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REVIEW

Post-acute Sequelae in COVID-19 Survivors: an Overview

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Abstract

In the acute phase of SARS-CoV-2 infection, varying degrees of clinical manifestations have been noticed in patients. Some patients who recovered from the infection developed long-term effects which have become of interest to the scientific and medical communities, as it relates to pathogenesis and the multidisciplinary approach to treatment. Long COVID (long-term or long-haul) is the collective term used to define recovered individuals of SARS-CoV-2 infection who have presented with persistent COVID symptoms, as well as the emergence of disorders and complications. Following the review of literature from major scientific databases, this paper investigated long COVID and the resulting post-sequela effects on survivors, regardless of initial disease severity. The clinical manifestations and multisystem complications of the disease specifically, cardiovascular, neurologic and psychologic, hematologic, pulmonary, dermatologic, and other ailments were discussed. Patients with chronic COVID-19 were found to experience heart thrombosis leading to myocardial infarction, inflammation, lung fibrosis, stroke, venous thromboembolism, arterial thromboembolism, "brain fog", general mood dysfunctions, dermatological issues, and fatigue. As the disease continues to progress and spread, and with the emergence of new variants the management of these persisting symptoms will pose a challenge for healthcare providers and medical systems in the next period of the pandemic. However, more information is needed about long COVID, particularly concerning certain patient populations, variability in follow-up times, the prevalence of comorbidities, and the evolution of the spread of infection. Thus, continued research needs to be conducted concerning the disease pathology to develop preventative measures and management strategies to treat long COVID.

Keywords Long COVID-19: Long-term effects of COVID · Post-acute SARS-CoV-2 · Chronic COVID-19 · Late sequelae after coronavirus · Long-haulers

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the continuing pandemic. Despite immunization efforts, COVID-19 has infected over 476 million people worldwide, with an increasing prevalence due in part to emerging, readily transmissible strains of the virus, as of March 24, 2022 [1]. Fomites, direct touch, and/or airborne transmission via respiratory droplets can all cause the virus to spread from person to person [2]. The viral load, as well as the severity of symptoms like cough and sputum production, are the most critical determinants in a virus's potential to propagate infection [2]. Because these characteristics can change quickly during a person's infectious phase, the basic reproduction number R0 is used to define the transmissibility of an infectious illness [2]. This value is equal to the number

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of susceptible individuals to whom an infectious individual can transmit the disease during the contagious period, quantifying the ability to spread [2].

The Delta and Omicron variants of SARS-CoV-2 generate more infections and spread faster than previous variants of the virus [3–6]. As new variants emerge, the ability of these viral strains to cause long-term complications must be thoroughly investigated [7]. It is important to anticipate that one variant may cause damaging long-term effects over others, and patients infected could develop long-term symptoms that may require additional support and more rapid and intense treatment strategies to combat their long-term symptoms [7, 8].

Patients with varying degrees of disease severity during acute infection, including those with silent/asymptomatic infections, may develop post-COVID complications. These post-acute symptoms and clinical findings are still being studied by the medical and research communities [9]. Although clinical manifestations differ, respiratory complications are a typical occurrence among patients. SARS-CoV-2 is unique in that many individuals have had long-term viral problems. Long COVID (also known as long-term or long-haul) refers to a group of COVID-19 individuals whose symptoms linger for an extended length of time [10]. There are two definitions of post-acute COVID-19 in the guideline, according to the National Institute for Health and Care Excellence (NICE): (1) ongoing symptomatic COVID-19 syndrome, defined as symptoms lasting 4 to 12 weeks after the beginning of acute symptoms; and (2) post-COVID-19 syndrome, defined as symptoms lasting more than 12 weeks after the onset of acute symptoms [11]. Beyond early reports of patients feeling fatigued for months following initial infection, long-term COVID-19 has expanded to represent a wide spectrum of disorders and sequelae of symptoms that may emerge [12, 13]. Previous research has found out that COVID-19 infection may cause lung fibrosis, venous thromboembolism (VTE), arterial thrombosis, heart thrombosis, and inflammation which impedes blood flow within the heart causing cardiac tissue damage and myocardial infarction, stroke, "brain fog," dermatologic problems, and general mood dysfunctions [12, 14]. A full blood count, kidney and liver function tests, a C-reactive protein test, and an exercise tolerance test (recording amount of dyspnea, heart rate, and oxygen saturation) are all suggested by the NICE guideline [11]. If patients have chronic respiratory symptoms for more than 12 weeks following an acute illness, a chest X-ray is also indicated [11].

Furthermore, a study conducted on COVID-19 patients observed the prevalence of long-term symptoms following COVID-19 infection [15]. These patients had no symptoms before their initial COVID-19 positivity; nevertheless, patients seeking treatment 4 weeks to 6 months after their initial COVID-19 diagnosis may have long-haul COVID, especially if they were hospitalized during the acute phase of infection [15]. Although the extent of these long-term consequences is broad, individual patients' characteristics have been proven to predict the symptoms people will exhibit, and how long they may last. Managing the long-term consequences of SARS-CoV-2 infection in this population will continue to be a major challenge for health care services as the pandemic lasts [16]. The purpose of this paper is to describe the pathophysiology of COVID-19, the evolution of long-term COVID-19, and identify and review some of the most common complications associated with the disease, such as cardiovascular, neurologic, psychologic, hematologic, pulmonary, dermatologic problems, and other injuries.

Methodology

For articles published between January 1, 2020 and March 24, 2022, literature searches were conducted using the online databases PubMed, Google Scholar, and Medline Plus. Long-term effects of COVID-19, long COVID-19, chronic COVID-19, post-acute SARS-CoV-2, late sequelae of coronavirus disease, and long-haulers were the focus of a review of relevant material. The inclusion of relevant peer-reviewed publications was based on their applicability to the topic.

COVID-19 Long-Haulers

Since emerging in December 2019, COVID-19 has proved to be highly challenging to manage, with a total of 476,504,993 confirmed cases and 6,107,468 confirmed deaths as of March 24, 2022, as reported by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [1]. Measuring the rate and capacity of viral transmission is complicated. The severity of the infection seems to fluctuate from person to person given the virus's ability to be transmitted among the symptomatic, the asymptomatic (confirmed cases that do not experience symptoms all through the period of infection), and presymptomatic cases (confirmed cases that display delayed onset of symptoms later during infection) [17]. The intensity of symptoms and the viral load are important in determining the virus's ability to spread, as both can vary at any point throughout the infectious period [2].

In the human body, the ACE2 (angiotensin-converting enzyme 2) receptor can be detected in brain cells, in cells of the lungs, the heart, the gastrointestinal tract, the liver, the spleen, the kidneys, in mucosal cells, and vascular endothelial cells [7]. Viral replication begins when SARS-CoV-2 enters human cells and binds to the ACE2 receptor [7]. As the virus develops, the infected cell triggers a cascade of

events involving immune cells and cytokines that produce an extensive inflammatory response [7].

Research not only confirmed the physiologically convincing example of autoantibodies targeting type I IFNs (interferons) in COVID-19, but it also revealed that autoantibodies in COVID-19 target a variety of additional immune pathways [18]. In individuals with COVID-19, autoantibodies were also found against numerous tissue-associated antigens, as well as associations between these autoantibodies and inflammatory clinical indicators such D-dimer, ferritin, C-reactive protein, and lactate [18]. Many of the tissue autoantibodies found were in a variety of physiological compartments that have been linked to the post-COVID-19 syndrome [18]. Autoantibodies against the orexin receptor HCRTR2 (hypocretin receptor 2), for example, have been found to decrease orexin signaling in vivo, which is critical for controlling wakefulness and appetite [18].

The scientific community sought to develop a vaccine to immunize the world population against the virus. However, shortly after developing vaccines against the virus, new variants of the virus started to emerge worldwide, with the Delta and Omicron variants being the prevailing variant of the virus [3, 4]. Twice as contagious, the Delta and Omicron variants proved to be another big challenge. These variant strains has displayed the ability to cause significant illness among the unvaccinated and cause some fully vaccinated individuals to get infected and experience a phenomenon known as breakthrough infections [3, 4, 19]. Most infections can be prevented with the COVID-19 vaccine; however, breakthrough infections can be expected as no vaccine is 100% effective [19]. Furthermore, people who are fully vaccinated and contract COVID-19 are less likely to acquire serious illnesses than individuals who are unvaccinated and contract COVID-19 [19]. Therefore, on July 27, 2021, the Centers for Disease Control and Prevention (CDC) advocated for increasing COVID-19 vaccinations and released renewed guidelines for vaccinated individuals to continue using face masks indoors in public areas [3].

The bulk of individuals infected with COVID-19 experience mild or moderate illness, with 10% to 15% developing a more severe form of sickness and 5% advancing into a critical state [20]. Depending on disease severity, it could take up to 2 to 3 weeks for an individual to recover from COVID-19 [20]. Some studies have indicated that one in five individuals may take up to 5 or more weeks to recover fully [20]. Among these findings, new developing data also suggests that following a SARS-CoV-2 infection, a broad spectrum of symptoms can persist in an individual for an unknown prolonged period after the body clears SARS-CoV-2, a condition now referred to as long COVID [7].

Individuals having long COVID have reported a plethora of symptoms. A recent study conducted by Aiyegbusi OL et al. [20], which gathered prevalence data from several articles, indicated that the ten most common symptoms were fatigue 47% (95% CI 31–63), shortness of breath 32% (95% CI 18–47), muscle pain 25% (95% CI 13–37), joint pain 20% (95% CI 13–27), headaches 18% (95% CI 9–27), cough 18% (95% CI 12–25), chest pain 15% (95% CI 9–20), changes to sense of smell 14% (95% CI 11–18), changes to sense of taste 7% (95% CI 4–10), and diarrhea 6% (95% CI 4–9) [20]. The data would suggest that individuals experiencing five or more symptoms in week 1 of acute infection were more likely to develop long COVID regardless of their gender or age [20]. A similar pattern of ongoing symptoms can also be seen with individuals who survived earlier outbreaks of coronavirus infections, such as SARS in 2003 (severe acute respiratory syndrome) and MERS in 2012 (Middle East respiratory syndrome) [13], causing further concern regarding COVID-19.

In another study designed to further comprehend the prevalence of long-haul symptoms, 693,375 infected individuals who did not demonstrate any long-haul signs preceding their COVID-19 diagnosis were analyzed [15]. The data revealed that 9.4% pursued treatment once it was established that they had long-haul symptoms, the most common symptom being difficulty with breathing [15]. The study also suggested that more female patients (approximately 63.5% of the patients) experienced long-haul COVID symptoms compared to their male counterparts [15]. Finally, data gathered from another cross-sectional study, conducted by Tosato et al. attempted to discern the prevalence and recognize any pattern of persistent symptoms in patients 65 years of age and older (with a mean age of 73) who had recovered from COVID-19 [21]. The data depicted that over 80% of the patients who convalesce from COVID documented one or more symptoms, with fatigue, dyspnea, joint pain, and cough being the most common [21]. The data also indicated that the older population who experienced symptoms during acute COVID-19, especially fatigue, is associated with greater chances of persistent symptoms that can linger more than 2 months after discharge [21]. Figure 1 depicts the most common symptoms during post-acute COVID-19.

Cardiovascular Complications

Individuals admitted to the hospital for an acute COVID-19 infection face a remarkably greater risk of mortality with cardiac injury and elevated levels of cardiac troponin [7]. Data from a cohort study showed that approximately 2 months after being diagnosed with COVID-19, the patients displayed persistent myocardial inflammation and elevated levels of cardiac troponin, with chest pain being the most common manifestation among patients [7]. Myocardial inflammation has also been detected in young people and athletes, post-recovery despite being deemed low-risk for severe COVID-19 [7]. Along with cardiac symptoms, there

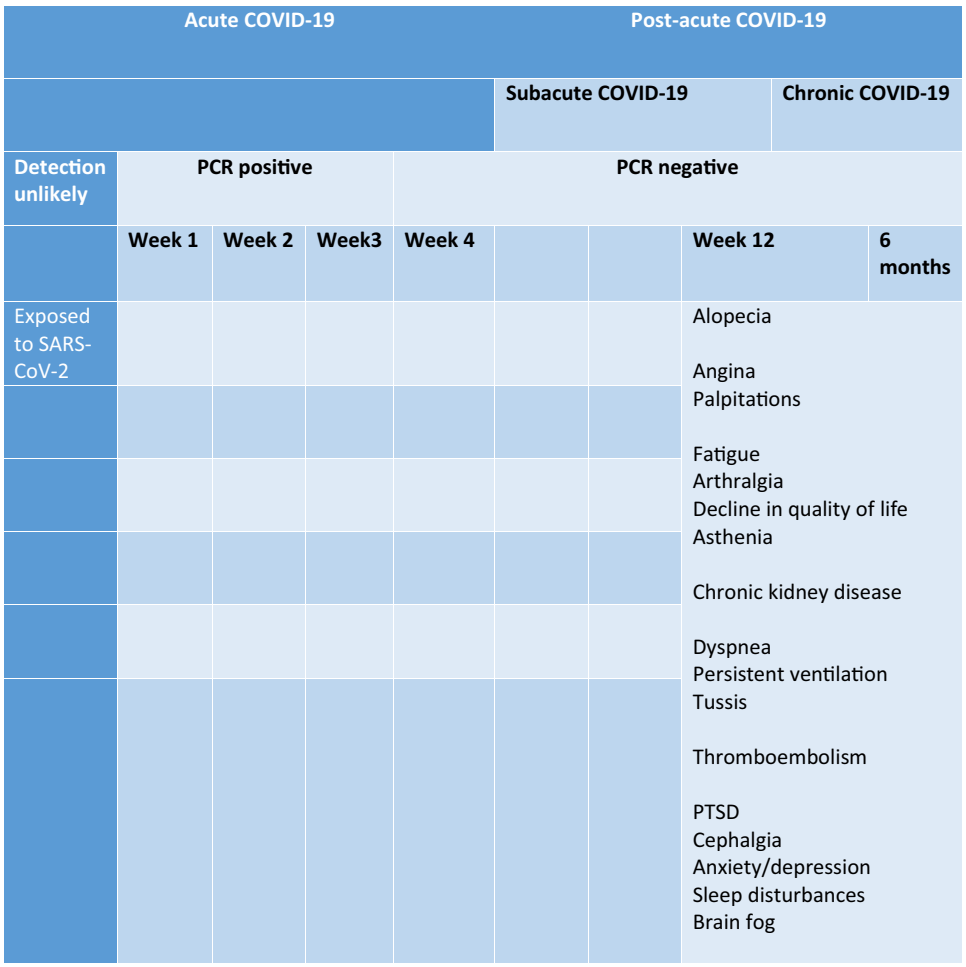

Fig. 1 COVID-19 symptom timeline. Note: Data recreated from Nalbandian et al. defining persistent symptoms seen among post-acute COVID-19 patients [13]

is new data that indicates possible autonomic dysfunction arising post-infection, manifesting as POTS (postural orthostatic tachycardia syndrome) [7].

Utilized public medical services data sets from the United States Department of Veterans Affairs were used to construct a cohort of 153,760 people with COVID-19, as well as two arrangements of control cohorts with 5,637,647 (contemporary controls) and 5,859,411 (historical controls) people, to gauge dangers and 1-year burdens of pre-determined cardiovascular occurrences [22]. It was shown that, past the initial 30 days after the infection, people with COVID-19 are at increased hazards of cardiovascular disease spreading over a few classifications, including cerebrovascular problems, dysrhythmias, ischemic and non-ischemic coronary illness, pericarditis, myocarditis, cardiovascular breakdown, and thromboembolic illness [22]. These dangers were obvious even among people who were not hospitalized during the intense period of the contamination and expanded in a reviewed design as indicated by the consideration set during the intense stage (non-hospitalized, hospitalized, and owned up to serious consideration) [22]. The outcome provides proof that the likelihood and 1-year burden of cardiovascular sickness in overcomers of intense COVID-19 are significant [22]. Care pathways of those enduring the intense episode of COVID-19 ought to incorporate thoughtfulness regarding cardiovascular wellbeing and sickness [22].

Pulmonary Complications

Analogous to the individuals who had endured ARDS (acute respiratory distress syndrome) due to other lung disease processes, SARS-CoV-2 infection can leave individuals with prolonged dyspnea that can be with or without dependence on long-term oxygen, fibrotic damage of the lung, and has also been proven to be problematic when weaning patients off the ventilator is attempted [13]. The dyspnea mentioned above is the most recorded persistent symptom with prevalence ranging from 42% to 66%, with a decrease in lung diffusion capacity being the most reported physiologic abnormality [13].

A recent post-acute COVID-19 study conducted in the USA indicated 6.6% of individuals experienced persistent hypoxemia requiring supplemental oxygen, and 6.9% of individuals required continuous positive airway pressure or

some other source of breathing support [13]. In Spain, a national cohort study was conducted with 1800 individuals that needed tracheostomies at some point during their course of acute COVID-19 and reported that post-infection, only 52% of the patients were weaned off mechanical ventilation successfully [13].

Researchers in Wuhan, China, implemented a prospective cohort study that evaluated the long-term consequences of acute COVID-19 through an extensive in-person evaluation of 1733 infected individuals 6 months from the onset of symptoms; of which, 349 patients underwent a chest CT (computed tomography) at the 6-month mark [13]. Close to 50% of the 349 patients presented with irregular chest patterns, with an overwhelming majority showing ground-glass opacities [13]. The pulmonary vasculature was also affected by macrothrombosis and microthrombosis, as both have been detected in 20% to 30% of COVID-19 patients [13].

Air trapping on CT is prevalent in individuals with prolonged symptoms following COVID-19 infection, according to Cho and Villacreses et al. perspectives' investigation [23–25]. The percentage of lung impacted by air trapping was comparable across COVID-19 severity categories (ambulatory, 25.4%; hospitalized, 34.6%; and requiring intensive care, 27.3%) and lasted for more than 200 days in 8 of 9 people scanned [23–25]. This is a significant result when evaluating the long-term pulmonary repercussions of COVID-19 infection, and it might be related to the development of post-viral constrictive bronchiolitis, a condition found with other viral infections, including adenovirus infection [23–25].

Neurological and Neuropsychiatric Complications

Although it is unclear exactly how COVID-19 can induce neurological engagement, current postulations implicate retrograde neuronal transmission, hematogenous pathways, indirect innate immunity, and adaptive immunity [26]. It is postulated that minor nerve fiber damage may also occur during the transition into long COVID [26]. A study conducted by Bitirgen et al. used CCM (corneal confocal microscopy), a non-invasive method of real-time, high-resolution imaging, to quantify sub-basal corneal nerve morphology and dendritic cell density in individuals with long COVID and those without long COVID [26]. CCM has been a reliable method for showing corneal nerve fiber loss in various neuropathies, fibromyalgia, and inflammatory and demyelinating nerve damage [26]. The CCM findings in the study exhibited corneal nerve fiber damage in those with neurological symptoms at 4 and 12 weeks after being diagnosed with COVID-19 [26]. The study also indicated correlations between corneal nerve fiber damage and the severity of long COVID, neuropathic pain, and musculoskeletal symptoms consistent with previous study findings in patients with neuropathies and fibromyalgia [26].

For 3 to 5 months after infection, macrophages from people with mild COVID-19 exhibit altered inflammatory and metabolic expression [27]. Monocyte-derived macrophages expressed greater levels of pro-inflammatory chemokines after COVID-19, increasing neutrophil recruitment [28]. White matter-specific microglial activation was detected in a mouse model of mild respiratory SARS-CoV-2 infection induced by intranasal SARS-CoV-2 transmission [29]. A similar example of noticeable white matter-specific microglial activation was seen in human brain tissue from 9 persons infected with COVID-19 [29]. CSF (cerebrospinal fluid) cytokines/chemokines were enhanced in mice for at least 7 weeks after the illness; CCL11 (C-C motif chemokine ligand 11), which is linked to neurogenesis and mental function, was one of the chemokines that remained elevated [29]. People with long-COVID and had cognitive adverse effects (48 participants) had higher CCL11 levels than those with long-COVID and did not have cognitive side effects (15 subjects) [29]. In addition, week 1 revealed impaired hippocampal neurogenesis, decreased oligodendrocytes, and myelin loss in sub-cortical white matter, and persevered until no less than 7 weeks, following mild respiratory SARS-CoV-2 contamination in mice [29].

As reported by Stephenson et al. a study conducted by Miller et al. revealed wide-ranging psychological and psychiatric symptoms such as, but not limited to, anxiety, depression, and stress in approximately 10% of the children and young people seen with long COVID [30]. A similar study conducted on 1560 children and young people, of an average age of 15 years, displayed neurocognitive pain and mood symptoms [30]. However, neither study indicated any substantial discrepancies between children and young people with long COVID and/or a COVID negative control group [30].

Other neurological complications include loss of taste and/or smell and abnormal sensitivity to temperature in patients with diabetes [26]. Recent studies investigating cognitive function indicate that SARS-CoV-2 may cause septic encephalopathy and other immunological responses such as microglial activation [7]. Common complaints of COVID patients on hospital admission include cognitive impairment, seizures, hypoxic brain injury, corticospinal tract deficits, altered mental status, and an overall sense of "brain fog" [7, 31]. Currently, there is not enough data to determine which patient population is most at risk or impacted most by COVID-19 neurological symptoms.

Ocular Complications

Patients with COVID-19 have a prevalence of ocular symptoms ranging from 2% to 32% [32]. ACE2 receptors on

human host cells and cleavage by protein TMPRSS2 (transmembrane serine protease 2) are expressed on the cornea and limbus but observed in lower levels on the conjunctiva [32, 33]. As a result, patients infected with SARS-CoV-2 can present with damage to the cranial nerves, pupils, lacrimal system, conjunctiva, sclera/episclera, retina, choroid, and anterior chamber of the eye, among other components of the eye [32]. Overall, conjunctivitis or conjunctivitis-like symptoms such as epiphora, hyperemia, and chemosis appear to be the most common manifestations [34]. These symptoms have been observed in the early stages of the disease in outpatient settings or during hospitalization for severe disease [34]. Non-specific ophthalmic symptoms such as photophobia, dry eye, foreign body sensation, and blurry vision have also been reported [34].

Renal Complications

Data from a retrospective, observational study that reviewed 3993 hospitalized individuals (18 years old and above) diagnosed with COVID-19; found that 46% of patients developed AKI (acute kidney injury), and 19% needed dialysis [35]. Of those with AKI who recovered from COVID-19, 35% of them could not regain their baseline renal function [35]. Detailed assessment of kidney outcomes in long COVID remains limited, though one study showed that survivors of COVID-19 post-30-day infection had a higher risk of AKI, eGFR (estimated glomerular filtration rate) decline, ESKD (end-stage kidney disease), MAKE (major adverse kidney events), and steeper longitudinal decline in eGFR after the acute phase of illness [36].

Endocrine Complications

A cross-sectional study performed in Bangladesh with 734 COVID-19 patients attempted to analyze the presentations, developments, and complications of COVID-19 while also stressing emphasis on diabetic patients [37]. Of the 734 COVID-19 patients, 19.8% were already diagnosed with diabetes and 1.4% were diagnosed with new-onset diabetes [37]. It was observed in diabetic patients that the frequency of the use of insulin almost tripled during infection [37]. Some of the patients that recovered also reported persistent symptoms, including body aches, general discomfort, and disruption of sleep [37]. In addition, the raised blood glucose levels may cause diabetic ketoacidosis which is a fatal condition in type 1 diabetics [38]. However, exercise can be beneficial; it has been seen to reduce inflammation, which is linked to high blood sugar levels and the development and progression of diabetes [38]. Furthermore, some data indicate that SARS-CoV-2 may also initiate pancreatitis among those with acute COVID infection [7].

Hematological Complications

Decreased exercise tolerance and breathlessness are symptoms reported by patients after their initial COVID-19 infection. While the mechanisms of long COVID are still unknown, autopsy reports indicate elevated levels of endothelial dysfunction and thrombosis [39]. In a study conducted by Fogarty et al. which examined fifty patients approximately 2 months after their SARS-CoV-2 infection, it was reported that 25% of those recovering from COVID-19 displayed continuously elevated D-dimer levels and prothrombotic changes in hospitalized and non-hospitalized individuals as far out as 4 months after acute infection was resolved [39]. Disseminated thrombosis of platelet and fibrin-rich thrombi containing neutrophils and activated Factor 12 have been identified all through the pulmonary vasculature in post-mortem studies of acute COVID-19 [39]. New evidence proposes that the pulmonary thrombi in COVID-19 patients are derived from within the lungs instead of an embolism to the lungs [39]. When Factor 12 activation was evaluated by Fogarty et al. they were unable to find any substantial differences in recovering patients ($n = 20$) and the control patients ($n = 17$; $p = 0.16$, 95% CI −0.15–0.03) [39]. However, Factor 8 activity which can affect thrombin generation was elevated in patients recovering from COVID-19 infection [39]. The study also observed elevated VWF: Ag (von Willebrand factor antigen) levels in recovering patients compared to the control patients [39], suggesting possible VWF-ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) axis impairment also being a factor in vascular thrombosis.

Dermatological Complications

Hair loss is the most prevalent dermatological symptom [13]. About 20% of patients that recover from COVID-19 have reported experiencing hair loss [13]. In addition, six distinct dermatological clinical patterns have been observed: (1) confluent maculopapular/erythematous/morbilliform rash, (2) purpuric/vasculitic pattern, (3) urticarial rash, (4) livedo reticularis/racemosa-like pattern, (5) chilblain-like aural pattern, and (6) papulovesicular exanthem [40]. COVID-19 patients had a 5.95% overall prevalence of cutaneous symptoms [41]. The maculopapular rash (37.3%) was the most prevalent skin involvement in middle-aged women with intermediate disease severity [41]. Patients with vascular lesions had a more severe illness than those with chilblain-like and urticaria-like lesions [41]. Patients with chilblain-like lesions improved in 72% of cases without the use of any medication [41]. SARS-CoV-2 infection in children has a different general clinical presentation, course, and outcome than in adults, as do the cutaneous symptoms of kids [42]. COVID-19 cutaneous symptoms in children

included chilblain-like lesions, erythema multiforme, urticaria, and an inflammatory multisystemic illness similar to Kawasaki disease [42].

Gastrointestinal Complications

COVID-19 can cause general disarray in the gut. It can change and upset the microbiome, disrupt the natural flora, allow room for opportunistic infections to arise, and help induce nausea, vomiting, and diarrhea [7]. Even though the gut microbiota has been linked to the development and/or maintenance of GI diseases [43], research relating the human microbiota to COVID-19 is still not fully understood [44]. In addition, the gut microbiota can impact viral transmission and illness progression in a variety of ways, altering bacterial composition [43].

Musculoskeletal Complications

An extension cohort study that interviewed COVID-19 patients at 3 months and 6 months after recovery indicated that 89% of the patient population had one or more persistent symptoms [45]. In addition, 74.6% of the patients experienced, at the minimum, one rheumatic and musculoskeletal symptom with fatigue, joint pain, and myalgia most reported, followed by generalized back pain, lower back pain, and neck pain [45]. Girdle pain/stiffness with acute-phase reactant elevation resembling polymyalgia rheumatica was the most common (41%) clinical picture at the presentation of musculoskeletal complications in another post-COVID-19 study, followed by oligoarthritis (32%), and polyarthritis (27%) [46].

Discussion

Clinical manifestations of the novel COVID-19 (SARS-CoV-2) may be distinct; however, in comparison to other coronaviruses such as SARS and MERS infections, persistent dyspnea and fatigue were commonly reported among the three infections [2, 20, 47–49]. A meta-analysis of twenty-eight follow-up studies revealed that at 6 months post-hospitalization, 25% of patients admitted with SARS and MERS had decreased lung function and reduced exercise capacity [48]. These studies also indicated that at 1-year post-infection, PTSD (posttraumatic stress disorder), anxiety and depression, and reduced quality of life were observed in these patients, indicating the impact of COVID-19, eventually, will yield similar results [48]. An additional study with patients infected with SARS observed that after 2 years, lung functions, specifically FEV1 (forced expiratory volume in 1 min), FVC (forced vital capacity), and TLC (total lung capacity), was reduced by 11%–18% [50]. Furthermore, DLCO (diffusing capacity for carbon monoxide) was decreased by 27% [47]. Based on the data from other coronaviruses, early recognition of dyspnea and functional limitations after COVID-19 infections requires ongoing evaluation to predict potential long-term complications for COVID-19 survivors [48]. While COVID-19 seems to have a higher infectivity rate and lower mortality compared to SARS and MERS [49], these previous infections exhibit similarities with COVID-19, allowing researchers to utilize knowledge of their long-term implications on the survivors to help guide predictions of chronic effects of these long-haul COVID-19 patients [51, 52].

Long COVID appears to be like syndromes that can occur after a variety of different illnesses [53]. Neurasthenia and encephalitis lethargica was coined 150 years ago to describe weariness, anxiety, sadness, and neuralgia that commonly occurred following viruses like influenza, though a direct link has yet to be shown [53]. Chronic fatigue syndromes, sometimes known as post-infectious fatigue syndromes, have since been linked to a variety of infectious disorders, including brucellosis, Q-fever, giardiasis, mononucleosis, and flavivirus infections like dengue fever [53]. Excessive tiredness is a significant symptom in all these illnesses, and numerous additional concomitant symptoms appear to match important symptoms observed with long COVID [53]. Researchers revealed that post-infectious syndromes caused by various bacteria have similar clinical symptoms, implying that the host reaction may be more important than the etiological cause [53]. The biology of post-infectious fatigue syndromes remains a mystery, as does the pathogenesis of long COVID [53]. Certain symptoms, such as impaired taste/smell and dyspnea, appear to be exclusive to long COVID, suggesting that it is conceptually distinct from other post-infectious disorders [53].

Variants and Vaccinations

The identification of specific VOIs (variants of interest) and VOCs (variants of concern), to prioritize global monitoring and research, and to inform the ongoing response to the COVID-19 pandemic, was prompted by the emergence of variants that posed an increased risk to the global public health, according to the WHO (World Health Organization) [4]. As predicted early on in the pandemic, the inability to fully control the spread has been due to the development of novel variants of the virus, including but not limited to the Delta variant (B.1.6.17.2 lineage) that was first identified in India; Gamma (P.1 lineage) first identified in Brazil; the Lambda (C.37 lineage) variant first identified in Peru; and now the Omicron (B.1.1.529) variant identified in South Africa [4, 12, 54]. These variants of concern (WHO-labeled Delta from lineage B.1.617.2 and WHO-labeled Omicron from lineage B.1.1.529 with sub-variants of BA.1, BA.1.1,

and BA.2) show that the efficacy of vaccinations and therapeutics in neutralizing the virus may be decreasing [4, 12, 54]. Given the identification of these variants, it remains unclear how long-haul COVID-19 will be impacted [12, 54]. Kang et al. observed that participants with the variants are more likely to disseminate the virus due to a higher presymptomatic viral load, with 73.9% of transmissions occurring before the onset of symptoms [55]. It should be noted that individuals fully vaccinated were less likely to spread the virus when compared to unvaccinated persons, or those with only one dose of immunizations [55].

The risks of developing symptoms for 28 days or more following a post-vaccination infection were reduced when two vaccine doses were given [8]. When combined with the previously observed reduced risk of infection overall, this data shows that those who have had double immunization have a lower risk of long COVID [8]. It is currently unclear if the differences in strains and transmissibility are related to changes in the molecular pathways that explain why only certain people are prone to developing lengthy COVID-19 symptoms [55], hence, the need for additional studies on this subject matter. Vaccines have a higher impact on disease severity and survival than they do on infection prevention [53]. It is unclear if immunization protects against long COVID in patients infected with Delta and the now-dominant Omicron, as well as potential future variations [53]. It is being investigated if immunizations might have a therapeutic impact against long COVID [53]. However, because immune-mediated pathogenesis is one of the postulated mechanisms supporting long COVID, there is a theoretical possibility that vaccination might induce or aggravate long-COVID-like symptoms [53]. So far, the data on this topic is inconclusive [53].

COVID-19 has caused an unprecedented amount of morbidity and mortality on a global scale [13]. Clinical and scientific evidence is increasing on the long-term effects of COVID-19 on multiple organ systems [13]. Many studies have suggested that the residual effects of the infection such as dyspnea, fatigue, chest pain, cognitive disturbances, and joint pain can decline the quality of life and impact future immunity to other viral infections [12, 20]. Cellular damage secondary to an elevated innate immune response, inflammatory cytokine production, and a hypercoagulopathic state induced by COVID-19 viral infection may contribute to these sequelae [13]. The mechanisms that trigger the post-acute and chronic long-term manifestations of COVID-19 are not fully understood [37]. However, direct viral effects on the immune system can be due to several hypotheses, including persistent viremia due to immune response paresis and fatigue, causing reinfection or relapse of the viral infection and symptoms, cytokine- and hypoxia-induced injury, and autoimmunity [12, 37].

Most of the long COVID-19 data pertain to the general population, with little evidence concentrating on elderly persons and children. Sudre et al. [56] discovered that advanced age, female sex, increased body weight, and the development of more than five symptoms during the first week of acute COVID-19 were substantial predictors of long COVID-19 [15, 56–58]. Children, while being diagnosed with COVID-19 at a lesser rate than adults [59, 60], might suffer from complications and sequelae such as MIS-C (multisystem inflammatory syndrome in children) [61]. In the weeks following infection, this is marked by fever and multiorgan dysfunction [61]. In children, the overall prognosis is excellent, and most with cardiovascular problems recover within a few weeks [12, 62, 63]. However, a minority of patients had consistently lower ejection fractions and unsolved coronary artery anomalies months later, casting doubt on the long-term effects of MIS-C [12, 62, 63].

Clinical Management of COVID-19 Long-Haulers

A broad spectrum of symptoms is seen to persist in COVID-19 long-haul patients [51, 64]. It was also observed that individuals with less severe infections display numerous and persistent symptoms despite sequential nasopharyngeal COVID-19 tests being negative [51, 65]. In the UK, an app-based COVID-19 symptom study revealed that one out of every ten persons may still have symptoms 3 weeks after infection, while symptoms may persist in others for some months post-infection [8, 65]. These persistent symptoms may include fatigue, dyspnea, chest/joint pain, bone, ocular, and dermatologic manifestations [64]. Continued monitoring of these patients is necessary to understand the extent and severity of these long-term effects [64]. Post-hospital care for COVID-19 survivors has been identified as a major research priority, and management guidelines for these long COVID patients are still being developed [13]. Home pulse oximetry may be used to monitor individuals with chronic pulmonary symptoms, and some studies have proposed repeated PFTs (pulmonary function tests) and 6MWTs (six-min walk tests) for patients with persistent dyspnea, as well as high-resolution chest CT examinations at 6 and 12 months [13]. Corticosteroid therapy may be indicated for a sub-set of patients with post-COVID inflammatory lung disease [13]. Clinical trials of antifibrotic therapies to limit/prevent pulmonary fibrosis for post-COVID patients are currently in progress; however, lung transplantations may be performed for fibroproliferative lung disease after ARDS due to COVID-19 [13]. ASTEX (activated specialized tissue effector extracellular) vesicles are cytoprotective and antiviral in human lung epithelial cells subjected to SARS-CoV-2 [66–68]. It inhibits SARS-CoV-2 infection and its pathogenic consequences by

suppressing mTOR signaling, which in turn alters the transcriptome of infected cells [66–68].

Due to the observed increase in thrombotic events during the acute phase, hematological therapy may involve extended post-discharge and prolonged thromboprophylaxis for up to 45 days in patients with more favorable risk-benefit ratios in COVID-19 [13]. However, at this point, personal patient considerations for risk-benefit ratios should determine prescriptions for thrombolytic prophylaxis [13]. Direct oral anticoagulants and low-molecular-weight heparin are favored over vitamin K antagonists because they do not require therapeutic level monitoring and have a lower risk of medication interactions [13]. Antiplatelet drugs, such as aspirin, have not yet been identified for thromboprophylaxis in COVID-19 and are now being explored as a long-term thromboprophylactic therapy [69].

For patients who develop cardiovascular problems during the acute phase or have chronic heart symptoms, cardiovascular care may involve several clinical and imaging examinations every 4 to 12 weeks [69]. Although initial theoretical concerns linked elevated ACE2 levels in COVID-19 with the use of RAAS (renin-angiotensin-aldosterone system) inhibitors, they have been demonstrated to be safe and should be continued for people with stable cardiovascular disease [65, 69]. Patients with inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome may benefit from a low-dose beta-blocker to lower adrenergic activity and control heart rate [70, 71].

The injectable medication remdesivir, as well as the active components of Paxlovid and Merck's molnupiravir, were as effective against BA.1 as they were against the initial SARS-CoV-2 strain [5]. Evusheld, which is authorized in the USA to help prevent COVID-19 infection in persons at risk of severe disease, was the most effective antibody therapy against the BA.2 variation [5, 6]. Antibodies sold by Regeneron and GlaxoSmithKline were far more effective against BA.2 than they were against the BA.1 Omicron strain, though not as effective as they were against earlier variants of the virus [5, 6].

Conclusion

Long COVID individuals, also referred to as long-haul or long-term, are people whose COVID-19 symptoms remain for an extended period (between 4 weeks and 6 months) after the body has cleared the SARS-CoV-2 infection. Some of the most common complications include the pulmonary, cardiovascular, hematological, endocrine, gastrointestinal, neurological, neuropsychiatric, renal, dermatological, and musculoskeletal systems. Common disorders and symptoms that long-term COVID-19 patients may experience include heart thrombosis and inflammation potentially causing myocardial infarction, lung fibrosis, stroke, venous thromboembolism, arterial thromboembolism, "brain fog", general mood dysfunctions, dermatological issues, and fatigue.

As new variants of SARS-CoV-2 emerge, these viral strains continue to cause long-term complications. One variant may cause more damaging long-term effects than other strains, and infected individuals could require additional support and more rapid and intense treatment. This makes managing the after effects of COVID-19 infection even more difficult for healthcare providers in the next stage of the pandemic. Continued monitoring of these individuals is necessary to comprehend the extent and severity of these long-term symptoms.

A greater understanding of the pathogenesis and methods for treating long COVID is necessary to decrease the burden. Post-hospital care of COVID-19 survivors has become a significant research priority, and adequate guidelines for the management of these patients are still being developed. It is unclear if the differences in strains and transmissibility are related to changes in the molecular pathways that explain why only certain people develop long-term symptoms, hence the need for additional studies. Scarce literature in certain patient populations (including children), variable follow-up times, and the prevalence of comorbidities are all contributors to the disease sequelae.

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