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From brain fog to COVID toe: A head-to-toe review of long COVID

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ABSTRACT

With the World Health Organization's announcement of the end of the coronavirus disease 2019 (COVID-19) public health emergency, both clinicians and patients may think that the COVID-19 era is over. While the pandemic may have ended, acute infections continue to occur as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus transitions to the endemic phase. After initial COVID-19 infection, approximately 20% of patients experience persistent symptoms for more than 4 weeks. This clinical phenomenon is often termed "long COVID" but many other terms exist in the literature including "Post-COVID-19 syndrome," "Chronic COVID-19," "long haul COVID," "post-acute COVID-19 syndrome," "long-term sequelae," and "post-acute sequelae of SARS-CoV-2 infection," among others. For the purposes of this review, we define long COVID as symptoms occurring more than 4 weeks after initial infection. Long COVID manifests in a wide variety of symptoms, including cough, fatigue, muscle weakness, cognitive impairment, shortness of breath, and chest pain. In fact, current literature indicates that long COVID has effects throughout every major organ system. Within this review, we compile and summarize the available data regarding symptoms of long COVID using a head-to-toe approach. This review is meant to be comprehensive covering the following organ systems: neurologic, cardiac, pulmonary, gastrointestinal, hepatic, renal, genitourinary, hematologic, musculoskeletal, and integumentary. The purpose of this narrative review is to provide a broad and inclusive resource for clinicians on long COVID symptomatology, pathophysiology, and potential treatments.

Keywords: Long COVID, Post-COVID-19 syndrome, Long COVID outcomes, Persistent COVID-19 symptoms, Infectious diseases

INTRODUCTION

With the World Health Organization (WHO) announcing the end of the coronavirus disease 2019 (COVID-19) public health emergency on May 05, 2023, clinicians may be tempted to think that COVID-19 is a thing of the past.[1] While acute infection with COVID-19 may be decreasing, providers are likely to encounter patients with persistent illness long after acute COVID-19 infection. Per the January 2023 Center for Disease Control's (CDC) Household Pulse Survey, approximately 1 in 10 patients still report symptoms of long COVID.[2] Long COVID is a phenomenon extensively discussed in the literature, with various names used to refer to it, such as "long COVID," "long haul COVID," "Post-COVID-19 syndrome," "Chronic COVID-19," "post-acute COVID-19 syndrome," "long-term sequelae," and "post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection," among others. This diversity in nomenclature is also reflected in the

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definition of long COVID. In general, long COVID refers to persistent or unresolved effects of COVID-19 illness that occur beyond 4 weeks from the initial onset of symptoms.[3-7] According to the guidelines from the UK's National Institute for Health and Care Excellence, long COVID can be further categorized into ongoing symptomatic COVID-19, where symptoms continue for 4 to 12 weeks after the initial illness, and post-COVID-19 syndrome, where symptoms persist beyond 12 weeks.[8] Other classifications of long COVID consider the duration of symptoms, such as subacute if symptoms resolve within 3 months or chronic if symptoms persist after 3 months.[9,10] For the purpose of this literature review, we define long COVID as symptoms persisting or occurring 4 weeks after the initial SARS-CoV-2 infection to encompass a large body of evidence and provide a comprehensive understanding of long COVID.

Regarding the prevalence of long COVID, the literature reports varying numbers. One study suggested that approximately 20% of individuals initially infected with COVID-19 will experience long COVID, while others report a range of 22–69%.[5,9,10] However, it is generally agreed on in the literature that individuals hospitalized for the treatment of acute COVID-19 are more likely to experience long COVID, with one study estimating a prevalence rate of 80% in this population.[3] The variation in reported prevalence is likely attributed to different strains of the COVID-19 virus and their virulence. Multiple studies indicate common risk factors associated with the likelihood of developing long COVID symptoms, including the severity of acute COVID-19 illness, female sex, older age, initial dyspnea, and comorbidities, particularly asthma.[5,7,11-13] Conversely, early viral clearance has been linked to protection against developing long COVID.[5] Commonly reported symptoms in the literature include cough, fatigue, muscle weakness, cognitive impairment, shortness of breath, and chest pain.[10,14] However, long COVID presents a wide range of clinical manifestations making it particularly challenging to identify consistent outcomes. Other articles have attempted to summarize the information by focusing on the organ systems most prominently affected.[15-17] Our objective is to provide a comprehensive and inclusive narrative review for clinicians on long COVID symptomatology, pathophysiology, and potential treatments. To the best of our knowledge, this is the first review article that compiles the available data on long COVID, encompassing all organ systems, and providing a complete head-to-toe analysis.

Neurologic

Neurologic symptoms during acute COVID-19 infection vary from 36.4% to 82.3%, with many of these symptoms persisting well after acute infection resolves.[18] Studies have indicated that over half of non-hospitalized COVID-19 patients continue to experience symptoms beyond 4 months.[19,20] These symptoms vary greatly and include headache, depression, anxiety, fatigue, cognitive impairments, tinnitus, vertigo, and taste and smell disturbances.

The SARS-CoV-2 virus is implicated in the pathophysiology of these symptoms. The virus colonizes the nasal cavity and then infiltrates the brain and cerebrospinal fluid through the olfactory nerve.[21,22] After binding to the angiotensin-converting enzyme 2 (ACE2) receptors found in the brain stem, the neurons and glial cells are damaged. This damage results in demyelination and neurological complications.[21,22] Cognitive deficits, anxiety, depression, and sleep disturbances have been associated with enhanced cytolytic granule expression in memory T-cell subsets.[23]

Symptoms

Tinnitus and vertigo have been commonly reported in patients experiencing long COVID. In one large prospective cohort study in Germany, patients reported vertigo (60%) and tinnitus (30%) at a mean period of 43.2 ± 23.4 weeks after infection. Approximately 20% of patients reported their symptoms as severe.[24]

Premraj *et al.* also reported various neurological symptoms experienced by post-COVID-19 patients in a large meta-analysis. The prevalence of neurologic symptoms was as follows: Fatigue (37%), brain fog (32%), memory issues (28%), headache (15%), anosmia (12%), and dysgeusia (10%). In addition, there were reports of neuropsychiatric conditions which became more prevalent over time, including sleep disturbances (31%), anxiety (23%), attention disorder (22%), and depression (17%). Interestingly, the prevalence of neurological symptoms tended to be lower in patients requiring hospitalization compared to those who did not.[18]

In another systematic review, one in three long COVID patients were diagnosed with generalized anxiety disorder (29.6% [Interquartile range (IQR) 14.0–44.0%]), one in four with sleep disorders (27%, [IQR 19.2–30.3%]), one in five with depression (20.4% [IQR 19.2–21.5%]), and one in eight with posttraumatic stress disorder (13.3% [IQR 7.3–25.1%]).[25] According to a large 2-year retrospective cohort study, adults were at an increased risk of receiving a new diagnosis of anxiety, cognitive deficit defined as memory or attention deterioration, seizures, insomnia, mood, and psychotic disorders in the first 6 months after acute COVID-19 infection. Conversely, children were not at an increased risk for mood disorders but were at an increased risk of encephalitis.[26]

Treatment

Studies have not directly identified effective therapy for treating or preventing post-viral neurological impairments.

Some institutions have created COVID-19 clinics specializing in certain aspects of long COVID symptomatology. One neurology-based clinic reported on medications utilized for neurologic symptoms, including antidepressants, benzodiazepines, gabapentin, amantadine, and modafinil although dosing and efficacy were not reported.[19] In addition, several nutraceuticals have been studied for the purpose of alleviating long COVID symptoms.[27,28] One systematic review suggested that high-dose intravenous Vitamin C, with doses ranging from 0.8 to 3 g/kg 3–4 times weekly, may be an option for the management of persistent fatigue. These data are largely extrapolated from its efficacy in other chronic disease states such as cancer and post-viral syndromes.[29] A randomized control trial found a daily oral dose of Vitamin D3 5000 international units for 2 weeks reduced the duration of cough and dysgeusia compared to lower doses. No other symptoms were significantly improved by Vitamin D supplementation.[30]

In addition to Vitamins C and D, proprietary supplements have been investigated for the treatment of long COVID symptoms. One study published by Rossato *et al*. reported on the effect of Apportal® on chronic fatigue after COVID-19 infection. This supplement contains multiple group B vitamins, amino acids, and plant extracts. After 28 days of daily supplementation, all indices of general fatigue, mental fatigue, and quality of life were significantly improved.[31] Another study proposed the use of palmitoylethanolamide and luteolin (PEA-LUT) for the treatment of chronic olfactory impairment in combination with olfactory training. This double-blind, randomized, and placebo-controlled trial included 185 patients with prior COVID-19 infection and chronic olfactory impairment lasting longer than 6 months. Patients in the treatment arm received ultramicronized PEA-LUT 770 mg daily in combination with olfactory training while the control group received olfactory training alone. The intervention group had significant improvement in olfactory threshold, discrimination, and identification (TDI) scores. In the intervention group, 56% of patients recovered to a normal TDI score compared to only 10% of the control group ($P < 0.00001$) with no increase in adverse effects.[32]

Probiotics have also been trialed for the management of neuropsychiatric symptoms, given the proposed link between gut microbiota and long COVID manifestations in the brain. A randomized, double-blind, and placebo-controlled trial evaluated the efficacy and safety of a systemic enzyme and probiotic complex for post-COVID-19 fatigue symptoms in 200 patients. After 14 days, subjects receiving the systemic enzyme/probiotic supplement exhibited a significant reduction in physical and mental fatigue scores. Of note, inclusion criteria only required a confirmed diagnosis of COVID-19 followed by a negative polymerase chain reaction test, so patients may have been included who did not meet the definition of long COVID.[33] In summary, several proprietary supplements have been studied with positive results, suggesting a potential role for vitamin and nutrient supplementation. However, there are several issues limiting the application of these studies including small sample sizes and unavailability of specific formulations. It is unclear whether these results are generalizable to similar supplements. Larger studies are needed to further investigate treatments of neurologic and psychologic disorders in long COVID.

Cardiac

COVID-19 affects the cardiovascular system in a variety of ways and many studies report cardiovascular symptoms in patients with long COVID. Reported signs and symptoms range from chest pain and palpitations to severe manifestations including myocarditis and major cardiovascular events such as myocardial infarction, stroke, and arrhythmias. There are many proposed mechanisms to explain these widespread cardiovascular effects of COVID-19. ACE2 receptors are present in myocardial tissue, allowing direct binding of SARS-CoV-2. Proposed mechanisms for myocardial injury include direct cytotoxic effects, oxidative stress, inflammation, impaired oxygen delivery, and autoimmune responses.[7,14]

General symptoms

Chest pain, tachycardia, and palpitations are commonly reported by patients with long COVID. In a large, systematic review investigating the incidence of cardiac sequelae in long COVID, 17.5% of patients reported chest pain while only 0.77% of patients reported palpitations.[34] Elevated heart rate is also frequently described in long COVID patients. Radin *et al*. utilized Fitbit® data to compare baseline resting heart rates (RHR) to RHR 28 days after diagnosis with COVID-19. This study indicated that 13.7% of patients exhibited RHR elevations of >5 beats/min compared to their baseline RHR that did not return to baseline for more than 133 days.[35] Beta-blockers may be considered in the management of palpitations and/or tachycardia, but providers should ensure that other etiologies of tachycardia such as atherosclerotic disease and venous thromboembolism (VTE) have been ruled out.[36] Ivabradine is an alternative therapy that may be considered, with one small study reporting greater heart rate reduction with ivabradine 5 mg twice daily compared to carvedilol 3.125 mg twice daily. However, this study should be applied with caution given the small sample size and only 1 week of follow-up.[37]

Myocarditis/pericarditis

Given the inflammatory nature of COVID-19, it is not surprising that inflammatory cardiovascular conditions

including myocarditis and pericarditis have been observed in patients affected by long COVID. There are multiple studies reporting findings from cardiac magnetic resonance (CMR) imaging after infection with COVID-19. In one of the largest studies including 100 patients, 78% of patients had abnormal CMR findings, with 60% showing ongoing myocardial inflammation and 20% with pericardial effusion. CMR was performed at a median time of 71 days since a positive COVID-19 test indicating a long-lasting effect on the cardiovascular system.[38]

Major adverse cardiovascular events (MACE)

Much of the data surrounding MACE, including heart failure, myocardial infarction, stroke, and arrhythmias, is focused on the acute phase of COVID-19 infection. However, there is some evidence that correlates COVID-19 infection with MACE outcomes later in the recovery phase or in long COVID.[34,39] Ayoubkhani *et al*. report an increased risk of MACE in patients with a history of COVID-19 compared to controls (relative risk 3; 95% confidence interval [CI] 2.7–3.2).[39] At this time, it is difficult to distinguish the cause of MACE events in patients with a history of COVID-19 infection versus other risk factors such as lifestyle, obesity, and other comorbidities.

Postural tachycardia syndrome (POTS)

POTS is an uncommon but known complication of viral infection, with infection being implicated in 28–41% of cases.[40] POTS refers to an increase in heart rate of at least 30 beats/min on standing without the development of orthostatic hypotension.[41] While challenging to identify the exact incidence, numerous cases have been reported occurring up to 6–8 months after COVID-19 infection. Symptoms accompanying POTS can be quite distressing including excessive anxiety, fatigue, hypertension, and gastrointestinal (GI) or bladder dysfunction due to autonomic dysregulation and sympathetic activation.[41]

Treatment

Management of cardiovascular symptoms is similar in patients with and without long COVID. However, the efficacy of these strategies in long COVID patients is unclear given the different etiologies. The European Society of Cardiology published a review in 2022 regarding the cardiovascular impact of long COVID and current strategies for managing cardiovascular complications.[7] These strategies are shown in Table 1. Further studies are needed to better define treatments for cardiovascular complications in long COVID.

Pulmonary

While the exact incidence and prevalence rates of long-term pulmonary symptoms are unknown, the Office for National Statistics in the United Kingdom estimates that symptoms occur in approximately 12% of the population and can persist for up to 12 weeks post-infection.[42] Common pulmonary symptoms of long COVID include shortness of breath, wheezing, cough, fatigue, and decreased exercise capacity.[43-45] Possible risk factors for long-term pulmonary symptoms include female sex and history of respiratory comorbidities such as sleep apnea, asthma, chronic obstructive pulmonary disease, smoking, and cystic fibrosis.[45,46] COVID-19 causes lung injuries through various mechanisms, including alveolar damage, diffuse thrombotic alveolar occlusion, and airway inflammation.[47] This ultimately leads to impaired interstitial remodeling and damage to both the vasculature and autonomic nervous system resulting in impaired gas exchange and potential lung fibrosis.[47,48]

It is well-known that changes in lung imaging and lung function are prevalent in acute disease.[49,50] Lung function may continue to be abnormal post infection though the timeframe of these pulmonary changes is still limited in the literature. One large systematic review reports that 54.3–83% of adult patients <50 years old had lung computed tomography abnormalities following recovery from COVID-19 infection. However, it is unknown if all patients in this study met our definition of long COVID.[51] Sonnweber *et al*. suggest improvements in lung function as soon as 3 months post-infection, while Watanabe *et al*. suggest that these changes can persist for at least 12 months.[49,52]

Cough and shortness of breath

Shortness of breath and chronic cough is both commonly reported symptoms of long COVID. The prevalence of shortness of breath is approximated to be 60% whereas the prevalence of chronic cough has been reported from 7% to 10%.[43,53] Chronic cough during long COVID may result from neuroinflammation and tracheal hypersensitivity. Neuromodulator agents such as gabapentin and pregabalin can be considered to alleviate chronic cough in long COVID. Antimuscarinic agents such as tiotropium have been postulated to reduce cough through the reduction of tracheal sensitivity.[53] Literature pertaining to pharmacologic management of shortness of breath is limited to the acute phase of COVID-19 infection. However, there is some evidence that links COVID-19 infection to the development of asthma.[54] Given that uncontrolled asthma symptoms also present as chronic cough and shortness of breath, providers may consider bronchodilators or corticosteroids given their efficacy in both the acute setting and in the treatment of asthma.[53,54]

Interstitial lung disease (ILD)

The inflammatory nature of COVID-19 often leads to alveolar destruction and remodeling, which may ultimately result

Table 1: ESC strategies for management of cardiovascular complications of long COVID.[7]

Condition	Recommendations
Generalized symptoms such as chest pain or palpitations without underlying cardiovascular cause	Consider periodic ECG monitoring due to the risk of development of further cardiovascular complications. Manage comorbidities including weight and diet with tailored exercise, stress reduction, and/or pulmonary/cardiac rehabilitation.
Myocarditis	At present, no difference in management compared to patients without COVID-19. Consider EMB to determine subtype to guide specific treatment.
Pericarditis	The efficacy of oral NSAIDs and/or colchicine is currently being evaluated for COVID-19-associated pericarditis.
Acute coronary syndromes	Treat in accordance with current ESC/AHA guidelines.
VTE prevention	No current evidence for the efficacy of prolonged thromboprophylaxis post-acute COVID-19.
POTS	Correct reversible causes including dehydration and temperature management. If ongoing symptoms occur, can consider beta blockers, graded exercise programs, and/or compression stockings that provide 30–40 mmHg counter pressure.

ESC: European society of cardiology, ECG: Electrocardiogram, EMB: Endomyocardial biopsy, NSAIDs: Nonsteroidal anti-inflammatory drugs, AHA: American heart association, POTS: Postural tachycardia syndrome, VTE: Venous thromboembolism, COVID: Coronavirus disease

in long-term ILD and lung fibrosis.[55] The exact incidence rate of ILD is unknown. In the COVID-FIBBROTIC study, 27.4% of patients had ongoing radiological abnormalities 12 months after infection and 22.7% demonstrated residual fibrotic changes.[56] In another retrospective review, 13.8% of patients presenting to an outpatient pulmonology clinic with long COVID respiratory symptoms were suspected to have new ILD.[57] In addition, a single-center, prospective, and observational study indicated that 10.8% of patients with persistent respiratory symptoms were found to have new ILD.[58]

Corticosteroids are typically trialed in patients found to have ILD, although the optimal dose and duration of steroids are unknown. In a small retrospective cohort study of post-COVID-19 patients diagnosed with ILD, 30 patients were treated with oral corticosteroids at a maximum initial dose of 0.5 mg/kg prednisolone for at least 3 weeks. This regimen resulted in improvement in dyspnea, lung function, and exercise capacity (measured by the 6-min walking distance [6MWD] test).[58,59] A 6-week randomized and controlled trial comparing two different treatment doses of corticosteroids is currently underway to determine the impact of steroid use in this patient population.[59] Antifibrotic therapy such as nintedanib, sirolimus, and pirfenidone has also been proposed for patients with post-COVID-19 ILD. At present, there is inadequate evidence to support its widespread use.[55]

Pulmonary rehabilitation

The American Thoracic Society in combination with the European Respiratory Society recommends early pulmonary rehabilitation for individuals experiencing long-term respiratory symptoms, especially in patients with a history of severe COVID-19 infection.[60] A prospective study conducted by Nopp *et al.* evaluated the outcomes of outpatient pulmonary rehabilitation using the endpoints of the 6MWD test, Borg dyspnea score, and the modified medical research council tool.[61] The study included 64 participants and the primary endpoint, 6MWD, showed an increase of 62.9 m from baseline. Improvements in pulmonary function tests (forced expiratory volume in 1 s and diffusing capacity of the lungs for carbon monoxide [DLCO]) were also observed. Feelings of dyspnea, functional status, and quality of life were also improved at 6 weeks, indicating that pulmonary rehabilitation may be a crucial tool in patients with long COVID experiencing respiratory symptoms.[61]

Further, research is needed to determine the long-term (>12 months) effects of COVID-19 on the respiratory system, particularly in individuals who experienced severe disease. Studies should investigate how lung remodeling and decreased pulmonary function impact the population and the potential development of other pulmonary conditions due to these changes.

Gastrointestinal (GI)

There is a high prevalence of post-COVID-19 GI symptoms, with incidence varying from 3% to 79%.[62] Reported symptoms may be non-specific such as diarrhea, constipation, abdominal pain, heartburn, nausea, and vomiting. In addition, gut dysbiosis and development of irritable bowel syndrome (IBS) have also been described. These symptoms are likely related to the high prevalence of ACE2 receptors in the GI tract, providing a means of entry into the cell for the SARS-CoV-2 virus. This viral entry can lead to lymphocyte infiltration and diffuse inflammation.[62] Natarajan *et al.* reported that the SARS-CoV-2 virus may be present in the GI tract long after initial moderate COVID-19 infection.

Study participants demonstrated prolonged shedding of SARS-CoV-2 RNA in the feces while no patients had ongoing oropharyngeal shedding. At 4 and 7 months, 12.7% and 3.8% of participants, respectively, exhibited fecal shedding of the virus.[63] This prolonged presence of the virus may explain the persistence of GI symptoms seen in long COVID.

General GI symptoms

A wide variety of GI symptoms have been reported in patients with long COVID. One large systematic review and meta-analysis indicates an overall incidence of 12%. [Table 2] illustrates the incidence of various GI symptoms.[64] One prospective cohort study involving 1475 patients gives insight into the onset and duration of GI manifestations of long COVID. This study highlighted that GI symptoms during the acute COVID-19 infection were associated with a 4 times greater odds of persistent GI symptoms (odds ratio [OR] 4.29, 95% CI 2.45–7.53). On average, symptoms lasted up to 8 months after acute infection. In addition, patients with GI symptoms were more likely to be younger, female, and reported subjectively higher stress levels and a more severe acute infection than those without persistent GI symptoms.[65] An additional prospective cohort study, conducted by Columbia University, reported a possible association between persistent GI symptoms after long COVID and mental health symptoms with an adjusted OR of 16.5, 95% CI 6.97–38.9.[66]

Treatment

Given the link between gut dysbiosis and GI symptoms, focusing on restoring gut microbiota may be helpful in relieving GI symptoms, including IBS.[67,68] Wang *et al.* proposed using the WTP diet, which consists of whole grains, traditional Chinese foods, and prebiotics. Previously, the WTP diet showed benefits in patients with type 2 diabetes by decreasing proinflammatory bacteria in the GI tract. This case report investigated the use of a novel proprietary formula based on the WTP diet given as a supplement titrated to three doses daily. After 2 months, the patient reported an increased appetite, decreased need for antiemetic medications, and decreased anxiety and palpitations. This case report highlights a potential role for dietary interventions, although proprietary formulations may be difficult for patients to access.[69]

Patients may seek symptomatic relief of long COVID GI symptoms with medications such as antiemetics, laxatives, or anti-diarrheal. However, there is no current evidence to guide medication selection. A variety of dietary supplements have been proposed as potential treatments for long COVID symptoms. Crudele *et al.* reported on a dietary supplement including hydroxytyrosol, a supplement with antioxidant properties, that may impact residual SARS-CoV-2 virus residing in the GI tract. At present, evidence is limited to pre-clinical studies, necessitating the need for further research.[70] Research should focus on optimal dietary interventions and antioxidant supplements in patients with persistent GI symptoms to restore GI flora and resolve inflammation.

Hepatic

Liver injury is common in patients with acute COVID-19, occurring in 15–65% of hospitalized patients.[71] The primary mechanism of liver injury is similar to other organ systems, with the SARS-CoV-2 virus entering the liver and bile duct through interaction with ACE2 receptors. Additional mechanisms include hypoxia-related ischemia, drug-induced liver injury, oxidative stress, and immune-mediated destruction.[72] While liver function usually improves with recovery from acute infection, persistent liver dysfunction can occur. Prospective cohort studies report similar incidences of liver function test (LFT) abnormalities.[73-75] Most notably, Liao *et al.* followed 461 patients for 12 months to detect the trajectory of liver function after hospitalization. At admission, 28.4% of patients had at least one abnormality in LFTs, and 34.5% exhibited LFT abnormalities at discharge. Elevations decreased over time but persisted in 13.2%, 16.7%, and 13.2% of patients at 3, 6, and 12 months, respectively. At 12 months, the predominant elevation was in gamma-glutamyl transferase, although elevations were minimal. Persistent abnormalities in LFTs were more common

Table 2: Frequency of persistent GI symptoms in patients with long COVID.[64]

Symptom	Frequency (%)	95% Confidence interval (%)
Abdominal pain	14	4–38
Constipation	19	5–55
Diarrhea	1	4–23
Dyspepsia	20	6–50
Irritable bowel syndrome	17	6–37
Loss of appetite	20	8–43
Nausea/vomiting	6	1–21

GI: Gastrointestinal, COVID: Coronavirus disease

in males and patients with higher body mass index or baseline liver dysfunction. Patients with persistent liver dysfunction demonstrated a high prevalence of fatty liver disease.[75] Of note, all patients with an alanine transaminase (ALT) >2 times the upper limit of normal at any outpatient visit were prescribed glutathione and glycyrrhizin tablets for hepatoprotection, but the dose and duration were not described.[75] Although all patients received this therapy, there are no data regarding the effect of glutathione and glycyrrhizin on persistent liver dysfunction. Placebo-controlled trials are necessary to determine the future use of these supplements in patients with long COVID-induced liver dysfunction.

While the literature indicates that persistent abnormalities in LFTs are not uncommon, studies did not report on the synthetic function of the liver, as other laboratory markers such as international normalized ratio (INR) and platelet count were not reported. Longer follow-up studies should investigate the progression of persistent liver injury and the incidence of chronic liver disease after acute COVID-19 infection.

Renal

Acute kidney injury (AKI) has been observed after the first 30 days following a COVID-19 diagnosis.[76] The severity of AKI varies based on pre-existing renal dysfunction and the severity of COVID-19 illness. Severe AKI may progress to prolonged renal dysfunction resulting in a longer recovery time and possible chronic renal replacement therapy. Furthermore, patients with chronic kidney disease (CKD) are at an increased risk of both contracting COVID-19 and developing a COVID-associated AKI, resulting in continued progression of CKD. This relationship demonstrates the bidirectional nature between COVID-19 and renal function.[76] Studies suggest that the decline in renal function after acute infection is attributed to ongoing inflammation, kidney fibrosis, and functional deficits despite serum creatinine levels returning to baseline.[76] One large cohort study included 89,216 veterans and demonstrated long-term adverse kidney outcomes linked to COVID-19 infection. The study indicated a higher risk of AKI in patients 30 days after acute infection compared to matched patients without a history of COVID-19 infection (adjusted hazard ratio [aHR] 1.94; 95% CI 1.86–2.04). The risk of developing end-stage renal disease was also significantly increased (aHR 2.96; 95% CI 2.49–3.51).[77]

Treatment

Renin aldosterone angiotensin system (RAAS) inhibitors are widely used for nephroprotection, hypertension, ischemic heart disease, and heart failure. Initially, there was concern that because RAAS inhibitors increase the expression of ACE2 receptors, patients taking these medications would be at an increased risk of contracting the SARS-CoV-2 virus and experiencing a more severe form of the disease.[78] A Swedish registry study with nearly 1.5 million patients described the effect of RAAS inhibitors on the risk of hospitalization and mortality from COVID-19. The RAAS inhibitors in the study included ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid antagonists (MRAs). The use of ACEIs or ARBs was associated with a reduced composite risk of hospitalization and mortality from COVID-19 (hazard ratio [HR] 0.89, 95% CI 0.82–0.96). However, there was no such association with the use of MRAs (HR 0.97, 95% CI 0.84–1.12).[78] These results suggest that the benefits of RAAS inhibitors outweigh the effects of increased ACE2 receptor expression. The potential benefits include improvement in endothelial function, cardiovascular and renal protection, anti-thrombotic effects, anti-inflammatory properties, and neurohormonal blockade.[78] Providers should consider the addition or continuation of either ACEIs or ARBs in patients with appropriate indications such as renal disease. However, further research is indicated for the use of ACEIs and ARBs in the prevention of COVID-19-induced renal dysfunction.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have also demonstrated nephroprotection in the management of diabetes and heart failure. It was thought that these properties may potentially extend to COVID-19-related renal dysfunction. However, a double-blind, randomized, and controlled trial did not demonstrate the benefit of dapagliflozin in patients hospitalized for COVID-19 despite being well-tolerated.[79] Data regarding the potential benefit of long COVID is non-existent. Given these findings, it is reasonable to continue SGLT2 inhibitors for the management of other comorbidities, but there are no data to support initiation for the treatment of long COVID symptoms.[79]

Genitourinary

Long COVID symptoms affecting the genitourinary system have recently gained attention. Common symptoms include overactive bladder (OAB), referred to as COVID-19 Associated Cystitis (CAC), male infertility, and erectile dysfunction (ED). However, data on this topic are limited to retrospective cohort studies and case reports.[80-82] The SARS-CoV-2 virus is known to interact with ACE2 receptors, which are highly expressed in the genitourinary tract. In addition, fever associated with acute COVID-19 infections may have long-lasting effects on sexual dysfunction and male fertility.[80]

Urinary symptoms

There is a discrepancy in the literature regarding the characterization of the urinary symptoms caused by

COVID-19 infection. The proposed nomenclature includes lower urinary tract symptoms, OAB, or its own unique term known as CAC.[83-85] This discrepancy is partially caused by a lack of appropriate studies classifying symptomatology. The SARS-CoV-2 virus is not the first virus known to cause issues within the urinary tract. The Epstein-Barr virus, human papillomavirus, cytomegalovirus, and adenovirus are all associated with OAB symptoms.[86,87] Given this knowledge, it makes sense that the SARS-CoV-2 virus may cause similar symptoms within the lower urinary tract. The systemic inflammation in COVID-19 infection has been proposed as a potential mechanism. Once inflammation damages the lining of the bladder, proinflammatory cytokine release results in chronic, bothersome symptoms.[85,87] Direct viral invasion of the bladder endothelial cells through ACE2 receptors is another proposed mechanism. It is unclear whether the virus is introduced through the urine or bladder capillaries.[88]

Lamb *et al.* surveyed patients enrolled in a urology clinic 10–14 weeks post-COVID-19 infection. The authors showed an increase in OAB symptoms using symptom scores and quality-of-life surveys. Through these surveys, 71% of participants described their condition as new onset and reported that urinary frequency, urgency, and nocturia significantly impacted quality of life.[84] Roberts *et al.* used surveys to describe the incidence rate of CAC. Their study included 1895 participants and found an incidence rate of 36.6%, with 22% of those patients reporting a new onset of urinary symptoms.[85] Finally, Zachariou *et al.* examined the effects of long COVID in a Greek long-term care facility. Of the patients who were hospitalized for COVID-19 and transferred to the facility, 66.6% of patients reported new-onset symptoms and 33.3% of patients reported worsening symptoms of OAB.[89] Further, research is needed to determine the spectrum, treatment, and duration of urinary symptoms.

Male infertility

It is well-known that an infection can cause short-term male infertility due to the impact on sperm cells within that cycle, predominantly attributed to fever.[81,90] As the body's temperature rises, the ability to maintain the cooler body temperature in the testes required for sperm production decreases, leading to abnormal or improperly functioning sperm.[80] These effects are often limited due to the life cycles of sperm cells. While this knowledge is not new regarding the impact of infection on sperm quality and quantity, the long-term effects of COVID-19 infection still need to be investigated.[81] A common theme in the proposed pathophysiology relies on the expression of ACE2 receptors which are present in the specialty cells of the testes.[81] Other possible mechanisms include the destruction of sperm through leukocytes, reactive oxidative species, and cytokine storm.[80]

Evidence of COVID-19's effect on male infertility is supported by several small studies. In one retrospective cohort study, Gacci *et al.* identified 11 men with severe disruptions in their semen profile, eight of whom were azoospermic.[91] In terms of how long sperm production is affected, sperm count and motility were reduced for 72–92 days post-infection. This duration outlasts other viral infections and is approximately one cycle of spermatogenesis.[90,92,93] Mannur *et al.* present the only prospective data in regard to male infertility post-COVID-19 infection. In this case report, a patient being followed at an infertility clinic developed a mild case of COVID-19 infection. Before the infection, the male had a documented normal semen analysis. A second semen analysis was performed 43 days after his recovery from acute infection, which showed abnormal results. Sperm count and motility improved at 4 months, but sperm morphology was still negatively affected. This case report alludes to concerns that long-lasting effects occur in mild cases of COVID-19 and may take longer to recover than expected.[94]

Erectile dysfunction (ED)

Development of ED has been reported after COVID-19 infection though the exact incidence is unknown. The SARS-CoV-2 virus can damage vasculature in the penile tissue and reduce oxygen delivery, making it difficult to achieve an erection. Other factors may also contribute including low testosterone, impaired lung function, poor cardiovascular health, or worsening of other comorbidities. In addition, long COVID effects such as anosmia, dysgeusia, brain fog, depression, and chronic fatigue may play a role in the development of ED.[90,95]

No pharmacologic treatments have been evaluated for the management of ED after COVID-19 infection. If a patient presents with newly diagnosed ED, health-care providers should evaluate the cardiovascular status and lung health. Further, research is needed to fully establish the relationship between COVID-19 infection and long-term urological and sexual dysfunction.

Hematologic

Hematologic complications such as thromboembolic events are well-known consequences of acute COVID-19 infection. While the incidence of VTE in long COVID is controversial, other hematologic disorders such as anemia and prolonged hypercoagulability have been reported. In addition, various case reports provide insight into rare complications of long COVID including hemophagocytic lymphohistiocytosis

and pancytopenia.[96-98] The pathophysiology of hematologic manifestations of long COVID is multifactorial. Most notably, the SARS-CoV-2 virus promotes a hyperinflammatory response with the production of procoagulant and proinflammatory cytokines including interleukin-8 and tumor necrosis factor-α.[99,100] This promotes the secretion of von Willebrand factor (vWF) and tissue factor which ultimately leads to a prothrombotic state.[99,101]

Effects on coagulability

Acute COVID-19 is strongly associated with increases in VTE, but the relationship between VTE risk and long COVID is less clear. Multiple studies report prolonged abnormalities in hematologic markers after COVID-19 infection. In a prospective study of patients hospitalized for COVID-19, 50% exhibited elevations in D-dimer levels on diagnosis of COVID-19, and D-dimer levels remained persistently elevated in 6.4% of patients at 4 weeks.[102] A second longitudinal study of 150 patients reported increased D-dimer levels in 25.3% of patients post-COVID-19 infection at a median of 80.5 days (IQR 44–155 days).[103] Another prospective study of 50 patients investigated markers of endothelial dysfunction at a median of 68 days after COVID-19 infection. The authors reported an increase in endogenous thrombin potential, peak thrombin, vWF, and factor VIII compared to healthy controls.[104]

Although it is clear from the literature that patients may experience sustained abnormalities in coagulation factors, patients with long COVID do not appear to be at an increased risk of VTE events. Desai *et al*. reported that rates of VTE ranged from 0.48% to 1.9%, similar to other patient populations after hospital discharge.[105] The CORE-19 registry reported the incidence of VTE in 4906 patients at 90 days after hospital discharge, which corroborates the data presented by Desai *et al*. In this study, VTE events occurred in 1.55% of patients, although a higher risk was seen with advanced age, cardiovascular risk factors, CKD, and intensive care unit stay.[106] In the early days of the COVID-19 pandemic, the concern for VTE post-infection was high. Interestingly, post-discharge thromboprophylaxis was prescribed in 13.2% of patients in this study, which was associated with a significant reduction in the primary composite outcome of VTE, arterial thrombotic events, and all-cause mortality (OR 0.54; 95% CI 0.47–0.81). However, major bleeding also occurred in 1.73% of patients. Given that the rate of major bleeding exceeded the incidence of VTE, the authors concluded that the risk of post-discharge thromboprophylaxis outweighs the benefits.[106] Recent literature does not support broad or extended outpatient use of thromboprophylaxis, though it was previously utilized in the early stages of the pandemic.[107] Multiple trials, including MICHELLE, PREVENT HD, and ACTIV-4C, investigated the use of thromboprophylaxis after discharge with mixed results.[108-110] However, the trials were limited to 35 days of pharmacologic therapy, limiting the applicability to patients with long COVID. In July 2021, the American Society of Hematology (ASH) published updated recommendations for post-discharge anticoagulation in patients with COVID-19. These guidelines recommended against the use of outpatient thromboprophylaxis, but noted that this was a conditional recommendation based on low-quality evidence. Based on these guidelines, clinicians should individualize the assessment of bleeding and thrombotic risk. Post-discharge thromboprophylaxis may be reasonable in patients judged to be at high thrombotic risk and a low risk of bleeding.[111]

Complete blood count abnormalities

COVID-19 may also have long-lasting effects on hematologic cell lines, resulting in anemia, thrombocytopenia, leukocytosis or leukopenia, and even rare reports of pancytopenia. Galúcio *et al*. conducted a cross-sectional study of 260 patients with long COVID who were followed for up to 985 days. Patients who experienced long COVID symptoms for more than 1 year were more likely to have low hemoglobin levels and increased lymphocyte counts.[112] The CovILD study was a prospective, multicenter, and observational cohort study which followed 108 patients for serial clinical and laboratory evaluations up to 360 days after COVID-19 onset. At 60 days, hyperferritinemia, iron deficiency, and anemia were present in 35%, 24%, and 9.3% of the cohort, respectively. By 360 days, only 4.6% of patients still exhibited anemia, showing recovery over time. Both iron deficiency and anemia were associated with impaired stress resilience, although there was no association with exercise capacity, quality of life, or fatigue.[113]

Thrombocytopenia after COVID-19 infection has also been reported. In one cohort study, delayed phase thrombocytopenia occurred in 11.8% of patients three to 4 weeks after virus onset and was most commonly seen in elderly patients or patients with lymphopenia.[114] A systematic review evaluated 45 cases of Immune thrombocytopenic purpura (ITP) with 20% of patients developing thrombocytopenia 3 weeks after the onset of COVID-19 symptoms.[115] ITP is often difficult to manage. In this review, 29% were treated with intravenous immunoglobulin (IVIG), 22% with glucocorticoid monotherapy, and 24.5% were treated with combination therapy. Despite appropriate treatment, only 26 patients had a complete response.[115] ASH guidelines recommend dexamethasone 40 mg/day for 4 days or prednisone 0.5–2 mg/kg/day followed by a taper depending on response.[116]

IVIG may also be used as monotherapy or in conjunction with corticosteroids. Guidelines recommend IVIG 1 g/kg as a 1-time dose with repeat doses as warranted.[116]

Pancytopenia is another rare consequence of long COVID. In one case report by Wu *et al.*, a previously healthy 64-year-old female exhibited pancytopenia months after experiencing an asymptomatic COVID-19 infection. The patient improved with a 4-day course of dexamethasone 40 mg in combination with two doses of IVIG. At 1 week follow-up, the patient was again leukopenic and thrombocytopenic, indicating persistent pancytopenia.[96] While this presentation is rare, clinicians should be aware of potential hematologic effects found in asymptomatic or mild COVID-19 infection.

While hematologic manifestations have been linked to long COVID, data regarding management are limited. However, an interventional study published in 2022 suggested that combined aerobic and resistance training is associated with improvement in both biochemical and hematologic markers in patients with a history of COVID-19 and a previous sedentary lifestyle. Improvements were noted in hemoglobin, hematocrit, platelets, white blood cells, and D-dimer levels after 8 weeks. Clinicians should consider referring patients to physical therapy, personalized exercise programs, or exercise rehabilitation, as evidence indicates that these interventions may aid in recovery from COVID-19.[117]

Musculoskeletal

Approximately 1.71 billion people worldwide experience disabilities caused by musculoskeletal conditions.[118] In cases of long COVID, patients frequently describe symptoms of fatigue, myalgia, arthralgia, and diminished muscle strength and endurance.[118-120] These symptoms may continue from the initial illness or emerge weeks after the primary infection. Moreover, through small-scale studies and case reports, authors have documented decreased bone density, osteoporosis, and instances of osteonecrosis.[121-124] The prevailing theory of musculoskeletal disorders in long COVID attributes the infiltration of the SARS-CoV-2 virus through the abundant ACE2 receptors within the musculoskeletal system.[125] Other theories have been suggested to elucidate the long-term effects of COVID-19 on the musculoskeletal system. One proposed mechanism attributes musculoskeletal damage as a byproduct of harm to other organ systems. For instance, damage to the respiratory system results in hypoxemia and subsequently affects muscle metabolism.[126] Pro-inflammatory cytokines released during cytokine storm have also been implicated due to their myotoxic effects, directly impacting protein synthesis in the skeletal muscle.[125] Finally, reduced mobility during the initial infection results in muscle deconditioning and a prothrombotic state, contributing to many musculoskeletal effects seen in long COVID.[124,125]

Certain patient factors including advanced age, nutritional status, and other comorbidities may increase the risk of musculoskeletal disorders in long COVID. Advanced age is associated with the natural decline in muscle mass and function over time. When combined with the damaging effects of the SARS-CoV-2 virus, this decline is more dramatic.[120,126] Malnourishment is associated with decreased muscle mass and compromised immune function, putting patients at further risk of musculoskeletal complications. Interestingly, this is also true for patients with obesity.[127] In addition, prolonged corticosteroid therapy, which is often used in the treatment of long COVID, is associated with osteoporosis.[125,128]

Muscle fatigue and weakness

Fatigue is one of the most frequently reported symptoms associated with long COVID.[129] Silva *et al.* report a prevalence of fatigue ranging from 53% to 94.9%.[126] These symptoms can manifest in patients regardless of disease severity and may persist for weeks to months following infection.[13,127] However, the literature does not distinctively separate musculoskeletal-related fatigue from a general feeling of tiredness.[126,130] Much of the data concerning muscle fatigue and weakness originates from patients who were previously hospitalized for COVID-19. Paneroni *et al.* assessed post-discharge patients experiencing prolonged COVID-19 symptoms and found weakness in the quadriceps and biceps in 86% and 73% of patients, respectively.[131] Disser *et al.* report impairments in muscle strength and endurance which could be attributed to the proinflammatory effects and deconditioning linked with long COVID.[130] In addition, patients with extended hospital stays displayed a significant reduction in grip strength and 6MWD test performance 3 months after discharge.[127] On the contrary, Fanous *et al.* report a case in which no meaningful differences in muscle function tests were observed before and after COVID-19 infection, despite the patient self-reporting fatigue. These authors propose that altered cognitive functions or perceptions might be responsible for the reported fatigue.[132]

Arthralgias and myalgias

Both arthralgias and myalgias are symptoms previously observed in infections caused by SARS viruses.[124] The symptomatology of these infections was attributed to the cytokine storm, causing direct skeletal muscle damage along with deconditioning due to a prolonged disease period. Similarly, patients experiencing long COVID also report arthralgias and myalgias. Commonly reported

arthralgia sites include the humeral head, talus, and calcaneus. On the other hand, myalgias may be localized to one area of the body, or patients may complain of diffuse muscle pain.[118] In a literature review by Khoja *et al*., 18 out of 35 studies highlighted arthralgia and myalgia as the most frequent musculoskeletal pain symptoms reported over time.[118] The prevalence of musculoskeletal pain exhibited substantial variation in the literature, ranging from 0.3% to 65.2%. This broad range might be attributed to the diverse patient population and variable study designs included in the literature review.[118] Patients experiencing arthralgias typically present symptoms in the lower extremities about 1–3 weeks following the initial COVID-19 presentation. Carvalho-Schneider *et al*. identified an increase in arthralgia symptoms from 13% to 21% at 30 days and 60 days, respectively.[133] Treatment of persistent arthralgias and myalgias includes symptomatic management. Most commonly, nonsteroidal anti-inflammatory drugs may be administered to reduce pain and mitigate inflammation.[125,128]

Osteonecrosis

Long COVID has been linked to hypercoagulability, vascular inflammation, and bone resorption.[122] All of these factors may contribute to the development of osteonecrosis. Moreover, corticosteroid treatment in long COVID is often extended and at high doses, both of which elevate the osteonecrosis risk. Conventionally, osteonecrosis was reported to take at least 6 months to develop following corticosteroid treatment.[134] However, the hypercoagulability and inflammation observed in COVID-19 infection may expedite its onset.[135] A case series highlighted knee osteonecrosis in two separate patients. One patient, having received a cumulative dose of 900 mg of prednisolone over a 15-day period, developed osteonecrosis 25 days after corticosteroid treatment for COVID-19 infection.[121] Another patient experienced pain in both hips and the right knee 4 months after COVID-19 treatment involving 19 days of dexamethasone equivalent to 1413 mg of prednisolone. In both instances, bisphosphonate therapy was administered, resulting in clinical improvement.[121] Another case series demonstrated spontaneous avascular necrosis of the jaw in four separate cases in India. In these cases, avascular necrosis of the jaw occurred following 12–14-day courses of high-dose steroids. The authors caution that osteonecrosis can occur rapidly in patients following COVID-19 infection.[123]

Rehabilitation

The literature strongly supports optimizing nutrition and rehabilitation for patients presenting with musculoskeletal complaints in the context of long COVID. Adequate nutrition focusing on increased protein and vitamin D intake is vital for musculoskeletal recovery. The combination of protein supplementation and physical training resulted in improved walking capacity, bone density, and increased muscle mass.[127] The RECOVE trial demonstrated the benefits of a supervised exercise program for long COVID patients.[136] In this 8-week study, patients who received supervised resistance and endurance exercise with or without inspiratory muscle training demonstrated a significant difference in the lower body strength, fatigue, dyspnea, and depression when compared to patients who solely completed inspiratory muscle training or self-managed training exercises.[136] Rehabilitation protocols should prioritize muscle strengthening, mobility, and aerobic exercise with or without inspiratory muscle training.[126] Physical training aids in the restoration of muscle mass and strength, subsequently reducing deconditioning and fatigue seen long COVID.

Integumentary

The integumentary system exhibits three primary clinical manifestations in long COVID: Urticaria, maculopapular eruptions, and chilblain-like pattern (also known as "COVID toes"). The exact pathophysiology of these dermatological symptoms is unknown, and the role of COVID-19 in their direct or indirect pathophysiology is still a matter of debate.

Urticaria

Urticaria is mainly associated with moderate to severe cases of COVID-19 and may appear as a prodromal or early sign of the disease.[137] This rash primarily affects the trunk and limbs and typically lasts for about 1 week.[138] Chronic spontaneous urticaria is also linked to COVID-19 which is defined as urticaria occurring most days of the week for a period longer than 6 weeks. Of note, more than 50% of cases of chronic spontaneous urticaria are associated with angioedema.[138] Treatment options for urticaria rash associated with COVID-19 include low-dose systemic corticosteroids with or without antihistamines.[137]

Maculopapular eruptions

Confluent erythematous maculopapular/morbilliform rash is characterized by macules and papules, also known as maculopapular eruptions, which can include both flat and raised lesions. Most commonly, maculopapular eruptions primarily affect the trunk and limbs and are typically associated with pruritus. While this finding is most commonly associated with acute moderate to severe COVID-19 infection, there are reports of late appearance of maculopapular eruptions. One case series of seven patients

reported a delayed rash onset of 20–36 days from initial COVID-19 symptoms.[139] Management for these rashes usually involves topical corticosteroids, and more severe cases may require systemic corticosteroids.[137,140]

Chilblain-like pattern

The chilblain-like pattern, commonly known as "COVID toes," is primarily observed in young adults and children.[137] It manifests as plaques or patches most often on the feet and sometimes the hands with potential progression to blistering. Pain, burning, and pruritus are often associated with these lesions.[137] This rash may occur before, during, or after COVID-19 infection. In an international registry study of COVID-19 dermatologic manifestations, a chilblain-like pattern lasting more than 60 days after acute COVID-19 infection occurred in seven patients. In fact, one patient continued to exhibit a severe chilblain-like pattern for over 133 days.[140] A "wait-and-see" strategy is typically suggested in the treatment of "COVID toes."[137] If symptoms persist longer than 1 month, clinicians should screen for underlying causes. If symptomatic treatment is deemed necessary, one source recommends considering a combination of low-dose aspirin and topical corticosteroids, with oral prednisone reserved for severe cases.[141]

CONCLUSION

Although the CDC has announced the end of the COVID-19 pandemic, COVID-19 still represents a significant health threat. As we approach the endemic phase of the SARS-CoV-2 virus, acute infections continue to occur in the general population. The best defense against long COVID is to prevent the initial COVID-19 infection. In addition to the administration of vaccines, metformin titrated over several days to a total daily dose of 1500 mg has shown promising results in reducing long COVID symptoms when initiated within 3 days of an outpatient treated COVID-19 infection (HR 0.59 [95% CI 0.39–0.89; $P = 0.012$]). However, it is unclear if the same benefits would be seen in hospitalized patients or in patients who develop long COVID before metformin therapy.[142] Future research in this area is needed.

As demonstrated in this review, the long-lasting effects of COVID-19 are expected to impact patients for years to come. Current literature is mainly focused on the characterization and prevalence of long COVID. However, the literature is limited regarding the treatment of long COVID. To date, the medical community has attempted to treat long COVID symptoms according to the standards of care for the associated conditions, but it is unknown whether these treatments are effective. Clinicians are encouraged to conduct further research regarding the management of patients with long COVID. As we continue to understand the manifestations of long COVID, it is imperative that we adapt to the evolving nature of the SARS-CoV-2 virus.

Declaration of patient consent

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