# Evolving Perspectives on Long COVID: Insights on Pathogenesis, Risk Factors, and Strategic Management

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## Abstract

Long COVID is a medical condition that occurs when people experience symptoms that last long after they have recovered from acute COVID-19 infection. These symptoms can vary widely and impact multiple organ systems, with varying levels of intensity. Although the underlying pathophysiology is not yet well understood, it is believed to involve a complex interplay between the immune system, viral persistence, and other factors. Several risk factors can contribute to the development of long COVID, such as older age, pre-existing medical comorbidities, and the severity of the acute COVID-19 infection. Clarifying the underlying pathophysiology and risk factors associated with long COVID is important to develop effective prevention and management strategies. This review aims to summarize existing data on the pathogenesis and risk factors of long COVID, the challenges of diagnosing and managing long COVID and highlights the need for further research to improve our understanding of this complex condition."

**Keywords:** Long COVID, Pathogenesis, Risk factors, SARS-CoV-2, COVID-19"

## Introduction

### What is COVID-19?

When the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) pandemic in March 2020, it was not initially considered that the disease could have a chronic nature. The causative pathogen responsible for COVID-19 is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pandemic has rapidly spread across the world and has resulted in more than 774 million confirmed cases and 7 million deaths as of 25th February 2024, according to the World Health Organization (WHO Coronavirus (COVID-19) Dashboard, n.d.). As of the latest available information in 2024, Malta has reported 71 cases and 1 death in the last 28 days to 25th February 2024. As more knowledge is being gained about this virus, we are also gaining a deeper understanding of the immediate and lasting consequences of contracting SARS-CoV-2.

The virus invades cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Once inside the host cell, the virus replicates and matures, eliciting inflammation and immune cell activation (2). The ACE2 receptors can be found in various cells across the human body, such as the mucous membranes in the nose and mouth, lungs, heart, brain, digestive system, liver, kidneys, and spleen, as well as the cells lining the arteries and veins. This indicates that the virus can potentially harm multiple organs.

Fever, cough, sore throat, loss of taste or smell, body pains, and diarrhoea are among the symptoms of COVID-19. Recovery from mild cases typically takes 7-10 days, while severe/critical cases can take up to 3-6 weeks. The clinical severity of COVID-19 ranges from no symptoms to life-threatening illness (3).

### What is Long COVID?

Long COVID refers to a condition where symptoms

persist or arise following an initial COVID-19 infection and cannot be attributed to any other medical condition (2). It is characterized by various symptoms, such as fatigue, shortness of breath, cognitive and mental abnormalities, headaches, muscle and joint pain, taste, and smell dysfunction, coughing, hair loss, sleep problems, wheezing, sputum, and cardiac and gastrointestinal issues (4). **Figure 1** highlights the multidimensional nature of long COVID, affecting various organ systems and some of its associated multi-organ manifestations.

**Figure 2** illustrates the distinction between ongoing symptomatic COVID-19, which refers to patients experiencing symptoms 4 to 12 weeks after onset, and post-COVID-19 syndrome, which refers to patients whose symptoms persist for more than 12 weeks after onset.

## Pathogenesis of Long COVID

The development of long COVID, with its persistent symptoms, is thought to result from a combination of inflammation and oxidative stress

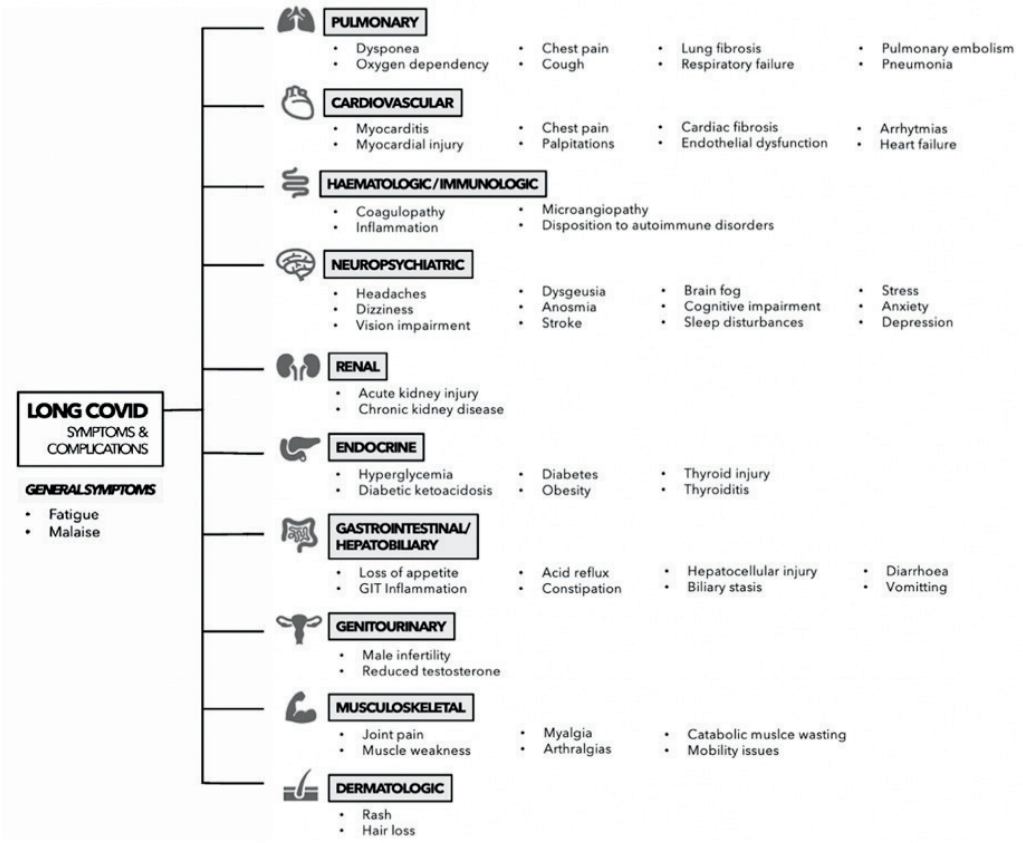


*Figure 1. Multi-organ complications associated with long COVID*
*Adapted from Crook et al., (2021); Nalbandian et al., (2021)*
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It can be challenging to diagnose long COVID due to its varying recovery period and diverse complications that may arise (5). The symptoms can either persist or be relapsing and remitting in nature and may involve the persistence of acute COVID symptoms or the development of new ones (3). Most individuals with long COVID have negative PCR tests, indicating that they have recovered microbiologically, but not clinically (6).

that weakens the immune response and allows the virus to persist. The virus and its remnants can also provoke ongoing inflammation, which leads to a cycle that contributes to long COVID (7).

### Entry of SARS-CoV-2 into host cell

The entry of the virus into host cells is facilitated by the ACE2 receptor, which is found on the surface of human cells. The coronavirus gains access to host

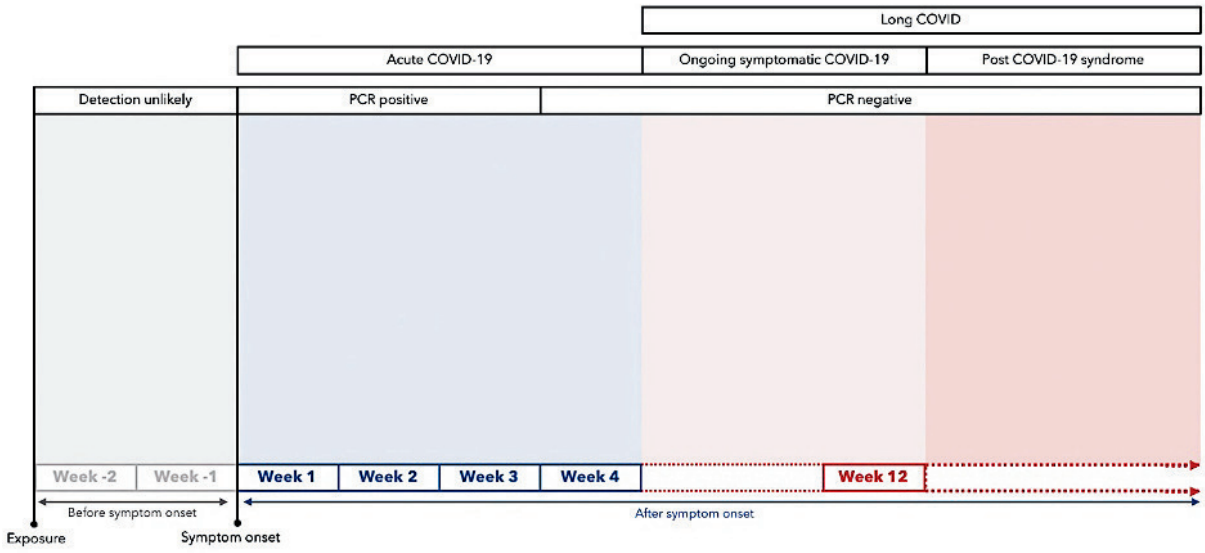


*Figure 2. Timeline of long COVID*
*Reproduced from Nalbandian et al., (2021); Raveendran et al., (2021)*
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cells by attaching to the ACE2 receptor using its spike protein, which acts like a key to unlock the door to the cell, as shown in **Figure 3**.

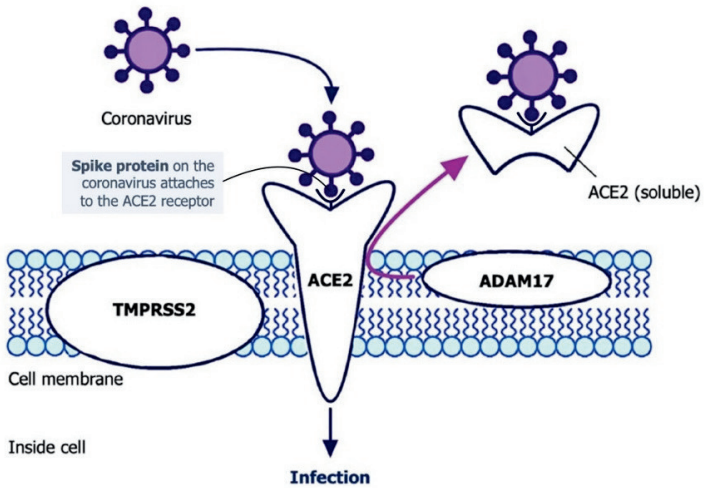


*Figure 3. Entry of coronavirus into host cell*
*Reproduced from Pradhan & Olsson, (2020).*
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Transmembrane protease serine 2 (TMPRSS2) then cuts the spike protein, aiding the virus in fusing with and entering the targeted cell. Eventually, the virus is then internalized into the cell through a process called endocytosis, where the virus is enclosed in a membrane-bound vesicle called an endosome (8). Once the virus has entered the cell, it begins to replicate itself by hijacking the cellular machinery of the host cell. This process leads to the production of new virus particles, which can then go on to infect other cells and cause the spread of the infection throughout the body (9).

The binding of the coronavirus to the ACE2 receptor in these tissues can cause damage and inflammation, leading to the symptoms of COVID-19. This mechanism also explains why certain populations, such as older adults and those with underlying health comorbidities, may be more vulnerable to severe COVID-19 disease (9).

ADAM17 (a disintegrin and metalloproteinase 17), also known as TACE (tumour necrosis factor-α converting enzyme), is a protein that regulates several cellular processes, along with inflammation (10). In the context of COVID-19, ADAM17 can cleave the ACE2 receptor, which releases its ectodomain in a soluble form This soluble form can bind to the virus and potentially hinder its ability to infect cells (11).

The spike protein of the coronavirus can induce ADAM17 activation, leading to the shedding of ACE2 from the cell surface. When ACE2 is shed from the cell surface, the number of ACE2

receptors available for the virus to bind to is reduced. This reduction in the number of ACE2 receptors can reduce the immune system's ability to control the infection, as the virus has fewer targets to attack (10). This can ultimately result in increased susceptibility to the virus.

Furthermore, the shedding of ACE2 can also contribute to the development of acute respiratory distress syndrome (ARDS), which is a severe complication of COVID-19.

The physiological role of ACE2 receptors is to degrade angiotensin II, maintaining a delicate balance in the renin-angiotensin-aldosterone system (RAAS). However, the downregulation of these receptors by the virus results in an escalation of angiotensin II levels, contributing to systemic injury, pulmonary fibrosis, pulmonary inflammation, and other pathological manifestations, which ultimately lead to COVID-19 progression, especially in patients with comorbidities, such as hypertension, diabetes mellitus, and cardiovascular disease (12). However, it is notable that while some studies have suggested a potential role for ADAM17 in the pathogenesis of COVID-19, further insight is needed to fully understand its precise role and the mechanisms involved.

## Genetic Factors Associated with Long COVID

The ACE2 gene codes for the ACE2 receptor, while the TMPRSS2 gene codes for the TMPRSS2, which is a serine protease that is expressed in many human tissues, such as the lungs, prostate, and colon (13). In the context of COVID-19, the expression of both ACE2 and TMPRSS2 in the respiratory tract is of particular importance, as this is where the virus primarily infects and replicates (9).

Genetic variation in the ACE and TMPRSS2 genes may be a contributing factor to the susceptibility, severity, and development of long COVID (14) but the findings are still inconclusive. A few notable studies have reported associations between certain ACE2 gene variants and COVID-19 severity. For example, the rs4646116 variant, which is situated in the ACE2 gene's promoter region, was linked to a higher likelihood of experiencing severe COVID-19. It was proposed that this variant might have an impact on the expression of ACE2 (15).

Cao et al., (2020) reported that individuals who carry the rs2285666 variant have been found to have an increased risk of experiencing severe COVID-19. This variant is thought to reduce the expression of ACE2, which may interfere with the immune system's ability to fight the virus.

The rs2106809 variant has been linked to an increased risk of contracting COVID-19 and developing severe disease. It is situated within an intron of the ACE2 gene and is believed to impact the splicing of ACE2 mRNA. Additionally, other studies found that this variant was more prevalent among men than women (17,18).

On the contrary, certain variants in the TMPRSS2 gene were correlated with a decreased risk for severe COVID-19. For example, the rs12329760 variant has been linked to reduced expression of TMPRSS2 and a lower risk of experiencing severe COVID-19 symptoms (19). Another example is the rs35074065 variant, which has also been associated with decreased expression of TMPRSS2 and a lower risk of severe COVID-19 (15).

Overall, these studies suggest that genetic factors, including genetic variations in the ACE gene, may contribute to the development of long COVID. It is important to note that these associations have been observed in different populations and may not be universal. The relationship between ACE gene variants and COVID-19 outcomes is an area of ongoing research, and further studies are needed to establish any definitive associations (14).

Numerous variants of the coronavirus have been identified and, while all of them have the potential to cause long COVID, certain variants have been more commonly linked to this condition. The Delta variant (B.1.617.2) has been found to be more strongly linked to long COVID compared to the

Alpha variant (B.1.1.7) and other variants (20). Moreover, being infected with the Delta variant is linked to an increased likelihood of being hospitalized and death compared to other variants (21). It is important to note, however, that long COVID can arise from infection with any variant of the coronavirus and the severity and duration of symptoms can vary greatly among individuals.

### Dysregulation of the Immune System

The underlying mechanisms of long COVID are not yet well understood, but recent evidence suggests that dysregulation of the immune system might have a part to play. Initially, the body mounts a strong pro-inflammatory response to the virus, but this can eventually result in immunosuppression, which may help to balance the immune system and preserve immunological homeostasis but can also contribute to long COVID (22).

Furthermore, dysregulation of the macrophage cascade has been linked to the pathogenesis of long COVID. Macrophages are immune cells that respond to infection and tissue repair. During the acute phase of infection, macrophages are recruited to the site of infection, where they phagocytose viral particles and infected cells. This initial response is crucial for clearing the virus and preventing further spread (3). However, in some individuals, macrophages may become dysregulated, leading to chronic inflammation and tissue damage. This dysregulation may be attributed to many factors, including genetic predisposition, pre-existing conditions, and the severity of the initial infection (23).

Coperchini et al., (2020) revealed that individuals with long COVID had higher levels of a protein called CCL18, which is produced by macrophages, than recovered individuals or healthy controls, implicating dysregulated macrophage activity which may contribute to the persistent inflammation observed in long COVID. The role of CCL-18 in healthy macrophages is to recruit and activate other immune cells such as T cells and eosinophils to the site of infection or inflammation. CCL-18 also promotes the migration of dendritic cells which play an important part in initiating adaptive immune responses (25). While the exact mechanisms by which CCL-18 contributes to dysregulated macrophage activity in long COVID are not fully understood, it has been hypothesized that CCL-18 may contribute to the persistent inflammatory response observed in this condition. This may potentially lead to long-term tissue damage and dysfunction (24).

Recovered patients may be susceptible to reinfection or viral reactivation, and previous studies suggest that viral RNA can persist in various body fluids and tissues, including respiratory secretions, blood, stool, and urine, for several weeks or even months after infection (26). Therefore, acute COVID-19 infection can cause long-term activation of the immune system, which may contribute to the onset of long COVID.

However, the presence of viral RNA may not necessarily signify that the virus itself is still replicating in the body. It is possible that the viral RNA detected during post-infection periods is simply residual genetic material from the initial infection that has not yet been cleared by the immune system or eliminated from the body (26). The duration and extent of SARS-CoV-2 RNA shedding can vary among individuals and may be influenced by many factors, such as disease severity and immune status (27).

## Risk Factors of Long COVID

Age, sex, severity of acute COVID-19 infection, pre-existing medical comorbidities such as obesity, heart disease and diabetes, socioeconomic status, and specific symptoms during acute infection are all significant risk factors for long COVID.

### Age

Age difference plays a significant role in the incidence and severity of long COVID. Older people and those with pre-existing medical

conditions are more vulnerable to developing persistent symptoms and are at greater risk of experiencing serious complications from COVID-19 (28). The immune system of older adults is less efficient, and the presence of comorbidities such as heart disease, diabetes, and respiratory disease, which are more common in older age groups, can worsen the severity of COVID-19 symptoms and increase the risk for long COVID (29).

Collier et al., (2021) evaluated the vaccines' efficacy against variants of concern. Results revealed that after the first vaccine dose, the levels of binding IgG or IgA and serum neutralization were lower in older patients, especially those aged over eighty. The study concluded that the elderly population is a high-risk population which requires specific precautions to improve their vaccine responses, especially in situations where variants of concern are present.

On the other hand, Subramanian et al., (2022) demonstrated the opposite trend, revealing that advanced age was associated with a reduced risk of experiencing long COVID. Specifically, individuals aged 30 to 39 exhibited a 6% lower risk, while those aged 70 and above had a 25% lower risk, in comparison to those aged 18 to 30.

One possible explanation for this is that older adults may be less likely to mount an overly aggressive immune response to the infection, which is considered to be one of the underlying mechanisms contributing to the pathogenesis of long COVID. This is because the immune system tends to weaken as we age, which may result in a less robust response to the virus that is less likely to cause persistent symptoms.

Moreover, older adults might be at a higher risk of having pre-existing health conditions. While these conditions can intensify the severity of the acute infection, they may also provide a degree of protection against long COVID. The reasoning behind this is that individuals with pre-existing medical conditions may have already been dealing with chronic symptoms related to their underlying health issues before contracting COVID-19. In other words, their baseline health condition may have prepared their immune system or physiological responses in a way that influences the course and manifestation of symptoms during a COVID-19 infection. However, this is a speculative interpretation, since the field of long COVID is still being actively researched, and the interplay between pre-existing health conditions and the outcomes of long COVID is complex and not yet fully understood (32).

Children present with milder clinical manifestations than in adults. One study found that children exhibited heightened levels of Angiotensin II with diminished degradation, coupled with lower ACE2 protein expression. Additionally, TMPRSS2 showed no age-related changes. These findings may partially account for the lower susceptibility of children to COVID-19 (33). it is noteworthy that the interrelation between age and long COVID is not yet well understood, and further insight is needed to better understand the factors that contribute to long COVID in different age groups.

### Sex

Studies have indicated a higher susceptibility to long COVID among women in comparison to men. In one study, electronic health records of COVID-19 patients were examined, and it was found that women had a greater risk of developing long COVID than men. Specifically, the study found that women were about 30% more likely than men to experience long COVID (20).

Carfì et al., (2020) analysed data from patients with confirmed or suspected COVID-19 and found that women reported more symptoms and had a longer duration of symptoms than men. The study also found that women were more likely to report fatigue, headache, and loss of smell and taste.

Although the specific causes of sex-based differences in long COVID are still unclear, they

could potentially be attributed to dissimilarities in immune response, hormone levels, and underlying medical conditions. Generally, women possess more robust immune responses compared to men, which could make them more vulnerable to autoimmune diseases and chronic inflammation (4). Hormone levels could also influence the immune response and inflammation in women. Besides, women have higher probabilities than men of suffering from underlying medical conditions such as thyroid disorders or autoimmune diseases, which could increase the risk of long COVID (22). Further insight is required to comprehend the fundamental mechanisms that give rise to these dissimilarities.

## Comorbidities

### Obesity

Obesity is linked to a state of chronic inflammation, which could increase the likelihood of experiencing long COVID. Moreover, obesity is recognized to impede immune functioning, rendering it more difficult for the body to combat infections, including COVID-19 (34).

A study revealed that there is a correlation between obesity and an increased risk of being hospitalized and dying from COVID-19, as well as an increased likelihood of experiencing long COVID symptoms, even in individuals with mild to moderate COVID-19 disease. The authors hypothesized that the systemic inflammation and immune dysregulation associated with obesity could increase the risk for long COVID (35).

Obesity increases the risk for long COVID due to the impact it has on the body's immune system and overall health. Obesity is a chronic condition that is associated with chronic inflammation, oxidative stress, and metabolic dysfunction, all of which can impair immune function and raise the incidence of severe COVID-19 and long COVID (36).Furthermore, obesity is correlated to several pre-existing medical conditions, which are also risk factors for severe COVID-19 and long COVID. Having these comorbidities can weaken the immune system and raise the risk of experiencing long COVID (37).

In addition, obesity is associated with respiratory dysfunction, such as reduced lung capacity and impaired gas exchange. This can make it more difficult to recover from pulmonary infections, including COVID-19, and increase the incidence of long-term respiratory complications (36). Moreover, obesity increases the risk of blood clotting disorders, such as stroke and thrombosis (38).

Given the growing evidence linking obesity to long COVID, it is essential to prioritize weight management and lifestyle interventions as part of the long-term care of recovered individuals, particularly those with obesity (34).

### Diabetes

Diabetic individuals are at a greater risk for severe COVID-19 disease, being hospitalized, and dying from COVID-19 (39). Furthermore, people who have diabetes and contract COVID-19 with mild to moderate symptoms have a greater probability of experiencing long COVID symptoms compared to those without diabetes (20).

Diabetes impairs the immune system's ability to fight the virus and increases inflammation in the body (40). Diabetes is linked with chronic low-grade inflammation, which can result in an exaggerated immune response when the body encounters a novel pathogen like the SARS-CoV-2 virus. This exaggerated immune response can cause harm to the body's tissues and organs and contribute to long COVID symptoms.

Additionally, diabetic patients have a higher risk of developing other health conditions that are also risk factors for long COVID, such as heart disease and obesity (41). Generally, individuals with diabetes should take extra precautions to avoid COVID-19 infection, and if they do contract the virus, they should be closely monitored for long COVID symptoms.

## Hypertension

Several mechanisms have been identified through which hypertension can increase the likelihood of long COVID. Firstly, hypertension is correlated to endothelial dysfunction, which is the impaired function of the cells that line the blood vessels. This results in inflammation and damage to the blood vessels, which might raise the incidence of blood clotting disorders and cardiovascular complications, both of which are risk factors for long COVID (42). Furthermore, hypertension is associated with comorbidities such as diabetes and heart disease, all of which are also risk factors for long COVID.

## Heart Disease

Individuals with pre-existing cardiovascular disease (CVD) have a higher risk of experiencing long COVID. Patients with underlying CVD are more likely to require hospitalization, admission to the intensive care unit, and mechanical ventilation, and they have a higher incidence of dying from COVID-19 (43). The underlying mechanisms of how pre-existing CVD increases the risk of long COVID are not well understood, but it is thought to be related to the chronic inflammation and immune dysregulation that are present in CVD patients. COVID-19 infection can further exacerbate these underlying conditions, leading to increased damage to the cardiovascular system and increased risk of long COVID (44).

## Chronic Lung Disease

Chronic lung disease, like chronic obstructive pulmonary disease (COPD) and interstitial lung disease, can increase the risk for long COVID in several ways. Firstly, these conditions can impair lung function and respiratory capacity, making it more difficult for individuals to recover from acute respiratory infections like COVID-19 (45). Secondly, chronic lung disease is associated with chronic inflammation and oxidative stress, which can weaken the immune system and make individuals more vulnerable to infections and complications (46).

Additionally, chronic lung disease can also increase the risk of comorbidities such as CVD and diabetes, which are also risk factors for long COVID. Finally, chronic lung disease is correlated to blood clotting disorders such as stroke and thrombosis, which can contribute to long-term complications of COVID-19 (28).

Many studies have explored the correlation between chronic lung disease and long COVID. For example, a study by Havervall et al., (2021) found that individuals with COPD were more likely to have persistent symptoms of COVID-19 six months after their initial infection compared to those without COPD. Similarly, a study by Carfì et al. 2020 found that individuals with interstitial lung disease had a greater risk of developing long COVID compared to those without pre-existing lung disease.

## Cancer

There is limited information available on how cancer increases the risk for long COVID, as research on this topic is ongoing. However, cancer is considered a risk factor for severe COVID-19 and may contribute to the pathogenesis of long COVID through several mechanisms.

Cancer itself can weaken the immune system, making individuals more vulnerable to infections and complications. Medical procedures like chemotherapy or radiation therapy that are employed to treat cancer can debilitate the immune system and intensify the likelihood of developing infections. Moreover, cancer itself and the related treatments can lead to chronic inflammation and oxidative stress, which can lead to long-term harm to various organ systems in the body, including the lungs, brain, and heart (48). Nevertheless, more exploration is needed to better understand how cancer affects the risk of long COVID.

## Demographic groups and Socioeconomic status

Recent studies have suggested that some

demographic groups are at greater risk of experiencing long COVID. For example, a study in the United States found that African American and Hispanic populations have a greater probability of experiencing long COVID compared to White populations (49). Additionally, Subramanian et al., (2022) demonstrated that when compared to white ethnic groups, a greater risk for long COVID was observed in Black Afro-Caribbean ethnic groups, mixed ethnicity, and other minority ethnic groups consisting of individuals with native American, Middle Eastern or Polynesian origins.

One possible factor is pre-existing health conditions that are more common among these groups, such as hypertension, obesity, and diabetes. These conditions have been identified as risk factors for severe COVID-19 and may also increase the likelihood of long COVID. Additionally, there may be genetic factors that contribute to the higher risk in these groups (50).

Another factor is structural racism and social determinants of health that may contribute to inequities in access to healthcare, among other factors. These inequities can lead to greater levels of stress and chronic health conditions, which all raise the risk for long COVID (51).

Subramanian et al., (2022) found that the risk of long COVID also rose as the level of socioeconomic deprivation increased. Individuals who were most socioeconomically deprived had an 11% higher risk compared to those who were least deprived. Socioeconomic deprivation is associated with a range of health disparities, including greater incidences of chronic health conditions, lower access to healthcare, and increased exposure to environmental hazards (52). All of these factors can collectively elevate the chances of experiencing severe COVID-19 symptoms and developing long COVID.

One possible factor is that individuals living in socioeconomic deprivation may be more likely to have jobs that require in-person work and have less flexibility for remote work (53). This may increase their exposure to the virus, leading to a greater risk of infection and subsequently, long COVID.

Additionally, individuals living in socioeconomic deprivation may have less access to healthcare and preventive services, making it more difficult to manage pre-existing health conditions that increase the risk for long COVID. They may also be less inclined to seek medical attention for symptoms related to long COVID, which could delay diagnosis and treatment (54).

Furthermore, individuals living in socioeconomic deprivation may have higher levels of stress and anxiety, which also increase the incidence of long COVID. Chronic stress has been shown to have a negative impact on the immune system, making it harder to fight off infections and recover from illness (53). Addressing these disparities through targeted interventions and policies could help reduce the incidence of long COVID in this population.

### Smoking

Subramanian et al., (2022) revealed that individuals who smoke or previously smoked had a higher incidence of reporting long COVID symptoms compared to those who never smoked. Smoking is known to impair lung function and reduce the body's ability to fight off infections. This can make smokers more vulnerable to respiratory infections, including COVID-19, and may increase the disease's severity (55).

Additionally, smoking is correlated to a range of pre-existing medical conditions, including heart disease, COPD, and cancer, which increase the risk of long COVID. Having prior health conditions can compromise the immune system, which in turn elevates the chances of developing long COVID. (56). Furthermore, smoking is known to cause oxidative stress and inflammation, which can further damage the body's organs and tissues. This can contribute to long-term complications, such as chronic fatigue, neurological symptoms, and

respiratory problems (55). Lastly, smoking is also a known risk factor for blood clotting disorders such as stroke and thrombosis (56). Quitting smoking can help decrease the incidence of severe COVID-19 and long COVID, as well as improve overall health and well-being.

## Severity of acute COVID-19 infection

A major contributing factor for developing long COVID is the severity of the acute infection. Individuals who experienced severe symptoms or required hospitalization are more likely to develop long COVID (57). It was pointed out that COVID-19 patients who are hospitalized in the ICU may also be at risk of developing post-intensive care syndrome. This suggests that there may be an interdependent correlation between the COVID-19 severity and post-intensive care syndrome (22).

## Presence of specific symptoms

Another risk factor for long COVID is the presence of specific symptoms during the acute infection. For example, individuals who experienced shortness of breath, fatigue, or headaches during acute infection have a greater probability to develop long COVID symptoms (20).

With an increasing number of individuals experiencing long COVID, healthcare systems are anticipated to face a significant challenge in providing long-term care. To tackle this challenge, it is essential for researchers to scrutinize the current literature to determine the risk factors linked with long COVID. Establishing clear criteria to recognize susceptible individuals can facilitate healthcare authorities in the early identification and treatment of the condition (7). Identifying these major risk factors may help to recognise those who are most at risk of developing long COVID, allowing for earlier interventions and management of the condition.

## Presence of specific symptoms

The development of long COVID has been linked with biomarkers that indicate the severity of COVID-19. For instance, individuals who experienced long COVID and had been hospitalized for COVID-19 had high levels of D-dimer and blood urea nitrogen, which increased their risk of pulmonary dysfunction three months after discharge (22).

High levels of D-dimer in COVID-19 patients are significant because it is a marker of blood clotting activation and the breakdown of blood clots in the body. COVID-19 can cause abnormal blood clotting, and high levels of D-dimer indicate that blood clotting is occurring in the body. This can lead to a greater risk of severe complications, such as stroke, heart attack, and pulmonary embolism (58). Therefore, monitoring D-dimer levels is important to identify those who may be at a greater risk for severe complications and may require more aggressive treatments such as anticoagulation therapy.

High levels of blood urea nitrogen (BUN) are significant because it is a marker of kidney dysfunction or injury (59).COVID-19 can affect the kidneys and lead to acute kidney injury, which can be a serious complication of the disease. Elevated BUN levels imply that the kidneys are not working efficiently enough to eliminate waste substances from the blood. This can lead to a build-up of toxins in the body, which can cause further damage to the kidneys and other organs (60). Monitoring BUN levels in COVID-19 patients is important to identify those who may be at a higher risk of kidney injury and may require more aggressive treatments such as dialysis.

COVID-19 survivors who showed elevated biomarkers of systemic inflammation and lymphopenia were also found to have radiological

lesions in different organs three months after they were discharged (61). To predict the advancement of long COVID, biomarkers of inflammation and lymphocyte counts should be considered alongside persisting symptoms in COVID-19 survivors (22).

Troponin is a protein biomarker that is commonly used to diagnose and monitor heart damage. High levels of troponin in long COVID patients may indicate that they have suffered some level of heart damage or injury, which could potentially lead to cardiovascular complications (62). However, it has been implied that elevated troponin levels may also be associated with chronic fatigue in long COVID patients.

Chronic fatigue is one of the most common and persistent symptoms reported by individuals with long COVID. It is characterized by profound and persistent exhaustion that is not relieved by rest. Although the exact cause of chronic fatigue in long COVID is not yet fully understood, experts have suggested that it may be related to inflammation and damage to various organs, including the heart (63).

It is important for healthcare providers to monitor troponin levels in long COVID patients to help identify those who may be vulnerable to developing cardiovascular complications and to identify long COVID patients who are at risk of developing chronic fatigue. More research is necessary to fully comprehend the relationship between troponin levels, heart damage, and chronic fatigue in long COVID patients, as well as to develop effective treatments for these symptoms.

To effectively manage the expected high number of long COVID patients, it is crucial to identify markers that can predict the onset of long COVID. Further research is needed to discover these predictors, which will aid long COVID clinics in prioritizing the most vulnerable individuals and providing care to those in need (7).

## Long COVID symptom assessment and management

Assessment and management of long COVID requires a multidisciplinary approach and collaboration between different healthcare professionals – as depicted in **Figure 4**. Assessment of long COVID should begin with a thorough medical history and physical examination, including evaluation of vital signs, respiratory function, and cardiac function (64). Diagnostic testing may also be necessary to evaluate specific symptoms or comorbidities. Serologic testing for viral antibodies may be helpful in identifying patients who have been infected with the virus and are exhibiting symptoms consistent with long COVID. In addition, imaging studies such as chest X-rays or CT scans may be needed to evaluate respiratory symptoms or potential complications (65).

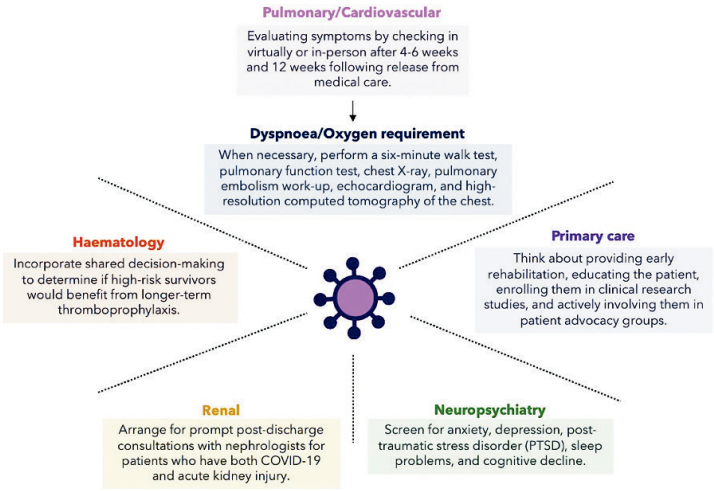


*Figure 4. Interdisciplinary approach to managing long COVID patients*
*Reproduced from Nalbandian et al., (2021)*
*Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Washington, USA*

Priority may be given to those with a higher risk of experiencing long-term COVID-19 symptoms, including individuals who had severe acute COVID-19, required ICU care, are elderly, and have pre-existing health conditions, such as respiratory

disease, obesity, hypertension, CVD, diabetes, CKD, post-organ transplant, or active cancer (29). It remains unclear how long these symptoms last and if they are exclusive to COVID-19 or related to pre-existing health conditions.

Management of long COVID is focused on symptom relief and improving overall quality of life. Treatment may include medications to address specific symptoms, such as pain or shortness of breath. Rehabilitation programs, including physical and occupational therapy, may be helpful for patients experiencing weakness, fatigue, or cognitive impairment. Psychological support and counselling can also be important for addressing the emotional impact of long COVID, which can be significant for patients and their families (66).

It is noteworthy that there is limited information on the long-term outcomes of patients with long COVID, and research is ongoing to better understand the condition and develop effective treatments. In addition, COVID-19 vaccination has been shown to be effective in preventing severe illness and hospitalization from the virus and may also help prevent long COVID (67).

Concisely, long COVID is a complex condition that requires a comprehensive approach for assessment and management. A multidisciplinary team of healthcare professionals is essential for providing appropriate care and improving outcomes for patients. Ongoing research is required to gain a deeper comprehension of the condition and develop effective treatments.

## Long COVID symptom assessment and management

In conclusion, long COVID is a serious and ongoing health concern for individuals who have experienced a COVID-19 infection. While the exact mechanisms underlying long COVID are still not fully understood, the condition can manifest in a variety of symptoms that can persist for months after the initial infection has resolved.

Moving forward, it is clear that more research is needed to better understand the causes and potential treatments for long COVID. This includes investigations into the underlying pathophysiology of the condition, as well as studies aimed at developing targeted interventions to improve outcomes for affected individuals. Additionally, efforts should be made to raise awareness of long COVID among healthcare providers, as well as the general public, in order to facilitate early diagnosis and appropriate management of the condition.

In terms of clinical management, there is currently no specific treatment or cure for long COVID. However, there are various interventions that may help to alleviate symptoms and improve the quality of life for affected individuals. These may include physical therapy, cognitive behavioural therapy, and pharmacologic interventions such as pain medications or antidepressants.

In summary, long COVID is a complex and multifaceted condition that requires further exploration and clinical attention. By continuing to study and address this issue, we can work towards improving outcomes for individuals affected by long COVID and better understanding the long-term impacts of COVID-19 on global health.

## Author Contributions

KL contributed to the analysis and interpretation of the data and was responsible for drafting the manuscript. MZM provided critical revisions for the manuscript.


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## Disclosure Statement

The authors involved in this project declare no conflicts of interest.

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