**Literature Review**

INTRODUCTION

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a term used to describe a collection of persistent symptoms that last longer than the standard two-week recovery period following acute COVID-19 infection. The symptoms of long COVID are varied for each individual based on the severity and may impact several organ systems. The purpose of this literature review is to summarize the current understanding of long COVID in terms of the symptoms, diagnosis, treatments, prevention and mechanism.

2.1.1 Epidemiology of Long COVID

The epidemiology of long COVID is still being studied, and several studies have found and provided valuable insights regarding its prevalence. A study of 25 observational studies, conducted by Martimbianco et al. (2021), discovered that among the 5440 participants, the prevalence of long Covid varied from 4.7 to 80%. According to a different study done in Jin Yin-tan Hospital in Wuhan, China, 76% of patients (1265 of 1655) have reported at least one symptom at the follow-up (Huang et al., 2021). Similar to this, a systematic study of the effect of long COVID found that 80% of SARS-CoV-2 infected patients experienced one or more long-term symptoms (Lopez-Leon et al., 2021). It is imperative to comprehend the mechanism of long COVID since recent data indicate that individuals who survive the acute phase of the illness are at risk for long-term sequelae with involvement of the skin, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal systems (Akbarialiabad et al., 2021).

2.1.2 Understanding Long COVID

Scientific studies show that there are several different types of symptoms that patients experience. The most frequently reported symptoms, according to a cohort study of 1733 patients in Wuhan, China, were muscle weakness and fatigue at 63%, followed by sleep issues with 26% and anxiety/depression at 23%. 76% of patients experienced at least one chronic symptom with a median follow-up of 186 days, with women reporting the highest rates (Huang et al., 2021). In another cohort analysis of 183 patients, fatigue, dyspnea, and muscle soreness persisted 35 days following hospitalization. These symptoms were also linked to lower assessments of physical and mental health, quality of life, and participation in active social activities (Jacobs et al., 2020). In a long-term trial of 180 non-hospitalized COVID-19 patients, 53% of patients experienced persisting symptoms, with exhaustion and loss of smell and taste and joint pain being the most common (Weihe et al., 2020). The symptoms of long COVID can range from joint pain, fatigue, headaches and more as identified by the previous studies. Therefore, Raveendran has clustered the symptoms into three categories which are respiratory symptom cluster, musculoskeletal symptom cluster and enteric symptom cluster. Each of these clusters specifies a set of symptoms (Raveendran et al., 2021). The respiratory symptom cluster includes symptoms such as cough, sputum, shortness of breath, and fever. The musculoskeletal symptom includes myalgia, joint pain, headache, and fatigue. Abdominal pain, vomiting, and diarrhea are the symptoms within the enteric symptom cluster.

2.2 CLINICAL MANIFESTATIONS

2.2.1 Symptoms of Long COVID

The most reported symptoms that were associated together with long COVID were researched and analyzed in many journals. Among all the studies, the most prominent symptom with the highest percentage among long COVID patients is Fatigue. Raveendran also had analyzed two primary symptom patterns in persons with long COVID based on the data obtained from a study that collected data via a COVID Symptoms Study App conducted by Sudre et al. (2021): 1) multi-system complaints, which include continuous fever and gastroenterological symptoms, and 2) exhaustion, headache, and upper respiratory complaints (shortness of breath, sore throat, persistent cough, and loss of smell).

Several long-COVID symptoms have been documented and linked to different organs which have the hACE2 receptor. A study conducted in July 2021 had analyzed the different symptoms and categorized them accordingly (Crook et al., 2021). The image below (Figure 2.1) was retrieved from the article shows the organs and symptoms that are related to each organ.

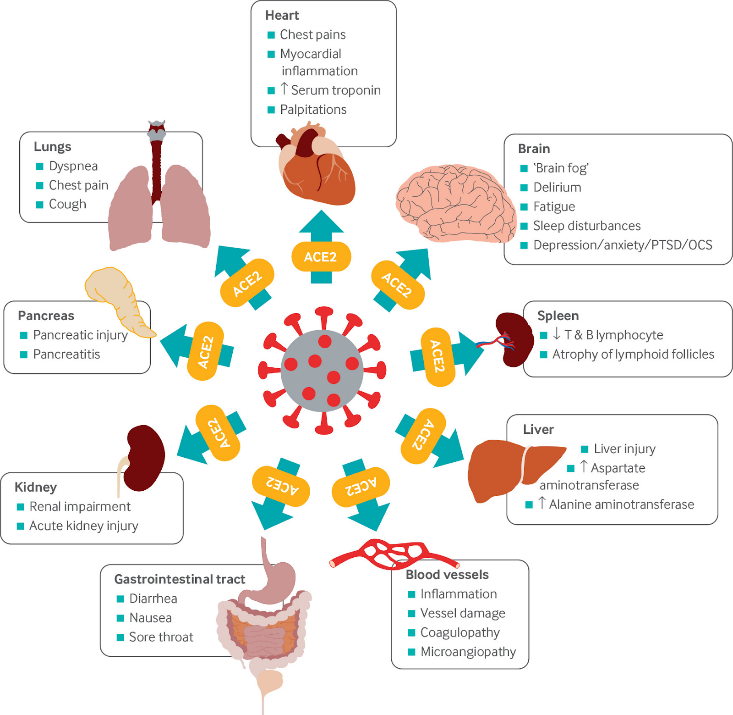


Figure 2.1: The presence of hACE2 receptors in each organ and long COVID symptoms associated with each organ. Diagram obtained from Crook et al (2021).

2.2.2 Severity and Duration of Symptom

Based on a systematic review of an article, it was found that there was a total of fifty-five long COVID symptoms that were identified. Among those fifty-five symptoms, the top five most prominent symptoms include fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) (Lopez-Leon et al., 2021). Fatigue, which is found to be the most common symptom of long COVID, was found to be present 100 days following the onset of the first acute COVID-19 symptom. The symptoms seen in post-COVID-19 patients share some similarities with those of chronic fatigue syndrome (CFS), which is characterized by severe, incapacitating fatigue, pain, neurocognitive impairment, disrupted sleep, symptoms of autonomic dysfunction, and worsening of overall symptoms in response to slight increases in physical and/or mental activity. There have been reports of headache and attention problems among other neuropsychiatric symptoms. According to the report, the causes of COVID-19 individuals' neuropsychiatric symptoms are complicated and multifactorial. The direct impact of the infection, cerebrovascular disease (including hypercoagulation), physiological compromise (hypoxia), drug side effects, and social elements of having a potentially fatal illness are possible connections among them. After receiving a COVID-19 diagnosis, adults are twice as likely to receive a new diagnosis of a psychiatric disorder, and the most prevalent psychiatric illnesses reported were dementia, insomnia, and anxiety disorders. Dyspnea which is found in a significant number of patients presented around 35% of patients who continued to have abnormal CT lung scans 60 to 100 days after the initial presentation. In addition, follow-up research among non-critical COVID-19 hospitalized patients in China found that two-thirds of patients continued to have abnormal radiography 90 days after discharge. Interestingly, another review paper from nature.com, showed a survey where more than 1.3 million people who had COVID-19, identified mental health issues including anxiety and depression gradually returned to normal, but there was an increase in the chance of neurocognitive conditions like dementia, psychosis, seizures, and brain fog for at least two years (Davis et al., 2023).

2.2.3 Risk Factors of Long COVID

During the acute phase of COVID-19, long COVID can happen to people of various ages and with varying degrees of illness severity. There are a number of risk factors that have been found, such as advanced age, the female gender, and having certain underlying illnesses like diabetes, obesity, and other metabolic disorders. Among these risk factors, women, older people, and those with obesity are the three most common factors that are frequently mentioned in multiple articles (Mendelson et al., 2020). An increased risk of long COVID has also been linked to the severity of acute diseases and hospitalization.

2.3 UNDERLYING MECHANISM OF LONG COVID

The mechanism of long COVID is still being studied and is not yet fully understood. However, the studies have identified the wide range of symptoms that the patients experience, allowing us to identify and analyze the mechanism of long COVID based on the respective system that is affected. Therefore, the mechanisms of long COVID were studied and reviewed by several articles where they categorized the mechanism of long COVID according to the symptoms caused and organs system affected. Furthermore, the symptoms of long COVID could affect the quality of life and also cause multiple organ damages to the individuals who developed acute COVID-19 (Pierce et al., 2021). Thus, the mechanism of long COVID and its manifestation is crucial to be analyzed and studied with great scrutiny.

2.3.1 Immunological Mechanisms

As a field of study that is still ongoing, there is limited literature in regards to the immunological mechanism of long COVID. Some studies have suggested that in addition to vaccination, the active immune system which promotes the innate and active immunity in the body, can aid in the prevention of acute COVID-19, ultimately reducing the risk of long COVID symptom development (Sciscent et al., 2021). Patterson et al. (2022) identified and confirmed the cause of the presence of persistent SARS-CoV-2 protein being the monocytes, CD14lo and CD16+, found in the body 65 weeks after the initial infection. It was also proposed that the intermediate monocytes remained in the circulation for a prolonged period due to the low presence of the CCL4 protein (regulates immune response and inflammation), which leads to an accumulation of non-classical monocytes (anti-inflammatory cells) that contain the S1 protein, identified to be associated with vascular inflammation. Patterson et al. (2022) proceeded to explain the presence of S1 protein in the non-classical monocytes due to the pre-existing CD14lo CD16+ cells that engulfs the virally infected apoptotic endothelial cells via phagocytosis.

A study conducted in 2021 by Huang. L stated that “The chronic or late-onset psychological symptoms after COVID-19 could be driven by a direct effect of virus infection and might be explained by several hypotheses including aberrant immune response, hyperactivation of the immune system, or autoimmunity”. This suggests that some individuals who have recovered from COVID-19 may experience chronic or late-onset psychological symptoms, and that there are several possible explanations for this phenomenon in relation to the immune response of the body. The first hypothesis is where the psychological symptoms are associated together with an aberrant immune response, where it leads to inflammation or other effects that occur in the brain or nervous system. The second hypothesis is due to the hyperactivation of the immune system. This event where the immune system is overactive despite the absence of the virus could be a possible explanation to the chronic and late-onset psychological symptoms. The final hypothesis is autoimmunity, where the healthy cells and tissues are mistaken for the virus and attacked by the body. This phenomenon may play a role in the development of long covid symptoms. Several other studies also support these hypotheses as a possible explanation to the underlying mechanism of the psychological symptoms of Long COVID (C. Huang et al., 2021).

Another proposed mechanism of long COVID for persistent in the body was identified where the viral RNA was found in the feces of long COVID patients (Wu et al., 2020). This goes to prove that the virus RNA persists in the human body including the gastrointestinal tract of the patient as exhibited from the study. A review had presented that a number of studies has demonstrated the SARS-CoV-2 virus in viral transmission via fecal-oral transmission (Cevik et al., 2020). However, these studies have focused on the viral transmission of the SARS-CoV-2 virus. The fact that the virus is able to survive in such an environment could provide a better insight to the underlying mechanism of the virus in regards to causing prolonged symptoms.

2.3.2 Viral Persistence and Latency

Long COVID's viral persistence and latency are still being studied and are not yet fully understood. After initial infection, some individuals continued to emit viral RNA from their respiratory tracts for a number of weeks or even months, according to a cohort study (L. Huang et al., 2021). In addition, a subsequent study reported in Nature in 2021 discovered that some people with COVID-19 who were mildly or asymptomatically ill continued to have detectable levels of viral RNA in their respiratory tract weeks after the initial infection (Gaebler et al., 2021). In order to completely comprehend the viral persistence and latency of long COVID and to develop efficient therapies and care techniques for patients who still have symptoms following their initial recovery, more study is required.

2.3.3 Organ Damage and Dysfunction

The clinical manifestation of long COVID has been identified to be associated with causing long term damages that causes impact to multiple organs systems at once. Not treating these prolonged symptoms can even lead to death. Pierce et al. (2021) determined the most common manifestations of long COVID and the organs that are usually affected by it where it causes disruption to the lungs, brain, heart and kidneys, ultimately affecting the quality of life. Since the clinical manifestations differ for each individual, it contributes to the difficulties of diagnosing the symptoms properly and identifying the organs affected. Fatigue, being one of the most common manifestations of long COVID, is a neurological dysfunction which was identified to cause dysfunction to the neuronal circuit in patients who experience fatigue for over six weeks (Astin et al., 2022). The acute phase of COVID infection, either mild or moderate, leads to inflammation which results in fatigue (Poenaru et al., 2021). The symptom fatigue, despite being a neurological dysfunction, is able to affect the cardiovascular system by causing high heart rates and lowered heart rates (Astin et al., 2022).

2.3.4 Psychological Factors

The psychological factors are primarily related to the neurological symptoms of long COVID including depressions, psychosis, and anxiety which is identified to persist amongst those who had contracted acute SARS-CoV-2 (Troyer et al., 2020). Uncertainty, loneliness, unnecessary fear, and depression are the common signs and psychological problems experienced after recovery of initial infection which induces neurological dysfunctions and fibrosis. These psychological signs are found to present in worse conditions for those who have a past history of psychiatric or psychological issues, developments disorders, domestic violence survivor, the elderly and children under the age of 12 years old (Ferrario et al., 2021). Other psychological symptoms were also reported; insomnia, acute stress disorder and intrusive thoughts and intense fear of dying. It was found by Ferrario et al. 2021 that without proper care, these psychological symptoms caused by long COVID could result in life threatening conditions and even lead to cognitive impairments. Furthermore, it was analyzed and estimated that 30% of patients experience at least one underlying symptom that progresses into a medical condition affecting the individual’s health after recovery from the acute phase (Buonsenso et al., 2022). This calls for a better understanding of long COVID‘s mechanism and identifies an accepted criterion in symptom duration where the manifestation of the illness takes place to help improve the healthcare system (Peluso et al., 2021).

An interesting case was identified where Mannarini and Rossi (2019) reported the occurrence of psychological problems caused by long COVID in patients that experienced the loss of a body part or limb due to the symptoms of the acute infection. They were found to express and feel shame, guilt, insecurity, and stigmatization and the fear of reactions by close family or friends. This goes to show that not only neurological related symptoms manifest psychological factors but external factors and stressors are to be included as potential causes.

2.4 DIAGNOSIS OF LONG COVID

2.4.1 Challenges in Diagnosing Long COVID

The diagnosis of long COVID poses as one of the greatest challenges for researchers in the fight against this illness. Medical professionals and researchers are working on the feasibility of diagnosing the symptoms of long COVID and its mechanisms. This was found to be conducted by identifying the indicators relating to the persistent responses (hyperinflammatory response, low antibody reaction, progressing viral load, and organ damage) caused by the acute infection (Vehar et al., 2021). However, the diagnostic criteria for long COVID posed a major challenge as studied by Raveendran et al. (2021). He had suggested that there are several factors that could affect proper diagnosis such as, effects of medications, COVID-19 complications, psychological issues, microbial infection and the reinfection of COVID-19, that could potentially exhibit similar symptoms of those from long COVID. Thus, it is important to rule out and filter the causes that are not related when conducting a diagnosis. Moreover, the unclear guidelines of long COVID also disrupts the diagnosis process, where it can affect the healthcare system in managing long COVID. Hence, a multidisciplinary approach was undertaken for community-based and specialist healthcare centers in managing, examining and treating long COVID was provided by the National Institute for Health and Care Excellence (NICE) (NICE, 2020).

2.4.2 Diagnostic Criteria, Tests and Imaging

The diagnostic criteria for long COVID symptoms was categorized into four main criteria by Oronsky et al. (2021). The criteria include and involve laboratory investigation, radiologic pathology, deterioration in functional status, and subjective symptomatic and quality-of-life parameters. Apart from that, the tests and imaging conducted differs for each symptom as they can be determined via various methods. As an example, a study that identified the recurrence of neuropsychiatric symptoms such as loss of taste, loss of smell, fatigue and headache (Graham et al., 2021), had proposed Magnetic resonance imaging (MRI) imaging (Nuzzo et al., 2021). Nuzzo et al. (2021) further explained that the use of MRI in patients suspected with neurological symptoms from long COVID provides better diagnostic results. Thus, concluding that standardized and refined guidelines are crucial to diagnose and manage patient care of long COVID symptoms.

2.5 TREATMENT STRATEGIES FOR LONG COVID

Long COVID symptoms are found to manifest in several ways where patients must be vigilant with their health. Excellence (2020) suggested an examination where the symptoms experienced and the pre-existing problems of a patient must be established in order to propose a suitable treatment option. It is recommended that evidence-based diagnosis and management strategies are conducted before providing treatment and care to patients. The NICE guidelines also stated that the clinical evaluation of long COVID is to begin 4 weeks following the acute infection of SARS-CoV-2 virus. However, regardless of the established guidelines, Nurek et al. (2021) identified a significant gap in treatment where individual treatments are not well assessed. Therefore, the treatment development will have to take several assessment factors into consideration where new upcoming therapies are guided based on treating the long COVID symptoms related to organs-specific dysfunction. Before any form of treatment is provided, the medical history and medical exams of each individual patient is to be taken into consideration as each patient presents with unique characteristics. Thus, conducting the treatment procedures based on the symptom-based strategy. Moreover, other underlying conditions of patients, not associated with long COVID symptoms, are to be analyzed to provide a proper treatment.

2.5.1 Treatment Strategies

The treatment strategies for long COVID are found to be under different aspects that cater to the different long COVID symptoms. The treatment options include immunomodulatory therapy, anti-viral therapy, rehabilitation and counseling. The type of therapy that goes for each symptom is determined by the diagnosis of the symptom using tests and imaging processes, where as an example, Nurek et al. (2021) suggested electrocardiography, chest imaging and pulmonary function testing for cardiopulmonary long COVID symptoms.

Different types of symptoms are connected to different types of biological pathways. Thus, each treatment strategy for each symptom would be unique. For example, it was revealed that mast cell activation syndrome (MCAS) is likely to present in long COVID patients; hypothesizing the mechanism is caused by the immunological dysfunctions caused by the SARS-CoV-2 virus (Weinstock et al., 2021). The MCAS induces inflammatory reactions in the body that results in allergy flare-ups (Glynne et al., 2021). To combat this, histamine antagonists or antihistamine due to their ability to reduce and regulate mast cells. The antihistamines were found to be used as a treatment option for COVID but Pinto et al. (2022) stated its application in long COVID remains unclear but is a potential therapeutic treatment. Immunomodulatory compounds such as Luteolin and quercetin, naturally occurring flavonoids, exhibit properties that may inhibit mast cells (Hagenlocher & Lorentz, 2015). These compounds may aid in reducing the systemic inflammation and boost the body immunity.

A treatment strategy or therapy for long COVID induced inflammation leading to multiple organ damage is a proper dietary supplement, as vitamins and minerals contain anti-inflammatory and anti-oxidative properties providing relief to the inflammations. Supporting this, a study has found that multi-vitamin supplements have helped to improve the conditions of long COVID symptoms (Naureen et al., 2021). Furthermore, natural compounds extracted from plant extracts of Eleutherococcus senticosus and Panax ginseng used in a study, showed improvement in the health of the 201-long term COVID patients providing a relief from the long-term symptoms (Rossato et al., 2021). Different types of vitamins and minerals such as nicotinamide ribose and Omega-3 are currently being studied for their properties and potential role in long COVID symptoms.

Antibiotic and antiviral compounds are investigated in regards to long COVID as the viral infection causes the immune system to be weak increasing the probability of opportunistic infections. The efficacy of drugs such as azithromycin, remdesivir, and favipiravir in the management of long COVID is being studied (Koc et al., 2022). Hohberger et al. (2021) studied the BC007 medication which treats autoimmunity by reducing the G protein-coupled receptor autoantibodies and reduces the fatigue symptom within patients. A study by Wood et al. (2021) identified the Coenzyme Q10 and D-ribose supplements showed potential in treating chronic fatigue but requires additional study to determine the mechanisms. Even antidepressant drugs have shown improvement in the symptoms induced as it is able to restore immunological functions and lowers peripheral inflammatory indicators.

While certain symptoms are to be treated by drugs, several symptoms can be alleviated by non-drug therapies such as physical therapy. Schrimpf et al. (2022) encouraged medical practitioners to encourage patients to undergo physical therapies to get relieved from the symptoms and improve overall health. However, the physical therapy regime for a patient is to be personalized based on certain thresholds as physical activities are potentially able to cause relapse of certain symptoms such as joint pain, chest pain and dyspnea (Vance et al., 2021). Physical exercises with the right rehabilitation protocols are able to encourage patients and continue to improve their health as well as symptoms.

2.6 PREVENTION OF LONG COVID

Long COVID is to continue to cause a significant impact on society on a global range as long as individuals are contracting the COVID-19. The acute infection poses as the root cause of long COVID symptoms. Therefore, the preventative methods and care for long COVID would primarily involve methods to avoid contracting COVID-19 itself. As for long COVID itself, the risk factors are to be considered as the individuals within the risk factors are more prone to experiencing a symptom and therefore are advised to increase their immunity.

2.6.1 COVID-19 Vaccines

The primary preventative care for long COVID would involve the prevention of contracting COVID-19 via vaccinations. Several vaccinations have been developed and approved by the FDA and CDC over the span of 2 years. The COVID-19 vaccination has greatly affected ro reduce the morbidity and mortality of the virus (Moghadas et al., 2021). Not only by just reducing the number of cases and deaths, the vaccinations have been found to affect the long-term symptoms of COVID-19. Several studies have identified a substantial decrease in the long-term symptoms of COVID due to immunization (Byambasuren et al., 2023). It is speculated that immunization reduces the effects of the virus on the organs and pathways resulting in the reduction of long-term symptom effects. The number of COVID-19 related deaths in Switzerland reported that around 40% involved individuals that had not received immunization whereas a 10% of death was seen in individuals with at least one dose of vaccination. These reports and studies goes to imply vaccination as a method of prevention for not only COVID-19 infection symptoms but for long COVID symptoms too.

2.6.2 Other Vaccines

Apart from COVID-19 vaccines, other diseases vaccines have been reported to show protective effects towards long COVID symptoms. Healthcare workers have stated that the influenza vaccine has shown to reduce the possibility of the SARS-CoV-2 virus infection and influences the severity of the acute infection. Supporting the statement, Taghioff et al. (2021) conducted a retrospective analysis of the influenza vaccination and presented a reduction in the risk of sepsis and deep vein thrombosis related to long COVID.

2.6.3 Nutrition and Diet Management

Nutrition and proper diet may not seem like a serious factor but it has been proven that with appropriate nutritional management, the symptoms of viral infections are reduced and are also used in the treatment of chronic illness (De Araújo Morais et al., 2021). The difference in the occurrence of COVID-19 infection between populations is speculated to have epigenetic polymorphism connected to the population’s nutrition by Cao and Li (2020). Vitamin D, an important nutrient for the body, has been revealed by Liu et al. (2022) to exhibit prospective properties against SARS-CoV-2 virus. Vitamin D has therapeutic effects where it may reduce the pathogenicity of the SARS-CoV-2 virus by influencing the renin-angiotensin-aldosterone system (RAAS). The vitamin D supplements were identified to reduce respiratory infections and are being studied in clinical trials to provide evidence of its effects against COVID-19 (Rastogi et al., 2020).

2.6.4 Repurposed Medications

The use of repurposed medications for other diseases is common and the same goes for COVID-19 infections. Repurposed drugs aimed for COVID-19 include hydroxychloroquine and ivermectin, candidate drugs used widely during the pandemic. The repurposed medications can be used to prevent the infection of SARS-CoV-2 virus, thus, preventing the occurrence of the long COVID symptoms. However, this theory is not proven to be true. There might be cases where the repurposed drug causes adverse effects towards the virus as these drugs are not developed for COVID-19 infections. The use of the repurpose drugs instead of established drugs for COVID-19 and vaccination may enhance the development of long-term symptoms. Regardless, the use of repurposed drugs is a wide research field that has high potential to develop more therapeutic agents against long COVID symptoms. This can be determined by using drugs specified for the various long COVID symptoms not only as preventative care but also as a treatment for long COVID patients.

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