40 mg/day)	Low dose prednisolone (starting dose: 10 mg/day	No differences between high versus low dose prednisolone	140

Figure 4: *Trials in Long COVID interventions [135-140]*

exercise capacity, muscular strength, QoL, and functional results can all be enhanced with pulmonary rehabilitation [144]. Additionally, early mobility would benefit these patients' functional, cognitive, and pulmonary status and could reduce hospital stays [143].

Mental health support: Long-term effects of Long COVID include mental health and psychological problems such as anxiety, sadness, PTSD, and suicidal ideation. Patients who need more help can be examined as part of their follow-up treatment and referred to a specialist for treatment. However, caution should be exercised to avoid pathologizing individuals, as physical symptoms of COVID-19 can skew responses to evaluation instruments [4,145-148].

Emerging treatments

Emerging options for Long COVID treatment are shown in Figure 6 [3,23,29,114,149-154].

Challenges of studying Long COVID

Extended COVID research involves several obstacles. First, there still needs to be an agreed-upon definition for the Long COVID condition, no well-defined clinical symptoms, and no fully explained underlying physiological processes. As a result, it is challenging to adequately recognize and diagnose the disease and differentiate it from other chronic diseases with comparable symptoms [155,156].

Second, the striking variability of symptoms between Long COVID patients highlights the need to understand how symptoms change over time in specific individuals and how this is related to their clinical outcomes. Additionally, identifying individuals at risk of developing Long COVID is crucial. For example, it is essential to investigate the potential relationship between disease severity, symptoms during the acute phase, comorbid conditions, and longer-term consequences. Furthermore, understanding whether the immune response of Long COVID patients differs from those who do not develop the condition is another piece of the puzzle [157].

Food Item/ Dietary Supplement/ Herbal tincture	Benefits
Bone Broth	• Contains immune-system supporting amino acids, minerals, and glutathione (GSH) precursors • Anti-inflammatory activity
Beetroot and Greens (steamed, roasted, or juiced)	• ↑se nitric oxide (plays a role in the innate immune response in the airways and has bronchoprotective effects) • Protective against oxidative stress and inflammation with potential to decrease vascular inflammation
Vitamin C	• Antiviral effects; Regulates proliferation and function of T- and B-cells and natural killer cells; Prevent and repair oxidative damage; Improves endothelial dysfunction • ↓se acute respiratory infection symptoms, severity, and duration; ↓se mortality rate in patients with SARS-CoV-2 pneumonia
Vitamin D	• Involved in chemotaxis, phagocytosis, and B- and T-cell function • ↓se viral cellular infection via ACE-2 and ↓se viral replication • May curb inflammation and lower need for oxygen therapy and intensive care support in patients with COVID-19
Vitamin K2	• Prevents hypercalcemia that can result from vitamin D supplementation
Zinc	• Essential for immune cell growth and differentiation • Involved in phagocytosis, NK activity, and T-cell response to infection • Modulates cytokine release; Has potential to ↓se virulence and incidence, severity, and duration of upper respiratory infection • Cofactor for over 200 enzymes involved in antioxidant defense
Magnesium	• Activates and ↑se functionality of Vitamin D • Inhibit calcium influx in immunocompetent cells which limits NF-κB activation, IL-6, and CRP and therefore ↓se systemic inflammation • Coadministration with Vitamins D3 and B12 in hospitalized patients with COVID-19 was associated with a significant reduction in the requirement for oxygen therapy and intensive care support.
Acetyl L-carnitine	• Transports long-chain fatty acids into mitochondria for oxidation and energy production • Remove metabolic by-products from cells; ↓se total fatty tissue; Improve lipid profiles and ↓se physical and mental fatigue • ↓se inflammatory mediators in intestinal and CAD, as well as inactivating the hepatitis C virus, which is an RNA virus like SARS-CoV-2
Hydroxytyrosol	• Powerful antioxidant phenol compound • Anti-inflammatory properties • Inhibit NO and PGE2 production, leading to a decrease in secretion of cytokines and Chemokines
Vitamin A	• Regulates neutrophil, macrophage, NK cell, T- and B-cell activity; Influences differentiation of dendritic cell precursors ; • Required for mucin secretion and supports mucosal integrity • May ↓se morbidity and mortality from infectious disease; Inhibits proliferation of several types of viruses • May help with olfactory loss; Modulates Th1-Th2 cell balance and may ↑se Treg response (and inhibit progression to Th17)
Vitamin B12	• Involved in leukocyte production and may enhance macrophage function and number of cytotoxic T-cells against viral infections • Has anti-inflammatory effects via regulation of NF-κB57 • May inhibit non-structural protein 12 protein (involved in SARS-CoV-2 replication)
Vitamin B6	• Involved in antibody, T-cell, and interleukin production and lymphocyte maturation • ↑se the interaction between cytokines and chemokines; ↓se ROS production • Attenuates platelet aggregation and clot formation • Pyridoxal phosphate (PLP) levels inversely correlated with systemic inflammation • ↓se IL-1β production by suppressing NLR family pyrin domain containing 3 inflammasome.
Probiotics	• Enhance innate and adaptive immunity, prevent colonization by pathogens, ↓se incidence and severity of infections and ↑se clearance • Healthy gut microbiota is associated with lower systemic inflammation and prevention of an excessive immune response • Commensal microbes and their metabolites may block viral entry into cells (e.g., SARS-CoV-2 via ACE receptor sites) and viral replication
Osha	• Anti-inflammatory effects; May support the viability of peripheral blood lymphocytes via an increase in reduced glutathione levels and activity of superoxide dismutase and catalase
Echinacea	• Virucidal agent; ↓se severity and duration of ARI when taken at symptom onset • ↓se pro-inflammatory cytokines involved in cytokine storm and ARDS

Figure 5: *Natural remedies for Long COVID; ↑se: increase; ↓se: decrease [141,142]*

Third, the wide range of study results highlights how challenging it is to accurately estimate the risk of Long COVID [156]. According to Munblit., *et al*. (2022), one of the main drawbacks of the Long COVID condition study is the absence of premorbid data for comparison. If a patient does not have asymptomatic abnormal tests before infection, any abnormalities are often referred to as post-COVID-19 disease [155].

Fourth, given that there may be long-term effects, there is a significant gap and constraint in the study on the state after COVID-19 in pediatric and adolescent development [155]. Finally, another inevitable restriction is the possibility that infants with SARS-CoV-2 infection who were not screened or did not seroconvert could contaminate the uninfected control group [156].

Figure 6: *Emerging treatment options for Long COVID [3,23,29,114,149-154]*

Future perspectives and applications of Long COVID research

Given the wide variety of viruses that can cause chronic diseases, the long-lasting phenomenon of COVID should not surprise. For instance, Epstein-Barr virus-induced infectious mononucleosis can produce lingering symptoms, and viral infection can cause the chronic neurological illness Guillain-Barré syndrome. However, the SARS-CoV-2 virus stands out due to the large number of cases and the harmful consequences of infection on several organ systems, including the heart, lungs, liver, brain, and kidneys. Therefore, determining how SARS-CoV-2 infection could cause this complex disease requires urgent research [157]. Further efforts are needed to compare the long-term outcomes between inpatients and outpatients. Finally, the number of participants with results of the SARS-CoV-2 antibody test in the acute phase and follow-up was limited. Therefore, a larger sample is needed to clarify the dynamic changes of antibodies against SARS-CoV-2 [157].

The central clinical, serological, imaging, and epidemiological characteristics of COVID-19 in acute, subacute, and chronic illnesses must be identified and characterized through ongoing and future research—making it easier to understand this unique disease entity's pathophysiology and natural history. Clinical investigations, such as prospective cohort studies and clinical studies, should be carried out in the present and future to build a substantial knowledge base and guide therapeutic practice in this field. Working committees and task forces should also regularly assess new evidence [5]. Age-aggregated data must be collected for future investigations since young children and adolescents will have different incidence and Long COVID characteristics. Moreover, more research is required to examine the relationship between the number and duration of persistent symptoms and the initial severity of COVID-19 [156].

The long-term results for inpatients and outpatients need to be compared further. Lastly, some people had positive SARS-CoV-2 antibody test findings throughout the acute and follow-up phases. Therefore, a larger sample will be required to understand better the future dynamic variations of antibodies against SARS-CoV-2 [21].

The requirement for treatment for those who have COVID-19 sequelae will undoubtedly continue to increase in the coming weeks, given the global reach of the pandemic. Using current outpatient infrastructure, creating scalable healthcare models and integrating disciplines will be necessary to meet this challenge and improve the long-term mental and physical health of COVID-19 survivors [5].

Conclusion

Long COVID has a complicated and multifaceted etiology. According to available data, the principal causes of Long COVID appear to be the seeding and persistence of SARS-CoV-2 in several organs, reactivation and response to unrelated viruses such as EBV, autoimmune disease, and unchecked inflammation. It is critical that the study into post-COVID-19 syndrome continue since Long COVID is still a mystery, and new variations of COVID-19's potential effects on the prevalence and severity of Long COVID are still a big unknown. More knowledge about the pathophysiology, risk factors, symptoms, and treatment options is needed to ease the burden and pressure on those with Long COVID and the healthcare systems that will try to assist them. Future studies must also consider biases and problems with the SARS-CoV-2 test, expand on viral onset research, include under-represented communities, and meaningfully include patients throughout the study process to improve Long COVID research.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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