Long-Term Effects of COVID-19: A Systemic Review

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ABSTRACT

The sequelae of long-term complications of COVID-19 have been reported in many studies. These complications are almost similar in both adults and children and were observed during infection with other coronaviruses like SARS-CoV and MERS-CoV. It is observed too that these complications develop in both previously symptomatic and asymptomatic individuals. The symptoms of long COVID start to manifest usually after 4-12 weeks of initial onset of SARS-CoV-2 infection. In the long run, COVID-19 affects various body parts in different ways. These majorly include respiratory, cardiovascular, hematological, inflammatory, immunological, and neurological disorders along with gastrointestinal, metabolic, renal, hepatic, and skin disorders. However, there is a lack of detailed summary of the clinical presentation and effects of long COVID in the literature. This review summarizes the current evidence of the long-term effects of COVID-19 in adults and children along with the presenting signs and symptoms in these patients. This finding highlights the need for future epidemiological studies to access the risk of long-term complications of COVID-19 in order to develop effective multi-disciplinary risk reduction and management strategies for long COVID in patients.


I. INTRODUCTION

As of May 18, 2022, a total of 520,102,853 confirmed cases of SARS-CoV-2 infection including 6,268,956 fatalities, have been reported globally by [1]. The clinical course of COVID-19 ranges from mild to severe disease. It has been estimated that almost 10-15% of COVID-19 patients develop severe disease and almost 5% patients progress to critical illness. Approximately 90% patients with COVID-19 usually recover within 2-6 weeks after infection. However, several patients develop persistent and lasting mild to severe symptoms after the acute onset of SARS-CoV-2 infection [2]. An early study characterized the persistence of clinical symptoms beyond 3 weeks and 12 weeks of initial onset of COVID-19 as ‘Long COVID’ or ‘Chronic COVID-19’ respectively [3]. Other studies have named the persistent symptoms as ‘Post COVID-19 syndrome’, ‘Post-acute COVID-19’, ‘Long-haul COVID’, ‘Post-acute sequelae of SARS-CoV-2 infection (PASC)’, ‘Long- haulers’, ‘Long-term COVID-19 effects’, ‘Post COVID-19 manifestations’, ‘Ongoing COVID-19’, ‘Persistent COVID-19 symptoms’ or ‘Long-term sequelae’ [4]. WHO has named this condition of ill health as ‘Post COVID condition’, however, it is most commonly referred as ‘Long COVID’ [5].

Different studies have reported a wide range of symptoms of long COVID among different populations of patients. The most commonly reported symptoms of long COVID include dyspnea, arthralgia, fatigue, chest pain and headache [6] and the most commonly affected systems involve the respiratory system, cardiovascular system [7] neurological system and hematological system. The Long-term effects of COVID-19 are considered to be the result of the direct and indirect consequences of disease. The direct effects include viral-mediated parenchymal damage in lungs and kidneys, viral-induced hypoxia and damage to peripheral nervous system (PNS), viral-induced changes in fecal microbiota, immune-mediated damage to blood-brain barrier (BBB), thromboembolism, endothelial and microvascular dysfunction, and immune-mediated microvascular and myocardial destruction [8]. The indirect effects include changes in behavioral, social, and economic conditions like loneliness, unemployment, decreased social contact, changes in exercise and diet, that can be differently experienced by individuals with COVID-19 or may be the reasons of some post-acute clinical manifestations of long COVID [9]. Emerging data suggests that COVID-19 has several long-term pulmonary and extrapulmonary manifestations. A study involving 1250 follow-up patients of COVID-19 reported that 33% of patients develop persistent symptoms of COVID-19 in 60 days follow-up after being discharged from hospital [10]. The findings of a large systematic review also suggest that almost 50% individuals with COVID-19 experienced persisting health problems at 6 months after being recovered from COVID-19. These health issues were most frequently seen in hospitalized individuals with acute COVID-19 [11]. Therefore, there is a need for evidence-based characterization of long-term effects of COVID-19, its signs, and symptoms along with the health outcomes of COVID-19 patients to
assist the scientific community in the clinical management of long COVID. This review summarizes the symptoms of long COVID and its long-term effects on various organs and organ systems of the body.

II. METHOD

This paper compiles reviews from several other papers elaborating the long-term effects of COVID-19 and post-acute COVID-19 sequelae. Papers were selected by doing literature search in PubMed, Google Scholar, and Elsevier’s Scopus from December 2020 to May 2022. We used keywords including SARS-CoV-2, Long-term effects of COVID-19, long COVID, and COVID-19 and organ systems. The comprehensiveness of literature search was extended by using combination of medical subject headings (MeSH) terms with the keywords. Only studies involving humans were reviewed for this paper without language restrictions. A total of 20 studies were included in this review for explaining the topics of interest.

III. DISCUSSION

A large cohort study including 73,435 patients of COVID-19 reported that malaise, fatigue, and musculoskeletal pain are the most common symptoms of general poor well-being of COVID-19 patients after 30 days of initial onset of disease and there is a higher risk of the need of outpatient care for these individuals. Individuals with long COVID also has an increased risk of developing clinical manifestations in various body organs like heart, lungs, and kidneys. These clinical manifestations can even develop in individuals who were not previously hospitalized with COVID-19 and the severity of risk increases from non-hospitalized individuals infected with COVID-19 to those who were hospitalized, and it is highest for patients admitted to intensive care units (ICUs) [9]. Here we have discussed long COVID along with its symptoms and effects on the various part of the body to present a better understanding of the long-term sequelae of the disease for providing better patient care.

IV. DEFINITION OF LONG-TERM EFFECT OF COVID-19

Currently, there is no consensus in the scientific community regarding a single definition of long COVID. However, WHO defines long COVID as Post COVID-19 condition that usually occurs after 3 months of initial COVID-19 onset in individuals with a probable or confirmed history of SARS-CoV-2 infection. Furthermore, in order to qualify as long COVID, symptoms have to last for at least 2 months without the ability to explain the condition with an alternative diagnosis. The common reported symptoms include shortness of breath, fatigue, cognitive dysfunction, along with other symptoms that generally impact everyday functioning of individuals. These symptoms may follow initial recovery after an acute COVID-19 episode or may persist after initial COVID-19 illness and can also relapse or fluctuate over time. A different definition may be appropriate for children [5].

Similarly, the Centers for Disease Control and prevention (CDC) defines long COVID as myriad of new, ongoing, or returning health problems that patients can experience after 4 or more weeks of initially being infected with SARS-CoV-2 [12]. It is most commonly defined as a condition with newly developed or continuing signs and symptoms after acute COVID-19. It includes both ongoing COVID-19 symptoms from 4-12 weeks and post COVID-19 syndrome after 12 weeks or more. Long COVID can occur in individuals of all age groups, but it occurs more frequently in adults as compared to adolescents and children.

V. SYMPTOMS OF LONG COVID

A wide range of symptoms comprise long COVID in adults and children, however these symptoms are also present among many other conditions. More than 100 symptoms or problems with everyday life activities have been reported. Therefore, the diagnosis of long COVID is usually based on the presence of persisting symptoms after recovery from COVID-19. The most reported symptoms include fatigue, sleep disturbances, memory problems, general discomfort and pain, depression, anxiety, sleep disturbances, post-traumatic stress disorder (PTSD), shortness of breath and difficulty in concentrating and thinking [4]. A systematic review of persisting signs and symptoms of post-acute COVID-19 illness identified 55 long-term effects of COVID-19 and found that 80% of COVID-19 patients experience 1 or more long-term symptoms of COVID-19. The five most frequent clinical manifestations of long COVID are fatigue, headache, attention disorder, hair loss and dyspnea in 58%, 44%, 27%, 25% and 24% COVID-19 patients, respectively. Other symptoms of long COVID can manifest due to lung disease including chest discomfort, cough, decreased pulmonary diffusing capacity, pulmonary fibrosis and sleep apnea, cardiovascular problems including myocarditis and arrhythmias, and neurological problems including anxiety, depression, attention disorder, dementia and obsessive-compulsive disorder (OCD). Several other unspecified symptoms like tinnitus, night sweat and hair loss can also manifest in long COVID [4]. A cross-sectional study including children under 18 years of age reported that the 66.6% and 27.1% children with COVID-19 experienced at least 1 persisting symptom of long COVID between 60-120 days and after 120 or more days of initially being infected with SARS-CoV-2, respectively. The ongoing symptoms experienced by these children included fatigue, rhinorrhea/nasal congestion, headache, persistent muscular pain, weight loss, arthralgia, skin rashes, altered smell, chronic cough, palpitations, diarrhea, and constipation that are similar to the symptoms observed in adults and adolescents [13].

The most common symptom of long COVID, fatigue, is reported to be present even after 100 days of initial onset of SARS-CoV-2 infection and is more commonly present in females as compared to males [14]. The symptoms observed in long COVID are similar to those of the chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME), which is characterized by the presence of severe pain and incapacitated fatigue, compromised sleep, neurocognitive disability, symptoms related to autonomic dysfunction and worsened global symptoms after minor improvements in

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cognitive or physical activity. CFS/ME, is clinically a complex condition [15]. In addition, several other neuropsychiatric symptoms of long COVID including anosmia, headache and attention disorders are reported. The risk for developing a psychiatric disorder after COVID-19 is 2 times greater for adults which may present with psychiatric conditions of dementia, insomnia, and anxiety disorders due to sleep disturbances [16]. Other persisting symptoms of long COVID include digestive disorders, cutaneous signs, weight loss, intermittent fever, palpitations, chills, red eyes, diabetes mellitus, discontinuous flushing, limb edema, stroke, mood disorders, throat pain, new hypertension, paranoia, and renal failure.

VI. RESPIRATORY SYSTEM

Respiratory system is found to be primarily affected in both acute and chronic phases of COVID-19, as evident by the manifestations of respiratory failure and pneumonia in the acute phase of disease. COVID-19 patients continue to experience ongoing respiratory symptoms for months after initial onset of illness including fibrotic lung disease, persistent cough, pulmonary vascular disease, and bronchiectasis [17]. A study reported that respiratory system problems constitute the highest burden of long COVID signs and symptoms at 6 months follow-up of individuals with COVID-19 that were not hospitalized during the initial 30 days of being infected. The most frequently observed signs and symptoms of respiratory problems include lower respiratory disease, respiratory failure, arrest, and insufficiency that further lead to an increased use of anti-asthmatic, expectorant and anti-tussive agents, glucocorticoids and bronchodilators [9]. Another study in Italy, involving COVID-19 survivors found that 53.1% of COVID-19 patients reported fatigue and over 43.4% of COVID-19 patients experienced residual dyspnea almost 4 weeks post-discharge [6]. The persistent respiratory problems may occur due to the direct viral attack or immune-mediated damage to lungs resulting in functional impairment and fibrosis. Functional impairment of lungs was also demonstrated by earlier studies of lung function tests, specifically the parameter of carbon monoxide diffusing capacity which was seen in recovered and post-hospitalized COVID-19 patients, 4 to 6 weeks after initial onset of disease. The functional impairment of respiratory system can further persist for years after recovery and leads to reduced quality of life and exercise capacity [18].

Evidence for these observed sequelae can also be extrapolated from outbreaks of Severe Acute Respiratory Syndrome-coronavirus (SARS-CoV) and Middle East Respiratory Syndrome-coronavirus (MERS-CoV), that share similar genomic characteristics of SARS-CoV-2. It is reported that a minority of SARS-CoV patients develop long-term continued radiologic abnormalities in the lungs [19], whereas 33% patients of MERS-CoV showed pulmonary fibrosis in radiographic examination after 82.4±66 days of discharge [20]. Similarly, available data of discharged COVID-19 patients after 4-6 weeks of initial onset of disease demonstrates residual abnormalities with ground glass opacity and pure ground glass opacity patterns on chest computed tomography (CT) scan of these individuals [21].

VII. CARDIOVASCULAR SYSTEM

The involvement of cardiovascular system in long COVID can be demonstrated by the symptoms of chest tightness, palpitations, arrhythmias, and chest pain. An increased burden of developing cardiovascular complications is associated with long COVID sequelae. These conditions include hypertension, cardiac dysrhythmias, circulatory signs and symptoms, coronary atherosclerosis, chest pain and heart failure with an increased use of anti-arrhythmic drugs, loop and thiazide diuretics, and calcium-channel and beta-blockers [9]. In a cohort study of 150 COVID-19 patients in Wuhan, China, heart failure and myocardial damage resulted in 40% mortality of individuals [22]. Patients with long COVID demonstrate clinical findings of myocarditis, myocardial inflammation, pericarditis, and cardiac fibrosis on cardiac magnetic resonance (CMR) and impaired left ventricular ejection fraction (LVEF) on electrocardiogram.

Cardiomyocytes of myocardial tissue are susceptible to the acute and chronic effects of COVID-19 due to the presence of angiotensin converting enzyme 2 (ACE2) receptors that results in 8-12% incidence of myocardial injury in COVID-19 [23]. The overactive pro-coagulant activity and systemic inflammation during acute COVID-19 persist even after recovery from initial infection and contribute to the clinical manifestations of long COVID. Other contributing factors include immune-mediated cardiac fibrosis and electrolytes imbalance. Similarly, use of azithromycin and hydroxychloroquine cause prolongation of QT that can lead to fatal arrythmias and torsase de pointes. The risk for developing cardiovascular problems in long COVID is related to acute disease severity, history of elevated troponin, pneumonia, and high viral load in COVID-19 patients. These findings are consistent with the findings of a meta-analysis of 591 SARS patients in which the risk of cardiovascular disease increases 2.1 times and 1.86 times within the first year and 10 years of hospitalization with pneumonia, respectively [23].

VIII. NEUROLOGICAL SYSTEM

The involvement of neurological system in long COVID is evident by the persisting neuropsychiatric, cognitive, or peripheral clinical manifestations among COVID-19 patients. The neurological conditions manifesting in long COVID include PTSD, anxiety, depression, OCD, brain fog, headache, non-restorative sleep, memory loss, ageusia, anosmia, malaise, postural orthostatic tachycardia syndrome (POTS) and fatigue. The risk factors are severity of acute COVID-19 disease, admission in ICU during initial onset of disease and the use of medications like corticosteroids and lopinavir-ritonavir. These manifestations can arise due to the leukocyte infiltration and modification of basement membrane caused by inflammatory mediators, transfer of megakaryocytes in alveolar tissue because of endothelial disruption and hypoxia as a result of prolonged release of cytokines [8].

Gustatory and olfactory dysfunction are the most frequently reported neurological problems of COVID-19. These problems persist for many months in adult COVID-19 patients, however, in children, gustatory and olfactory dysfunction resolve in several weeks. If not, it is indicative of
further complications requiring proper evaluation. Moreover, long COVID can also lead to encephalitis, Guillain-Barre syndrome (GBS) and stroke. Despite the milder clinical progression of COVID-19 in children, there is evidence of pediatric inflammatory multi-system syndrome (PIMS) which constitutes toxic shock syndrome, myocarditis, and Kawasaki-like disease. Various case reports are being published regarding the occurrence of PIMS and GBS among COVID-19 patients. However, the direct relationship of COVID-19 with these complications is yet to be determined [17].

IX. HEMATOLOGICAL SYSTEM

The observed hematological complications of long COVID include lymphocytopenia, thrombocytopenia, leukopenia, and elevated levels of C-reactive protein (CRP) and D-dimer. The values of these hematological parameters are highly deranged in severe disease. The coagulation related abnormalities in long COVID patients occur due to the activation of type-1 interferons by the innate immune system that promotes pro-coagulation and pro-inflammatory processes via endothelialitis, endothelial cells dysfunction and capillary leakage. Elevated pro-calcitonin and CRP levels along with thrombocytopenia and lymphocytopenia further increase the risk of thromboembolism in case of severe disease. The thromboembolic events occurring after an infectious disease are considered to be immune mediated rather than pure thromboembolic events. ICU admissions and severity of acute disease are the possible risk factors for coagulation abnormalities leading to thromboembolic events [17]. A study reported high levels of SARS-CoV-2 specific memory CD4+ T-cell responses in hospitalized patients that later became equal to the responses observed in patients that were not hospitalized during the first 4 months of onset of COVID-19 indicating the activity and differences in the immune responses between hospitalized and non-hospitalized patients with COVID-19 [24].

X. MULTISYSTEM INFLAMMATORY SYNDROMES

The hyperactive immune response in long COVID also presents with multi-system inflammatory syndromes like Guillain-Barre syndrome (GBS) in adults and pediatric inflammatory multi-system syndrome (PIMS). COVID-19 related immunological complications were also reported by many studies during the acute phase of disease which resulted in increased levels of plasma pro-inflammatory cytokines, lymphopenia and decreased peripheral blood T-cells count [25]. Almost 30 case reports have reported the presence of GBS in COVID patients. These findings are consistent with that of several pre-clinical studies showing the potential of coronaviruses to cause demyelinating diseases. Inflammatory, autoimmune and rheumatological diseases had also been manifested in previous outbreaks of Zika, Chikungunya, influenza, and Ebola viruses. However, there is lack of evidence on the mechanism leading to GBS in long COVID and the relationship between the two.

The multi-system inflammatory syndrome presents with clinical features involving persistent fever, severe gastrointestinal symptoms, multi-organ involvement, systemic hyper-inflammation, conjunctivitis, inflammatory oral-mucosal changes, and erythematous rash. As of June 2021, CDC subdivided the multi-system inflammatory syndrome in 3 classes along with the specific diagnostic criteria and abnormal laboratory markers [8].

The presentation of PIMS in children is also a consequence of long COVID. It is a collection of toxic shock syndrome, myocarditis, and Kawasaki-like disease. The reported number of cases of children presented with PIMS have reached over 700. However, there is still a need to study the detailed mechanism leading to PIMS in long COVID to collect useful information to prevent this adverse complication [17].

XI. OTHER BODY SYMPTOMS

Long COVID effects several other parts of the body causing obesity, diabetes mellitus and lipid metabolism disorders with evidence of increased hemoglobin A1c (HbA1c), triglycerides, low-density lipoproteins (LDL), and total cholesterol levels in the patients. It also causes increased burden of several digestive system disorders including dysphagia, gastrointestinal and esophageal disorders, and abdominal pain, evident by excessive use of histamine antagonists, anti-diarrheal agents, antacids, anti-emetic agents and laxatives [9]. Moreover, dermatological manifestations of long COVID including erythematous rash, herpetiform lesions, oral blistering, and ulcers, have also been reported. The onset of dermatological manifestations can occur during both acute and chronic phases of COVID-19. Systemic symptoms occur after a few days of the development of prodromal systems, or after a few weeks in case of PIMS. A study of 22 patients reported the presentation of varicella-like exanthem in COVID-19 patients from 2 days earlier to 12 days later the development of systemic symptoms [26]. A study involving 88 patients of COVID-19 in Italy, reported the clinical presentation of maculopapular, erythema multi-forme like macular and popular lesions in 20.4% patients. Almost 50% patients developed these symptoms at the initial onset of illness. Similarly, a total of 375 cutaneous lesions cases were reported by a nationwide surveillance system in Spain in which maculopapular, pseudo-chilblain, urticarial, vesicular and livedo/necrosis lesions were present in 50%, 19%, 19%, 9% and 6% of patients, respectively. In children, the most common dermatological presentation is rash that mimics Kawasaki pattern [17].

The effects of long COVID on renal system include wide range of tubular and glomerular diseases with high risk of collapsed glomerulopathy in patients with apolipoprotein L I (APOLI) variant. Similarly, adverse effects of long COVID on the endocrine system can be manifested by onset of recent diabetes, diabetes keto-acidosis, Graves thyrotoxicosis, worsening of pre-existing diabetes and sub-acute thyroiditis that are more common in patients with high viral load and severe acute disease [8].

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XII. CONCLUSION

The effects of long COVID can be manifested in almost all parts of the body with more common symptoms of respiratory, cardiovascular, neurological, multi-system inflammatory and hematological disorders. The symptoms of long COVID resemble that of chronic fatigue syndrome and can be observed in both children and adults. The post-acute sequelae of these complications further need to be explored to find the relationship of COVID-19 with these disorders.

REFERENCES


