Review

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Sequelae of long COVID, known and unknown: A review of updated information

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SUMMARY Over three years have passed since the COVID-19 pandemic started. The dangerousness and impact of COVID-19 should definitely not be ignored or underestimated. Other than the symptoms of acute infection, the long-term symptoms associated with SARS-CoV-2 infection, which are referred to here as "sequelae of long COVID (LC)", are also a conspicuous global public health concern. Although such sequelae were well-documented, the understanding of and insights regarding LC-related sequelae remain inadequate due to the limitations of previous studies (the follow-up, methodological flaws, heterogeneity among studies, *etc.*). Notably, robust evidence regarding diagnosis and treatment of certain LC sequelae remain insufficient and has been a stumbling block to better management of these patients. This awkward situation motivated us to conduct this review. Here, we comprehensively reviewed the updated information, particularly focusing on clinical issues. We attempt to provide the latest information regarding LC-related sequelae by systematically reviewing the involvement of main organ systems. We also propose paths for future exploration based on available knowledge and the authors' clinical experience. We believe that these take-home messages will be helpful to gain insights into LC and ultimately benefit clinical practice in treating LC-related sequelae.

Keywords COVID-19, SARS-CoV-2, sequelae, long COVID, follow-up

1. Introduction

Over three years have passed since the COVID-19 pandemic started. At present, Omicron and its subvariants are the predominant variants, but they are less likely to cause severe illness. However, the dangerousness and impact of COVID-19 should definitely not be ignored or underestimated (*1*). Other than the symptoms of acute infection, the long-term symptoms associated with SARS-CoV-2 infection are also a conspicuous global public health concern. The term "long COVID (LC)" is used to describe the post-acute sequelae of SARS-CoV-2 infection. According to estimates, there are approximately 65 million people globally suffering from LC (*2*). Huang *et al*. conducted a one-year follow-up of 1,276 COVID-19 survivors and found that although 88% of patients recovered and returned to work at 12 months, their health status remained poorer than that of controls not infected with SARS-CoV-2 (*3*). In an online survey of patients with COVID-19, Davis *et al*. found that the most common symptoms during follow-up (7 months) were fatigue, post-exertional malaise, and

cognitive dysfunction. Eighty-five-point-nine percent of participants experienced relapses triggered by exercise, physical or mental activity, and stress; of those, 86.7% had fatigue at the time of survey (*vs*. 44.7% in recovered patients). Forty-five-point-two percent of participants reduced their working time, and 22.3% did not work during the survey due to illness. Cognitive impairments and memory loss were common across all age groups (*4*). Recently, Hedin *et al*. conducted a prospective study of adult outpatients with COVID-19. They found that of 270 outpatients, 52% developed LC and 32% had post-COVID-syndrome. Fatigue was the most common symptom during follow-up. Sports and household activities markedly affect lingering symptoms. LC and post-COVID-syndrome are also not rare in outpatients. Thirty-two percent of patients took over 12 weeks to return to their usual health (*5*). Lopez-Leon *et al*. performed a meta-analysis of 15 studies investigating LC sequelae in 47,910 patients with SARS-CoV-2 infection, and they identified 55 LC sequelae. Approximately 80% of patients with COVID-19 developed one or more LC sequelae. The top 5 symptoms were fatigue (58%), headaches (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) (*6*). Recently, Davis *et al*. reviewed that the incidence of LC is approximately 50-70% in hospitalized patients, 10-30% in non-hospitalized patients, and 10-12% in vaccinated patients (*7*). The clinical characteristics of LC include: *i*) Multisystemic involvement: COVID-19 was originally regarded as a respiratory disease, but evidence indicates that SARS-CoV-2 infection may cause multisystemic abnormalities. Thus far, over 200 LC-related symptoms have been documented, in which multiple organs and whole-body systems are involved, including the respiratory system, circulatory system, central nervous system (CNS), digestive system, urinary system, and the reproductive system, along with the immune system and the vascular system (*7*). *ii*) Complicated and multifaceted mechanisms: The mainstream view is that the tissue damage throughout the body is mainly due to COVID-19-related abnormal immune response and inflammation rather than direct viral infection of the tissues and subsequent cytopathic effects (*7,8*). Moreover, damage to the immune system and blood vessel system may influence the other organs and systems and then cause secondary damage throughout the body (*9*). The complicated interaction among organs results in multifaceted and intricate pathophysiological mechanisms of LC. A patient seems to "recover" from SARS-CoV-2 infection, but the subsequent clinical manifestations of LC might be diverse and particular. Disorders in all systems might develop, such as cardiovascular disease in the circulatory system (*10*), diabetes (*11*), and cognitive impairment and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in the CNS (*12,13*). Noticeably, such illnesses seldom "resolve" with "recovery" from acute infection. They might persist for several years (*14*), of those, the problems of ME/CFS even potentially be lifelong (*15*). *iii*) Nonspecific and uncertain: Many reported LC-related symptoms are also common in the general public (*16*). These so-called nonspecific "LC-related symptoms", such as ME/CFS and cardiovascular disorders, can also develop and deteriorate in people with or without SARS-CoV-2 infection. In some cases, identifying whether a certain symptom is indeed attributed to COVID-19 or to a certain variant in patients with recurrent infection is quite difficult. In addition, most of the available evidence is derived from studies in hospitalized patients whereas information on a large amount of non-hospitalized patients remains unknown. The nature of selection bias might increase the uncertainty of LC-related symptoms. In this regard, knowledge of and insights concerning LC, particularly for the diagnosis and treatment of LC, are quite limited so far.

Currently, many reviews have discussed LC from different angles. Davis *et al*. provided a panoramic overview regarding LC-related key findings, mechanisms, symptoms, LC in children, and the role of vaccination on the basis of the latest literature available. They pointed out that the diagnostic and therapeutic options for LC remain insufficient. This situation might be improved by conducting clinical trials addressing leading hypotheses, enhancing LC-related studies by avoiding potential biases, designing viral-onset studies, *etc*. (*7*). Rabaan *et al*. summarized the effects of SARS-CoV-2 infection on multiple organs and systems. They attempted to elucidate the wide range of atypical COVID-19-related symptoms to improve clinical practice (*17*). Oronsky *et al*. reviewed persistent LC-related symptoms (syndromes) along with their underlying mechanisms. They raised awareness and alarm regarding the persistent post-COVID syndrome from the view of dysfunction of the immune system (*18*). Yong *et al*. systematically reviewed six LC-related inflammatory and serum biomarkers. They found that levels of C-reactive protein, D-dimer, lactate dehydrogenase, and leukocytes were greater in patients with LC. According to sensitivity analyses, levels of lymphocytes and interleukin-6 remained significantly elevated in patients with LC (*19*). Nalbandian *et al*. summarized the available information on epidemiological and clinical trends and predominant clinical manifestations of a post-COVID-19 condition. They suggested that standardization of the case definition and research methods would improve LC-related studies (*20*). Ma *et al*. systematically reviewed long-term sequelae in individuals with an asymptomatic SARS-CoV-2 infection. They found that patients with an asymptomatic SARS-CoV-2 infection may have long-term symptoms, such as loss of taste or smell, fatigue, coughing, and that the risk of those symptoms was significantly lower than that of symptomatic individuals (*21*). Zanini *et al*. contended that vascular pathologies after SARS-CoV-2 infection should be

seriously considered and treated since they were observed in patients with LC and because they markedly affected endothelial dysfunction, worsened pre-existing atherosclerotic plaques, and caused thrombo-embolic arterial or venous complications (*9*). In addition, there are numerous reviews focusing on endocrine disorders (*22*), the respiratory system (*23*), the cardiovascular system (*24*), anxiety and depression (*25*), cognitive fatigue (*26*), *etc*. These informative studies enriched the understanding and knowledge of and the insights regarding LC. However, studies particularly focusing on clinical issues are limited.

Accordingly, the current work has reviewed clinical issues based on the latest available literature (Table 1, onlin data: *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=140*) as well as the authors' clinical experience. Clinical practice regarding LC in the major organ systems will be discussed. This work will increase the knowledge of and insights into LC and ultimately benefit clinical practice.

2. The respiratory system

Initially, COVID-19 was identified as a respiratory disease, so the respiratory sequelae therefore received a great deal of attention and emphasis. The most commonly reported persistent respiratory symptoms (illnesses) include a chronic cough, shortness of breath, dyspnea, chest pain, decreased ability to exercise, acute respiratory diseases, fibrosis and lung disease, bronchiectasis, and pulmonary vascular disease (BOX 1). These conditions commonly develop three months after diagnosis and persist at least two months. Some may even persist over one year. Studies have reported that persistent abnormalities in lung function, such as a reduction in diffusion capacity, commonly develop in patients with initial severe lung involvement and pneumonia (*27-29*). The most common sequelae were reduced diffusion capacity, restrictive ventilatory defects (*28*), and persistent abnormalities on computed tomography (CT) imaging (*30*). Huang *et al*. reported that approximately 22% of patients with reduced diffusion (out of 1,733 patients) scored 3 on a severity scale (do not need supplemental oxygen), 29% scored 4 (requiring supplemental oxygen), and 56% scored 5-6 (requiring a high-flow nasal cannula or ventilation) (*28*). CT imaging is the most commonly used diagnostic tool for COVID-19. Roughly two types of abnormal CT findings might be observed in patients with COVID-19, namely pneumonia-related changes (inflammatory changes) and changes in COVID-19-related pulmonary fibrosis (CRPF, fibrotic changes). Fabbri *et al*. performed a meta-analysis to investigate persistent respiratory LC-related symptoms using CT scans and a pulmonary function test (PFT). They found that during a median 3-month follow-up, 50% of patients had inflammatory changes, whereas 29% of patients had fibrotic changes. The duration of follow-up was significantly associated with inflammatory changes and not significantly associated with fibrotic changes. Impaired gas exchange was more prevalent than restrictive impairment (38% *vs.* 17%) (*31*). Another meta-analysis also reported LC-related sequelae using CT scans and the PFT, and it found that the most common abnormality on the PFT was reduced diffusion capacity during the 6- and 12-month follow-up. The prevalence of restrictive impairment was lower at the 12-month follow-up (*vs.* 6-month). The pooled prevalence of persistent ground-glass opacities (GGO) was 34%, and that of pulmonary fibrosis was 32%. The prevalence did not decrease over the follow-up (*32*). Besutti *et al*. investigated CT abnormalities in surviving patients with severe COVID-19. They found that 55.6% of patients were normal and 37.5% of patients had non-fibrotic changes. Only 4.4% of patients had fibrotic abnormalities. The most common fibrotic abnormalities were subpleural reticulation (15/18), traction bronchiectasis (16/18), and GGO (14/18). After a 12-month follow-up, residual changes improved over time. They concluded that pneumonia might be the most common CT finding in patients after severe COVID-19 (*33*). Wu *et al*. conducted a 12-month follow-up in patients with severe COVID-19 who did not require mechanical ventilation. They found that their lung function improved over the follow-up. Accordingly, the prevalence of abnormal CT imaging decreased from 78% (three months) to 24% (12 months). Only 5% of patients reported dyspnea and 20% had persistent CT changes at 12 months during the follow-up (*34*). The aforementioned evidence indicated that a certain proportion of COVID patients will develop persistent diminishment of lung function and/or abnormal CT findings. The most common abnormality in CT imaging is pneumonia-related changes, which improve over follow-up. Only a minority of patients will develop fibrotic changes and dyspnea, indicating a poor clinical outcome. The risk factors for developing CRPF still require further identification and verification.

Box 1: Commonly reported persistent respiratory symptoms

i) **Airway disease**: COVID-19 related airway disease and obstructive lung diseases have been documented, and interstitial lung disease has garnered a great deal of attention. Air trapping may persist as long as 200 days after the initial SARS-CoV-2 infection in some patients. Cho et al. observed 100 patients with post-acute sequelae of COVID-19 infected over 30 days using a quantitative chest CT (*35*). They found that 13.2% of patients in hospital and 28.7% of patients in the ICU had GGO, rates which were significantly higher than that in ambulatory patients (3.7%). The total lung affected by air trapping was 25.4%, 34.6%, and 27.3% in the ambulatory, hospitalized, and ICU patients, respectively, but 7.2% in healthy controls.

ii) **Pulmonary vascular disease**: COVID-19 related coagulation dysfunction is well documented. The incidence of thromboembolism is reported to range from 20-70% (*36-39*). Attention should be paid to chronic thromboembolism or micro-occlusions triggered by inflammatory responses in patients with LC. COVID-19 related pulmonary hypertension was seldom reported, so it might be underestimated. Tudoran et al. indicated that the prevalence of pulmonary hypertension and right ventricular dysfunction in patients with mild to moderate COVID-19 was 7.69 and 10.28%, respectively, two months after hospitalization (*40*).

iii) **Persistent cough**: Chronic cough is reported in 7-10% of patients with LC, which is independent of the pulmonary pathology (*41,42*). Viral invasion of the vagal sensory neurons, along with the neuroinflammatory response, might be involved in the mechanisms of persistent cough (*43*). Treatments for a persistent cough include corticosteroids or antimuscarinic drugs, neuromodulatory agents, and language therapy (*44*).

iv) **Dyspnea:** Dyspnea, along with fatigue, is the most common LC-related symptom. Mechanisms of LC-related dyspnea might be multifaceted, including dysfunctional breathing with or without hyperventilation deconditioning, subclinical myocardial disease, and peripheral limitations on exercise due to microcirculatory dysfunction (*45-47*). Cardiopulmonary exercise testing (CPET) is commonly used to evaluate unexplained dyspnea as well as to identify the cause of dyspnea and exercise intolerance in these patients (*48*). Treatments for LC-related dyspnea including hyperbaric oxygen therapy, nebulized administration of S-1126, antileukotrienes, sodium pyruvate nasal spray, and pulmonary rehabilitation should be selected according to the pathophysiological state of the patient.

There is no specific treatment for respiratory LC sequelae. Other than symptomatic treatments, corticosteroids, antifibrotics, and lung transplantation have been considered and verified (BOX 2). However, no treatment has been rigorously verified and can thereby be recommended. Another important issue is the role of rehabilitation. Thus far, rehabilitation seems to be an emerging effective therapy against LC-related respiratory symptoms, which needs to be further verified.

Box 2: Available evidence regarding treatments for respiratory LC sequelae

i) **Corticosteroids:** Oral administration of prednisolone has been a treatment for LC. Myall et al. conducted an observational study to verify the efficacy of corticosteroids in treating respiratory LC sequelae. Thirty patients received prednisolone treatment (the maximum initial dose of 0.5 mg/kg for 61 ± 19 days) and experienced significant symptomatic and radiological amelioration (*49*). Dhooria et al. conducted a randomized trial to verify the efficacy of prednisolone in low (10 mg) and high (40 mg) doses. They found that both radiologic response functional capacity improved significantly and that dyspnea was significantly alleviated, but there were no significant differences between the low and high dose of prednisolone (*50*). These trials indicated the efficacy of oral administration of prednisolone, but evidence from a large, multi-center randomized controlled trial is needed.

ii) **Antifibrotics:** Thus far (Feb 2023), nintedanib (identifier: NCT04541680) and pirfenidone (identifier: NCT04607928) have been submitted for verification (*51*), and no more newer evidence has been reported.

iii) **Lung transplantation**: Lung transplantation seems to be the "last resort" to treat lung diseases. Bharat et al. verified the early outcomes after lung transplantation in patients with severe COVID-19 who had developed acute respiratory distress syndrome (ARDS). They found that all patients were weaned off extracorporeal support and survived in the short term. They concluded that lung transplantation is the only option for survival in patients with severe, unresolving COVID-19-associated ARDS (*52*).

3. The circulatory system

LC-related damage to the circulatory system is also highlighted because such damage commonly causes severe illnesses and can even be life-threatening. LC-related damage to the circulatory system commonly includes LC-related thrombosis (including vein thrombosis), endothelial dysfunction (along with its downstream damage), and pulmonary embolism and bleeding events *sensu stricto*; they should also include SARS-CoV-2 infection-related heart injury *sensu lato*, such as myocarditis, myocardial involvement, arrhythmia, and heart failure. Xie *et al*. conducted a prospective cohort study involving 150,000 patients with COVID-19 who had survived over 30 days from their initial SARS-CoV2 infection. They found that SARS-CoV2 infection significantly increased the risk of development of cardiovascular complications such as ischemic heart disease, arrhythmia, myocarditis, pericarditis, heart failure, and thromboembolic disease (*10*). SARS-CoV-2 may enter the host cells *via* ACE2. It can directly attack the myocardial cells and cause myocarditis. Moreover, it triggers abnormal inflammatory and immune responses, such as a cytokine storm, and further causes myocardial damage that may subsequently lead to arrhythmia and heart failure. Excessive release of cytokines like interleukin (IL)-6 and tumor necrosis factor (TNF)-α may contribute to endothelial dysfunction and cause various downstream injury, such as thrombosis and acute coronary syndrome. Thrombosis-associated pulmonary thromboembolism may cause lung injury, subsequently cause hypoxic pulmonary artery vasoconstriction, and finally increase pulmonary vascular resistance. In addition, SARS-CoV-2 infection may upregulate the expression of angiotensin II (Ang II) and downregulate the expression

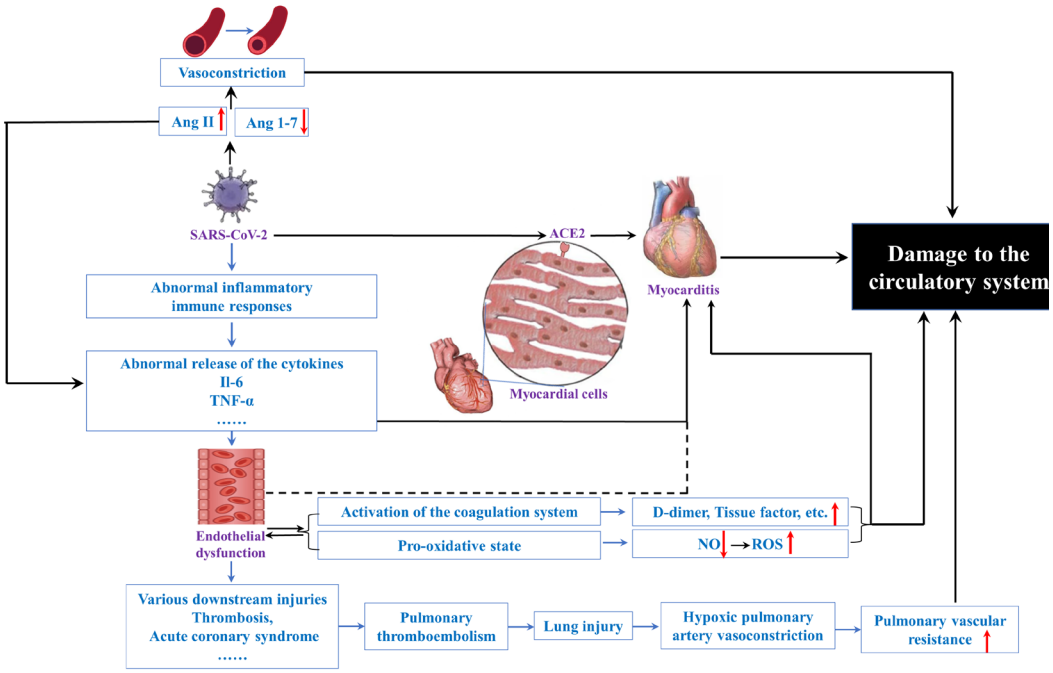

Figure 1. Mechanisms of COVID-19-related damage to the circulatory system.

of Ang 1-7 and lead to vasoconstriction. These complicated mechanisms contribute to damage to the circulatory system (Figure 1).

3.1. Thrombosis, vascular injury, and ischemic heart disease

Normal morphology and function of the vascular endothelium are protected and modulated by several anti-inflammatory cytokines and anti-clotting factors, such as nitric oxide (NO), prostaglandin I2 (PGI2), activated protein C, tissue factor pathway inhibitor, and Ang III. In a pathophysiological state, such as LC, obesity, or diabetes, inducted oxidative stress may activate generation of reactive oxygen and pro-inflammatory cytokines, suppress activation of NO and PGI2, induce apoptosis of vascular endothelial cells, and finally induce dysfunction of the vascular endothelium. Moreover, release of pro-inflammatory cytokines and pro-clotting factors may cause vascular inflammation, platelet aggregation, and thrombosis. SARS-CoV-2 may directly infect the vascular endothelium and damage it. Since endothelial dysfunction plays a vital role in disturbance of the microcirculation, thrombosis and vascular injury may cause illnesses throughout the body. In addition, long-term bedrest, particularly by patients with severe COVID-19, may cause their condition to deteriorate. Piazza *et al*. reported the prevalence of thrombotic events in patients with COVID-19. They found that the frequency of major arterial or venous thromboembolism, major cardiovascular adverse events, and symptomatic venous thromboembolism was highest in patients in the ICU, followed by the hospitalized non-ICU patients, while the frequency in outpatients was 0% for all (*53*). Their findings indicated that the risk of developing thrombosis is positively correlated with the severity of COVID-19. Interestingly, the prevalence of thrombotic events in hospitalized patients with COVID-19 is reported to be higher than that in patients with other critical diseases and other respiratory viral infections (such as influenza). Hence, some researchers have coined the novel term "COVID-19–associated coagulopathy," suggesting early preventive anticoagulation (*54,55*). Although several observational studies have suggested a benefit of anticoagulation, robust evidence including optimal selection of anticoagulants, their dose, and the duration of treatment remains insufficient (*54*). Viecca *et al*. evaluated the efficacy of tirofiban, an antiplatelet agent, in treating severe COVID-19 with hypercoagulability (*56*). They found that tirofiban might be effective in improving the ventilation/perfusion ratio in patients with severe COVID-19 and respiratory failure. They proposed administration of an antiplatelet agent to prevent cardiovascular complications in patients with COVID-19 pneumonia. Liu *et al*. verified that dipyridamole, another antiplatelet agent, helped to improve the clinical outcomes of patients with severe COVID-19 (*57*).

3.2. Myocarditis and myocardial involvement

Two sorts of myocarditis, namely COVID-19-related myocarditis and COVID-19 vaccine-related myocarditis, have been reported. Most of the reported cases of myocarditis involve young patients who underwent mRNA vaccination (*58*). A few studies have documented

COVID-19-related myocarditis. The current review will only discuss LC-related myocarditis, which is reported to be very rare but potentially life-threatening (*59*). The underlying mechanisms of COVID-19-related myocarditis are shown in Figure 1. Commonly, progression of COVID-19-related myocarditis is very fast. It usually causes rapidly progressive cardiogenic shock and fulminant biventricular failure (*60*). In this regard, COVID-19-related myocarditis is quite dangerous and commonly requires sophisticated use of multiple extracorporeal devices such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in the ICU.

Diagnosis of COVID-19-related myocarditis is difficult in current clinical practice. The gold standard diagnostic tool is an endomyocardial biopsy (EMB), which can also provide an etiological diagnosis (for example, identification of SARS-CoV-2 in the myocardium). However, EBM is seldom performed in patients without heart failure or ventricular arrhythmias, and particularly in young and/or low-risk patients, due to its invasiveness. Most of the cases are diagnosed based on symptoms (chest pain), an electrocardiogram (ECG), laboratory results (such as a troponin increase (*61*)), echocardiography, and cardiac magnetic resonance imaging. Ruling out obstructive coronary artery disease is also crucial. Due to the diagnostic difficulties, there are no compelling data on epidemiological characteristics. Thus far, only case reports and serial case reports with a small sample size are available.

Thus far, there is not much evidence for treatment of myocarditis. The American Heart Association recommends that treatments for cardiogenic shock fulminant myocarditis should include administration of inotropes and/or vasopressors and mechanical ventilation and using mechanical circulatory support for long-term management (*62*). Some researchers suggest using high-dose steroids (*63,64*) and intravenous immunoglobulins (IVIG) (*61*) to treat COVID-19-related myocarditis. However, using high-dose steroids is a double-edged sword that might cause adverse effects. Russell *et al*. reported that high-dose steroids might lead to a reduction in viral clearance and an increased mortality for all causes (*65*). Nonsteroidal anti-inflammatory drugs (NSAID) are not recommended for myocarditis due to their adverse effects (*62*). The efficacy of antivirals against COVID-19-related myocarditis remains unclear.

3.3. Heart failure

Heart failure is a final outcome of various heart diseases, such as myocarditis, arrhythmias, acute coronary syndrome, myocardial infarction, Takotsubo syndrome, and acute pulmonary embolism (*66*). Hence, many pathological factors in the context of COVID-19 can finally cause heart failure, or rather, LC can induce heart failure directly or indirectly. COVID-19-related heart failure is associated with abnormal inflammatory and immune reactions (Figure 1). Aging, arrythmias, and chronic kidney disease were identified as independent predictors of mortality in COVID-19 patients with heart failure. Nevertheless, elucidating the actual etiology causing heart failure, which might be a comprehensive result of interactions among these complex pathological factors, is sometimes very difficult. For hospitalized patients with heart failure, SARS-CoV-2 infection plays a role as an independent predictor of mortality. Moreover, COVID-19 is associated with many adverse outcomes (increased in-hospital mortality, longer hospital stays, and higher cost of hospitalization) in patients with heart failure (*67*). Accordingly, management of heart failure in the context of COVID-19 is extremely important in clinical practice.

A knotty problem is how to make a differential diagnosis between COVID-19-related acute respiratory distress syndrome (ARDS) and acute heart failure (AHF) because they share the same symptoms (dyspnea and fatigue). Sometimes, a patient can suffer from both ARDS and AHF, increasing the difficulty of differentiation. Palazzuoli *et al*. devised a method of distinguishing ARDS and AHF by comparing differences in their history, clinical manifestations, supplemental examinations, and laboratory results (*66*) (Table 2). Treatments for COVID-19 related heart failure should be selected to alleviate both COVID-19 and heart failure. The mainstay treatments for ARDS and AHF are also listed in Table 2. In addition, treatment with tocilizumab (TCZ), an IL-6 receptor antagonist, has also been reported. A meta-analysis indicated that the mortality of COVID-19 patients treated with TCZ was 12% lower than those not treated with TCZ (*68*). The efficacy and safety of TCZ treatment for COVID-19 were verified in several studies (*69,70*).

3.4. Arrhythmia

Arrhythmia (particularly atrial arrhythmias) is known to be one of the most common cardiovascular complications of COVID-19, whether in the acute phase of infection or LC (*71,72*). It is also the most significant factor causing new onset or deterioration of COVID-19-related heart failure (*66*). Commonly reported COVID-19-related atrial arrhythmias include atrial fibrillation (AF), flutter and supraventricular tachycardias (SVT), bradyarrhythmia, ventricular arrhythmias (VA), and sudden cardiac death (SCD). AF is the most common arrhythmia in patients with COVID-19 (*71,73*). Studies investigating arrhythmia in LC are limited. Xie *et al*. reported a significant increase in dysrhythmias and cardiac arrest between 30 days and 12 months after initial infection (*10*). AF, atrial flutter, and undefined ventricular arrhythmias increased in all patients with LC (*74*). Mechanisms of developing an arrhythmia are shown in Figure 1, but the long-term arrhythmic sequelae of

Table 2. Differential diagnosis between COVID-19-related acute respiratory distress syndrome (ARDS) and acute heart failure (AHF) and related treatments (Palazzuoli *et al.*, 2022)

Items	COVID-19-related ARDS	AHF
Differential diagnosis		
Clinical history of related risk factors	• High cardiovascular risk factors • COVID-19 contact history	• High cardiovascular risk factors • History of recurrent heart failure • History of myocardial infarction
Symptoms	• Prone position alleviates dyspnea • Fever • Persistent cough • Loss of taste and smell • Gastrointestinal symptoms • Isolated pulmonary crackles or diffuse reduction in pulmonary ventilation	• Orthopneic position alleviates dyspnea • Signs of pulmonary crackles • Systemic congestion • Murmur • Third heart sound
Laboratory results	• Mild increase in natriuretic peptides • Increased C-reactive protein and ferritin • Relative lymphopenia • Increased D-Dimer and fibrinogen	• Marked increase in natriuretic peptides and troponin
Gas exchange	• Hypoxemia with hypocapnia or hypercapnia associated with SPO2 < 90% • Respiratory acidosis	• Hypoxemia with or without hypercapnia, mixed acidosis or respiratory alkalosis
Chest radiography	• Normal cardiac shape with minimal or patchy opacities	• Enlarged cardiac shape with interstitial edema • Pulmonary venous congestion
Echocardiography	• No cardiac dilatation • Left ventricular hypertrophy • Normal or slight increase in pulmonary pressure	• Right heart failure with an increase in pulmonary pressure • Heart failure with a reduced ejection fraction due to myocarditis or worsening of chronic heart failure • High score for heart failure with a preserved ejection fraction • Pericardial effusion
Lung CT	• Pulmonary interstitial involvement and fibrotic changes • Dilatation of the main pulmonary artery branches	• Signs of post capillary hypertension and alveolar edema • Cardiac dilatation, hypertrophy • Distention of central vein
Magnetic resonance imaging	• Restrictive edema associated with mild pericardial effusion	• Segmental and global reduction in myocardial contractility along with signs of diffuse extracellular matrix deposition
Treatments	• Oxygen therapy to increase oxygen levels • Mechanical ventilation with a low tidal volume • Veno-venous extracorporeal membrane oxygenation • Intravenous fluids • Antiviral therapies • Appropriate antibiotic therapy • Corticosteroids: dexamethasone • Anti-fibrotic therapies: pirfenidone, alteplase	• IV vasoactive therapies, a combination of hydralazine and nitrate • Mechanical circulatory support: venous arterial extracorporeal membrane oxygenation, intra-aortic balloon pump, • Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers • Optimization of beta-blockers and ivabradine • Angiotensin receptor neprilysin inhibitors: sacubitril/valsartan • Hemofiltration therapy

SARS-CoV-2 infection remain unclear. Like myocarditis mentioned earlier, determining whether arrhythmia is caused by SARS-CoV-2 infection is difficult. EBM is also the gold standard to answer this question but is seldom performed. In this regard, antiviral therapies have to be fully considered.

3.5. What about the future?

Current robust evidence for treatment of LC is quite limited. Over three years have passed since the start of the COVID-19 pandemic, allowing investigation of the effects of LC on the circulatory system. Indeed, many clinical trials investigating LC and cardiovascular sequelae are ongoing, including rehabilitation programs, symptomatic therapies, metabolic modulators, immunomodulatory therapies, antifibrotic treatments, and anticoagulation (*75*). The results are eagerly anticipated. With advances in computer technology, studies based on mobile apps, artificial intelligence, big data, and machine learning are booming (*76*). Barrios *et al*. reported a telemedicine approach to manage anticoagulation in AF (*77*). Indeed, use of telemedicine in LC, and particularly in management of the patients with LC-related circulatory diseases, should have many advantages. It can reduce the exposure to SARS-CoV-2 infection and offer convenience to patients, caregivers, and clinicians. Other than management of the oral administration of medicines, remote but real-time monitoring of key indices, such as cardiac rhythm

(even remote ECG), is useful. Moreover, remote diagnosis, remote rehabilitation, remote robot-assistant rehabilitation, and remote diagnosis and treatment should be paths for future exploration, although at present there are still many technological and ethical concerns that need to be addressed. But what is needed first of all is a smart top-level design and reasonable development plan based on the pathophysiological nature of circulatory diseases in the context of LC.

4. The neurological system

Neurological and cognitive problems in LC are highly concerning because they are common in patients who have recovered from the acute phase of SARS-CoV-2 infection. Importantly, they may persist longer than three months after diagnosis (*4*) and might be long-term (even lifelong) sequelae of COVID-19 in some cases. Most of these neurologic symptoms are refractory and often relapsing. These features may greatly impact the quality of life (QOL) and activities of daily living (ADL) of patients. Nevertheless, understanding and knowledge regarding these neurologic symptoms are quite limited. Other than their mechanisms, the epidemiological features, clinical characteristics, diagnosis, effective treatment, and prognosis for these problems remains unclear due to the limitations of methodologies, the stage of the pandemic, and technology, all of which warrant further investigation in the future.

4.1. Symptomatologic issues

Involvement of neurological and cognitive systems is a marked feature of LC, and it commonly includes a wide spectrum of symptoms, including non-specific symptoms (fatigue, headaches, dizziness, and vertigo), sensory impairment (paresthesia, hypogeusia or ageusia, hyposmia or anosmia, tinnitus, and hearing loss), neuropsychological symptoms (memory loss and cognitive impairment), and neuropsychiatric symptoms (insomnia, depression, anxiety, and post-traumatic stress disorder (PTSD)). Moreover, ataxia, epilepsy, disturbance of consciousness, skeletal muscular symptoms, peripheral nervous symptoms, and other stroke-like symptoms were also reported (*78*). Kamal *et al*. found that LC-related symptoms would present as late as 20 days after the onset of infection. They found that fatigue was the most common symptom (72.8%), and only 10.8% of patients had no LC-related sequelae. Importantly, the severity of the sequelae was closely associated the severity of acute infection (*79*). Taquet *et al*. conducted a retrospective study of electronic health records to investigate neurological and psychiatric sequelae of COVID-19 (*80*). They found that 33.63% of patients suffered from the neurological and psychiatric sequelae during a 6-month follow-up. Patients with more severe COVID-19 are prone to have more neurological and psychiatric problems. Patel *et al*. conducted a meta-analysis investigating the long-term neurological sequelae in patients who recovered from severe COVID-19 (*81*). Their meta-analysis included seven studies involving 3,304 patients. They found that 20.20% of individuals had LC symptoms over two weeks after the acute phase, including headaches (27.8%), fatigue (26.7%), myalgia (23.14%), anosmia (22.8%), dysgeusia (12.1%), sleep disturbance (63.1%), confusion (32.6%), difficulty concentrating (22%), PTSD (31%), feeling depressed (20%), and suicidality (2%) Hugon *et al*. studied a cohort of 100 patients with COVID-19 and they found that 85% of patients had impaired ADL (*82*). The top 9 neurologic symptoms were cognitive impairment with brain fog (81%), headaches (68%), paresthesia (60%), ageusia (59%), anosmia (55%), myalgia (55%) dizziness (47%), pain (43%), and depression and anxiety (42%). Approximately 18% of patients had abnormal MRI imaging (white matter changes). However, the relevance between MRI changes and symptoms remains unknown.

Results from different studies display marked heterogeneity. The distribution of sequalae differs considerably among these studies. Most of these studies are single-center studies with a small sample size, so they might suffer from selection bias. Moreover, the different follow-up, criteria for inclusion/exclusion, and assessment tools used might contribute to this heterogeneity. Indeed, the distribution of LC symptoms is still puzzling.

Headaches are a common symptom presenting in both acute-phase COVID-19 and LC. Headaches are reported in approximately 11-34% of hospitalized patients. The characteristics of COVID-19-related headaches are that they are migraine-like, tend to recur, and intractable. Administration of common NSAIDs and/or anti-inflammatory medications seems to have little effect (*81*). Importantly, most of the patients who tend to develop headaches have not had migraines or their risk factors, indicating a close causal relationship between these headaches and SARS-CoV-2 infection (*81,83*).

Fatigue is also a common LC sequela reported in many studies. Approximately 34.0-72.8% of patients with COVID-19 reportedly suffered from fatigue (*81,84*). The duration of fatigue fell from 52% (at 6 months) to 20% (at 12 months) (*3*). LC-related fatigue is quite analogous to ME/CFS, which is closely associated with immune-inflammatory dysfunction (*85*). Davis *et al* reviewed the similarities between LC and ME/CFS from the perspectives of etiology, symptomatology, mechanisms, disease distribution, diagnosis, and treatment, and they concluded that SARS-CoV-2 infection might cause ME/CFS, where fatigue is a keystone connecting both (*7*). However, fatigue in LC is reportedly not associated with either the level of pro-inflammatory markers and cytokines (*84*) or the severity of COVID-19 (*81*). A plausible explanation is that LC-related-fatigue is

influenced by many pathophysiological factors and not limited to viral infection (*81*).

Neuropsychiatric symptoms include depression, anxiety, PTSD, and other neuropsychiatric problems (obsessive-compulsive disorder, insomnia, *etc*.) that are reported to be closely associated with COVID-19. Patients with COVID-19 may have double the risk of developing mood disorders (*86*). Approximately 30-40% of patients are estimated to have such neuropsychiatric problems (*87*), and that number is markedly higher than only 10% to 35% in other non-COVID diseases (*88,89*). Females and adolescents and young adults are more vulnerable to mood disorders (*90*). Mazza *et al*. observed LC symptoms in 402 patients and found that prevalent neuropsychiatric symptoms were PTSD (28%), depression (31%), anxiety (42%), obsessive-compulsive disorder (20%), and insomnia (40%) (*91*). They contend that these symptoms were associated with immune-inflammatory dysfunction. A meta-analysis reported that the prevalence of depression, anxiety, and PTSD was 20%, 35% and 53%, respectively, in 113,285 individuals (*92*). Another meta-analysis presented a pooled prevalence of depression (45%) and anxiety (47%) in patients with COVID-19 (*93*). Certainly, negative emotions (apprehensions regarding health and unemployment, dread of medical treatment, isolation, hospitalization, *etc*.) may directly cause mood problems, yet several studies have demonstrated that the abnormal immune-inflammation reaction seems to play a non-negligible role in the initiation, development, and deterioration of these neuropsychiatric symptoms (*91,94*). Since such neuropsychiatric symptoms are closely associated with QOL for a long time, close attention should be paid to mental health after acute COVID-19 (*90*), along with inflammation in these patients (*91*).

Cognitive impairment, colloquially called "brain fog," is a notable neuropsychological symptom of LC, and particularly the domains of attention, memory, and executive functions (*95*). Almeria *et al*. found that approximately 34.4 % of patients had cognitive problem. Cognitive impairments can be found in patients with acute-stage COVID-19, and patients with severe disease readily develop cognitive problems (*96*). These cognitive impairments can last at least four months after COVID-19 (*97*). Commonly, females, patients who had respiratory problems at the onset of infection, and patients admitted to the ICU are more vulnerable to developing cognitive problems. Another noteworthy problem is that persisting cognitive impairments and emotional deficits can also be found in young adults who recovered from mild COVID-19. Manukyan *et al*. observed the neuropsychological state of 40 young patients (age 19.9 ± 2.06, ranging from 18-27) who recovered from mild COVID-19 and found that performance on inhibition tasks and scores on depression subscale in these patients were worse than those of controls, even though there were no significant differences in anxiety and fatigue (*98*). Hence, the neuropsychological problems in young patients with mild disease cannot be ignored. However, due to the complex nature of brain fog, the available studies display a high level of heterogeneity. Use of subjective self-report assessments might contribute to this heterogeneity.

Other neurologic symptoms are also reported. Insomnia is the most prominent sleep disturbance. COVID-19 may worsen existing sleep disorders or "cause" a new sleep disorder (*99*). Sensory impairments, such as hypogeusia, ageusia, hyposmia, and anosmia, are noticeable symptoms in the acute phase. Approximately 60% of patients suffered from olfactory dysfunction during the acute phase, and it regarded as a long-term symptom in LC. But identifying such ageusia or anosmia as an LC symptom in patients whose only COVID-19 symptoms were sensory loss is sometimes difficult because the history of SARS-CoV-2 infection is uncertain (*100*). Encephalitis/encephalopathy have been well-documented in the context of COVID-19, but a biopsy study ruled out active encephalitis as a feature of SARS-CoV-2 infection (*101*).

The available literature often focuses on the association between these symptoms and SARS-CoV-2 infection and it pays little attention to the interactions among LC-related symptoms. SARS-CoV-2 might play a background role in the long-term pathophysiology of LC. Instead, interactions among LC-related symptoms might play a more important role in the progression of diseases. For example, does a COVID-related sleep disturbance worsen cognitive impairment? Does COVID-related sensory loss influence cognition? These questions are still unanswered and warrant further investigation.

4.2. Potential mechanisms underlying neurologic involvement

Thus far, mechanisms underlying how SARS-CoV-2 infection affects the nervous system, and especially the CNS, are not fully understood. There are too many internal/external factors involved. Moreover, the complicated interactions among these factors complicate and confuse the story. Several hypotheses have been put forth but require further verification.

i) **SARS-CoV-2 direct invasion hypothesis**: This hypothesis contends that many neurologic changes in the nervous system are the direct result of invasion by SARS-CoV-2. SARS-CoV-2 is a neurotropic virus, and ACE2 plays a role as a docking gene for cellular entry. Along with other genes such as neuropilin-1, basigin (BSG; CD147), and transmembrane protease serine 2 (TMPRSS2), SARS-CoV-2 can enter the brain (*102,103*). In addition, SARS-CoV-2-related cytokines, such as IL-6, IL-1β, IL-17, and TNF-α, may contribute to disruption of the blood-brain barrier (BBB) and allow entry of the virus (*104*). Other than the dysregulated BBB, another plausible route for neurologic entry of SARS-

CoV-2 is the olfactory system. The virus may invade nerve terminals by endocytosis, then be transported retrogradely, and trans-synaptically spread to other brain regions (*104*). Clinical evidence also corroborates this route, such as marked olfactory-related symptoms (hyposmia or anosmia) and abnormal MRI findings in the olfactory cortex (*105*) caused by SARS-CoV-2 infection. In addition, viruses can enter the brain carried by infected immune cells (*104*). However, this hypothesis remains controversial since direct evidence of viral invasion is insufficient. Bernard-Valnet *et al*. reported two cases of acute meningoencephalitis concomitant with COVID-19, but they found no evidence of SARS-CoV-2 infection in the patients' cerebrospinal fluid (CSF) (*106*). Pilotto *et al*. investigated 25 patients who suffered from SARS-CoV-2 related encephalitis and found that CSF samples were negative for SARS-CoV-2 RNA according to RT-PCR (*107*). Moreover, Kantonen *et al*. performed an autopsy on four patients with COVID-19 and found that all CNS samples tested with RT-PCR were negative for SARS-CoV-2 (*108*), which seems to rule out the direct infection of SARS-CoV-2 in the CNS. Another autopsy study in Germany also indicated that COVID-related changes in patients seemed to be mild, whereas marked neuroinflammatory changes in the brainstem were the most common finding (*109*). This refutes the contention that CNS damage is directly caused by SARS-CoV-2 infection. Hence, other than the effects of direct infection, abnormal immune-inflammatory reactions seem to play a more crucial role in LC-related symptoms in the CNS (*25*).

ii) **Abnormal immune-inflammatory reactions hypothesis**: This hypothesis contends that neurologic involvement is the result of abnormal immune-inflammatory reactions. In the context of COVID-19, the BBB might be disrupted (*102*). The circulating levels of pro-inflammatory cytokines, such as IL-6, and TNF-α, in patients are usually elevated (*110*). These cytokines, along with viral proteins and molecular complexes from damaged cells (such as nuclear protein high mobility group box 1) might enter the brain *via* the compromised BBB and trigger an innate immune response in macrophages in the brain and microglia, finally inducing brain dysfunction (*104*). This hypothesis has been verified by many bench (*94,111*) and bedside studies (*109,112*) and is therefore accepted by most researchers. SARS-CoV-2 infection may trigger excessive production of pro-inflammatory cytokines and cause many downstream pathological changes, such as headaches (*113*) and vascular and organ damage (*7*). Elevated inflammatory indices in patients with COVID-19 corroborate this hypothesis. Hyperinflammatory and hypercoagulable states, which affect all organ systems, might be a plausible explanation for LC symptoms (*100*). That said, involvement of the hypothalamic-pituitary-adrenocortical (HPA) axis is also possible. In the context of COVID-19, pro-inflammatory cytokines, such as IL-6, and TNF-α, were upregulated, and these cytokines activate the HPA axis. The HPA axis can also be activated by BBB dysfunction and neurovascular inflammation (*114*). Once the HPA axis is activated, release of norepinephrine and glucocorticoids increases, further inducing splenic atrophy, T cell apoptosis, and NK cell deficiency, thereby reducing systemic immunity. These immune-inflammation-related mechanisms comprehensively act on the CNS and finally cause brain dysfunction. Hence, anti-inflammatory therapy can be considered as a strategy to treat LC symptoms.

iii) **Dysautonomia hypothesis**: Many studies attribute the symptoms in LC to dysautonomia (*100,115,116*). The main idea of this hypothesis is that many COVID-19-related pathogenic factors, like oxidative stress, immune dysfunction, and an inflammatory reaction, may cause dysautonomia. Dysautonomia is what plays a vital role in causing the subsequent multi-organic symptoms. DePace and Colombo even commented that LC symptoms can be interpreted as "a pro-inflammatory state with oxidative stress and parasympathetic and sympathetic (P&S) dysfunction" (*100*). This hypothesis is plausible since P&S dysfunction indeed triggers almost all reported LC symptoms. Colombo *et al*. used autonomic treatments to treat patients with COVID-19 and found that SARS-CoV-2 infection significantly worsened autonomic dysfunction and related symptoms, but this dysfunction and these symptoms were ameliorated by autonomic treatments (*116*).

iv) **Dysbiosis of gut microbiota:** Now there is direct evidence that COVID-19-related gut microbiota might play a role in the development of cognitive impairment in LC (*117*) (see the section discussing the digestive system).

4.3. Available treatments

Thus far, there is no specific treatment for neurologic symptoms in LC, and symptomatic treatment is the mainstay. Supportive therapy is a keystone for COVID-19. Treatments for underlying diseases (such as diabetes) are also crucial. The efficacy/safety of antiviral, anti-inflammatory, steroid, and autonomic treatment is still uncertain.

4.4 Paths for future exploration

So many methodological and technological flaws have been stumbling blocks holding back the progress of the bench and bedside studies of LC. First, due to the multidimensional nature of neurological involvement, multidisciplinary collaboration should be advocated to compensate for the limitations of a narrow view of a single discipline. Second, to reduce heterogeneity among the different studies, clinical criteria for and definitions of LC should be standardized. Third, large-scale, multi-

center studies involving international collaboration should be conducted. Fourth, health education regarding LC and the value of vaccination should be conducted. Fifth, clinical studies should be more closely tied to biopsy findings. A biopsy study is limited by many factors, but its findings are greatly helpful in providing clinical insights and correcting possible biases regarding LC.

4.4.1. For diagnosis

i) More sensitive, specific, and reliable biomarkers (with limited invasiveness, if possible) that can be actually used in clinical practice should be identified. This must rely on advances in basic research. Use of bioinformatic technology might be a path to explore more novel biomarkers.

ii) Commonly used self-reporting scales for neuropsychological symptoms might potentially have observation bias and cause heterogeneity among different studies. Hence, more administered scales/batteries specially for LC-related neuropsychological symptoms should be considered and developed. Next-generation neuropsychological assessments should be devised following the principle of OMS (objective, multi-purpose, and simple) as described in previous studies by the current authors (*118-120*). Importantly, the latest computer technology should be capitalized upon (*76*).

4.4.2. For treatment

i) Verification of the efficacy/safety of several antivirals, anti-inflammatories, antioxidant drugs, steroids, and monoclonal antibodies in treating neurologic symptoms is underway. Novel treatments like electrical neuro-prostheses stimulation should be developed. The results are eagerly anticipated.

ii) Psychological interventions should be highlighted for those who suffer from LC-related depression, anxiety, PTSD, and suicidality. Family support and professional care are both important and therefore advocated for.

iii) Just as with other neurological diseases, the role of rehabilitation, and particularly the value of early rehabilitation (*121*), should be recognized and emphasized. Accordingly, novel technologies for and concepts of rehabilitation should also be devised and used to treat LC-induced disabilities, such as use of robot-assistant rehabilitation and remote rehabilitation.

5. The digestive system

Digestive system involvement is commonly reported with COVID-19 since ACE2 is widely expressed in the digestive system, including the gastrointestinal (GI) tract (esophagus, stomach, and small and large intestine), liver, and pancreas (*122*). Accordingly, symptoms in the digestive system are commonly reported, both in acute COVID-19 and LC. Although these symptoms are non-specific for SARS-CoV-2 infection, they usually bring discomfort and markedly impact the QOL of patients, hence requiring medical intervention.

5.1. Involvement of the GI tract

Commonly reported COVID-19-related symptoms include diarrhea, constipation, acid reflux, abdominal pain, and altered smell/taste. However, LC-related GI symptoms are not well identified. Blackett *et al*. conducted a 6-month follow-up in hospitalized patients and an online survey of patients with COVID-19 and found that the symptoms at 6-month follow-up were abdominal pain (7.5%), constipation (6.8%), diarrhea (4.1%), and vomiting (4.1%) (*123*). In total, 16% reported at least one GI symptoms during this follow-up. A recent prospective follow-up cohort study investigated the LC sequelae of the GI tract in 320 patients with COVID-19 and found that 11.3% of patients developed GI disorders at 1-month follow-up (*124*). Persistent symptoms were 8.4% at 3 months and 6.6% at 6 months. Symptoms at 3 months were irritable bowel syndrome (2.5%), diarrhea (2.2%), dyspepsia (1.9%), constipation (0.9%), overlap of dyspepsia-irritable bowel syndrome (0.6%), and abdominal bloating/distention (0.3%). A meta-analysis by Choudhury *et al*. reported that abdominal pain, diarrhea, along with hypogeusia or ageusia, loss of appetite, nausea and vomiting, dyspepsia, and irritable bowel syndrome are LC-related GI symptoms (*125*). They found that the frequency of GI symptoms was 12% in patients with COVID-19 and 22% in patients with LC. Frequent LC-related symptoms were diarrhea (10%), abdominal pain (14%), hypogeusia or ageusia (17%), loss of appetite (20%), nausea and vomiting (6%), dyspepsia (20%), and irritable bowel syndrome (17%). Importantly, they found that GI symptoms are not associated with severity of COVID-19 and that many patients with mild disease also possibly develop GI symptoms (*125*). Accordingly, loss of appetite, dyspepsia, irritable bowel syndrome, hypogeusia or ageusia, and abdominal pain might be the most common GI symptoms in LC. A point to keep in mind is that all these symptoms are non-specific for disorders in GI tract, so they also can develop due to the dysfunction of other systems.

5.1.1. Mechanisms underlying dysfunction of the GI tract

Thus far, mechanisms underlying dysfunction of the GI tract due to COVID-19 are not fully understood, and particularly the long-term effects of SARS-CoV-2 infection. The GI tract is mainly controlled by the autonomic nerves system. Theoretically, all pathological factors in the body, such as direct viral infection, abnormal immune- inflammatory reactions, abnormal gut microbiota composition, and an abnormal gut-brain

axis, may directly or indirectly influence the GI tract and cause various symptoms.

i) **Concept of PI-FGID:** The term "post-infection functional gastrointestinal disorders (PI-FGID)" is used to describe newly developing GI symptoms following infection-related acute gastroenteritis that meet the Rome criteria (*124*). The characteristics of PI-FGID are that it is: *i*) infection-related; *ii*) new onset; *iii*) independent (onset, development, and progression are independent of the initial infection); and *iv)* persistent. LC sequelae can be partly included in PI-FGID since transient GI symptoms in LC can trigger long-lasting FGID despite the situation during the initial infection (*126*). Likewise, PI-FGID has its independent mechanisms (not directly related to COVID-19), such as genetic predisposition and a pre-existing psychological disturbance (depression and/or anxiety). PI-FGID contributes to dysregulation of gut motility, visceral hypersensitivity, dysbiosis, increased intestinal permeability, bile acid malabsorption, and modifications of enteroendocrine cell and serotonin metabolism, which can partly explain the onset of GI symptoms.

ii) **Direct influence of viral infection:** Several studies have confirmed the direct influence of SARS-CoV-2 infection on the GI tract. SARS-CoV-2 RNA was found in stool samples from patients with COVID-19 (*127*). Natarajan *et al*. found SARS-CoV-2 RNA in 12.7% of stool samples in patients at a 4-month follow-up and in 3.8% at a 7-month follow-up (*128*). Gaebler *et al*. found that persistence of the SARS-CoV-2 antigen in the GI tract was approximately four months (range: 2.8-5.7 months) after infection (*129*). Zollner *et al*. noted the persistence of the SARS-CoV-2 antigen in the gut mucosa of LC patients developing inflammatory bowel disease seven months after the initial SARS-CoV-2 infection (*130*). Goh *et al*. noted the persistence of the nucleocapsid protein of SARS-CoV-2 in the appendix of patients 426 days after symptom onset (*131*). Another ongoing work found persistent abnormalities of lymphoid and myeloid cells in the GI tract up to 10 months after initial infection (*132*). All of the aforementioned evidence seems to imply a prolonged persistence of SARS-CoV-2 in the GI tract. Goh *et al*. even pointed out the possibility of the GI tract serving as a reservoir for SARS-CoV-2 (*131*).

iii) **Dysbiosis of gut microbiota** is a noteworthy GI change in patients with COVID-19 (*133,134*). Yeoh *et al.* checked the gut microbiota in stool samples from patients who recovered 30 days after SARS-CoV-2 infection. The composition of gut microbiota changed significantly in patients with and without COVID-19. Several gut commensals with known immunomodulatory potential, such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *bifidobacteria*, were lower in patients and remained lower in the samples collected 30 days after recovery from disease (*133*). Liu *et al*. reported higher levels of *Ruminococcus gnavus* and *Bacteroides vulgatus*, along with lower levels of *Faecalibacterium prausnitzii*, in patients with LC (*vs.* non-COVID-19 controls). This gut dysbiosis may persist at least 14 months. Low levels of butyrate-producing bacteria were closely associated with LC at a 6-month follow-up (*134*). These data prove the great impact of SARS-CoV-2 infection on the microecosystem. Dysbiosis of gut microbiota may affect not only the GI system but also the whole body. De Almeida *et al*. performed fecal bacteria transplantation (FMT) from patients with LC to healthy germ-free mice and they noted cognitive impairment and impaired lung defenses in these mice that were partly treated with the commensal probiotic bacterium Bifidobacterium longum (*117*). This study provides direct evidence that *i*) SARS-CoV-2 virus can remain in the GI tract for a long time even though the patient has recovered from acute infection and that *ii*) (3) dysbiosis of gut microbiota induced by COVID-19 plays a role in the development of COVID-19-related cognitive impairment.

Other than the aforementioned mechanisms, existence of inflammatory bowel disease indicated that abnormal immune-inflammatory reactions may play a role in the GI sequelae of LC (*130*). Mechanisms causing dysfunction in the GI tract might be complicated and multifaceted. Several bench studies have reported that crosstalk between neurons and intestinal epithelial cells might play a role in defense from infection, indicating the involvement of neuromodulation in GI immune-inflammatory regulation (*135,136*). The involvement of neuromodulation in LC sequelae requires further investigation.

5.1.2. Management of GI symptoms in LC and the future

Thus far, insights regarding selection of optimal treatments for GI sequelae in LC remain limited. Non-specific treatments such as supportive therapy and symptomatic therapy are the mainstay. Although there have been advances in the treatment of diseases like postinfection irritable bowel syndrome (*137,138*), whether those treatments can be used to treat SARS-CoV-2 infection remains unknown.

On the basis of known information, several paths may be considered for future research: *i*) Verification of exiting treatments for postinfection irritable bowel syndrome in patients with LC; *ii*) Previous studies indicated the possible long-term reserve of SARS-CoV-2 in the GI tract, so is administration of an antiviral to LC patients essential and effective? *iii*) Due to the involvement of dysautonomia, are neuroregulatory therapeutics, such as tricyclic antidepressants, or electrical neuro-prostheses stimulation of either the parasympathetic (vagus) or sympathetic nervous system, effective for LC patients? *iv)* Due to the gut microbial-related mechanisms, can FMT be effective in treating GI sequelae in LC? These issues should be addressed to explore optional treatments for the GI symptoms in LC

5.2. Involvement of the hepatobiliary system

Hepatic manifestations have been reported since early observational studies concerning COVID-19 (*139-143*), ranging from asymptomatic elevation of liver enzymes to decompensated hepatic function. A study has reported that approximately 14-53% of patients with COVID-19 developed abnormal liver function (*144*), whereas severe illness was associated with a higher incidence of liver dysfunction (*145*). In general, hepatic involvement in COVID-19 might be attributed to the direct cytopathic effects of SARS-CoV-2, drug-induced liver injury, hypoxia reperfusion injury, secondary infection, an auto-immune disorder, and a cytokine storm. COVID-19-related liver dysfunction was initially regarded as transient and was thought to recover along with the resolution of COVID-19. Recently, however, Liu *et al*. found that abnormal liver function was still observed in 11.2%, 9.5%, and 7.6% of LC patients at 3, 6, and 12 months after discharge, respectively (*146*). Liao *et al*. reported that abnormalities in a liver function test were observed in 25.1% of patients with COVID-19 at one month, 13.2% at three months, 16.7% at six months, and 13.2% at 12 months after discharge (*147*). These findings suggest that liver dysfunction might be a persistent LC sequela that is independent of recovery from acute COVID-19. Moreover, a novel entity known as post-COVID-19 cholangiopathy (PCC) has recently been reported occasionally (*148-152*). This syndrome usually manifests as cholestasis and jaundice during convalescence from COVID-19 and accompanied by marked increases in serum alkaline phosphatase and direct bilirubin, along with injury of the bile ducts on imaging. It is also referred to as "post COVID-19 sclerosing cholangitis." Hence, involvement of the hepatobiliary system is not rare and attention should be paid to it in clinical practice.

5.2.1. Underlying mechanisms of hepatobiliary dysfunction

Mechanisms underlying hepatobiliary dysfunction persisting after recovery from acute COVID-19 remain unclear. One plausible hypothesis is the persistent imbalance in immunity in LC (*153*). As described in the GI section, the GI tract might play a role as a reservoir for SARS-CoV-2 (*131*). This means that the virus will not disappear with recovery from acute infection. It might induce long-term abnormalities in the immune-inflammatory reactions and affect the whole body, certainly including the hepatobiliary system. Several current studies have reported a new-onset metabolic disorder during COVID-19 (*154-159*) that may increase the risk of developing metabolism-associated fatty liver disease (MAFLD). Milic *et al*. found that the prevalence of MAFLD increased from 37.3% on admission to 55.3% at follow-up (median 144.0 days (130.0-167.5)) in 235 patients with COVID-19 (*160*). A prospective cohort study by Liao *et al*. found that the prevalence of ultrasound-determined fatty liver disease increased from 18.5% at discharge to 71.4% after a 12-month follow-up (*147*). Accordingly, new-onset fatty liver disease also markedly contributes to the development of LC-related hepatobiliary dysfunction. Finally, cholangiocytes are known to exhibit a higher level of ACE2 expression than hepatocytes. This might trigger cytopathic and immunological effects during SARS-CoV-2 infection and ultimately induce cholangiopathy (*148*).

5.2.2. Treatment for hepatobiliary dysfunction

Most LC-related liver dysfunction is mild and requires no intervention. However, when patients present symptoms of liver injury, liver protective medication is recommended. Available evidence for PCC is rare so far. Ursodeoxycholic acid and obeticholic acid, which are mainly used to treat cholestatic diseases (*161*), are the medications most frequently used to treat PCC as an empiric therapy (*149*). When PCC develops into severe liver decompensation, liver transplantation is required. Faruqui *et al*. reported that 12 patients were definitively diagnosed with PCC; of those, five patients finally underwent liver transplantation due to persistent jaundice, liver failure and/or recurrent bacterial cholangitis (*162*). Durazo *et al*. reported a 47-year-old man who recovered from COVID-19-related ARDS and who subsequently developed end-stage liver disease from PCC (*163*). This patient underwent liver transplantation and survived at the 7-month follow-up.

5.2.3. Paths for future exploration

Liver injury after COVID-19 is not rare. However, most of the patients are asymptomatic. Hence, a regular liver function test and abdomen imaging screening are highly recommended for COVID-19 patients during convalescence. The prevalence of PCC is low but it is life-threating, so careful attention should be paid to it in routine clinical practice. During the COVID-19 pandemic, PCC should be listed as a potential diagnosis for all patients suffering from cholestatic liver disease of an unknown cause.

6. The urinary system

Renal complications and lower urinary tract symptoms (LUTS) are commonly reported in the context of LC. Acute kidney injury (AKI) is the most significant kidney disease in LC. Other kidney diseases, such as chronic kidney disease (CKD), glomerular diseases, and end-stage kidney disease, can also develop or worsen as a result of SARS-CoV-2 infection. Patients with COVID-19 are known to have a high risk of adverse kidney outcomes (*164*). LUTS is not rare in patients

with COVID-19. In early studies, some patients with COVID-19 presented with LUTS, such as frequent urination, that were believed to be associated with viral cystitis after SARS-CoV-2 infection (*165*). Crete *et al*. systematically reviewed the LUTS in COVID-19 and found that approximately 3-5% of patients with COVID-19 developed LUTS (*166*). A recent study investigated the relationship between LUTS and COVID-19 and found that augmented frequent urination was the most common urological symptom (*167*). Of those patients with COVID-19, 3.4% had frequent urination, 1.0% had dysuria, and 1.0% had acute urinary retention. Dysfunction of the detrusor muscle in the bladder might be a cause of LUTS in the context of COVID-19 (*168*).

Kidney sequelae play a key role in LC-related urinary sequelae and therefore cannot be ignored. This section will focus on kidney involvement.

6.1. AKI, the most common form of LC-related renal dysfunction

AKI is common in hospitalized patients with COVID-19. As per the definition in Kidney Disease: Improving Global Outcomes (KDIGO), AKI is defined as any of the following issues: "increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or urine volume < 0.5 mL/kg/hour for 6 hours". (*169*). A recent meta-analysis found that the pooled prevalence of AKI was 28% among hospitalized patients; of those, 9% required dialysis (AKI in Stage 3D) (*170*). Stage 3D AKI is even more common in patients requiring admission to the ICU. Hsu *et al*. reported that 2,361 of 4,221 (56%) patients with COVID-19 in the ICU developed AKI; of those, 876 (21%) patients underwent kidney replacement therapy (KRT) (*171*). Hirsch *et al*. reviewed medical records of 5,449 hospitalized patients with COVID-19 and found that 36.6% of patients developed AKI; 46.5% had stage 1, 22.4% had stage 2, and 31.1% had stage 3; of those, 14.3% required KRT (*172*). In total, 89.7% of patients requiring ventilation developed AKI (*vs.* 21.7% of those who did not require ventilation), and 96.8% of patients requiring KRT also required mechanical ventilation. Approximately 52.2% of patients developed AKI within 24 hours of intubation. Finally, 26% of patients were discharged, 39% were hospitalized, and 35% unfortunately died. Later, Hirsch *et al*. observed the impact of AKI on clinical outcomes in hospitalized patients with COVID-19 and found that risk of in-hospital death was higher in patients with AKI 1-3 and AKI 3D (*173*). A previously cited study also indicated that patients with COVID-19 who developed AKI had a significantly higher mortality rate than those who did not develop AKI (38% *vs.* 13%) (*171*). The estimated glomerular filtration rate (eGFR) is significantly reduced by COVID-19-related AKI (*77,164,174-176*). Bowe *et al*. reported that approximately 5% of non-hospitalized COVID-19 survivors suffered a 30% reduction in eGFR (*164*). A study in China conducted a retrospective and prospective follow-up to investigate the eGFR and reduced renal function in patients with COVID-19 and found that 8.3% of COVID-19 patients with AKI in acute phase suffered from decreased eGFR, which was significantly higher than the ratio in patients without AKI (*174*). These patients had worse renal function at follow-up. The frequency of a decreased eGFR in COVID-19 patients with AKI was 6.02% in patients with stage 1 AKI, 15.99% in patients with stage 2, and 17.79% in patients with stage 3, indicating that COVID-19 patients with AKI in the acute phase are prone to have worse renal function during follow-up. Several studies compared AKI in patients with and without COVID-19. Xu *et al*. found that AKI more frequently developed in patients with COVID-19 than those without COVID-19 (29% *vs.*18%) (*175*). Patients with COVID-19 who developed AKI had a lower eGFR than that of patients without COVID-19. The risk of in-hospital death was greatest for patients with COVID-19 and AKI, followed by those with COVID-19 and without AKI, and then those without COVID-19 and with AKI. Nugent *et al*. also found that COVID-19-related AKI may involve a greater reduction in the eGFR than non-COVID-19-related AKI (*176*). Huang *et al*. reported that 35% of patients with COVID-19 developed AKI, a figure that was significantly higher in patients without COVID-19 (13%) (*28*). The findings of these studies indicate that AKI is common in hospitalized patients with COVID-19 and that it is closely associated with prognosis.

That said, studies have indicated that preexisting CKD is a key risk factor for AKI. A prospective cohort study including 701 patients with COVID-19 found that the incidence of AKI was significantly higher in those with increased baseline creatinine (*vs.* normal baseline creatinine) (11.9% *vs.* 4.0%) (*177*). Available evidence indicates that CKD is an independent predictor of severe AKI (*178,179*).

However, renal sequelae in LC are not fully understood and still require further investigation. Nowadays, CKD, the severity of initial respiratory symptoms, and not being vaccinated (*180*) are known to be possible risk factors for developing AKI in LC. Due to the non-specific nature of the symptoms (dyspnea, fatigue, weakness, *etc*.), investigation of long-term renal sequelae is challenging.

6.2. Potential pathogenic mechanisms underlying COVID-19-related AKI and renal dysfunction

Mechanisms of COVID-19 related AKI and renal dysfunction are multifactorial and not fully elucidated. Similarly, they are comprehensive results of the direct effects of SARS-CoV-2 infection, abnormal immune-

inflammatory reactions, the influence of other organs, and treatment-related injuries. A large spectrum of COVID-19-related pathological processes, including tubular injury, endothelial damage, release of inflammatory mediators, activation of complements, micro- and/or macrovascular injury, rhabdomyolysis, hypovolemia, hypotension or septic shock, pro-coagulant status, and activation of the renin-angiotensin-aldosterone system, may contribute to acute/long-term renal dysfunction (*181-183*).

Acute tubular injury is the most significant mechanism involved in COVID-19-related renal dysfunction. Many biopsy studies have reported marked tubular necrosis in patients with COVID-19 (*184,185*). Acute tubular injury is most likely directly caused by a local and/or systemic response to SARS-CoV-2 infection, which may lead to hypotension, activation of the renin-angiotensin system, endothelial injury, activation of coagulation pathways, and mitochondrial injury (*184,186,187*). It is also associated with several indirect factors such as hemodynamic abnormalities, ARDS, hyperuresis, nephrotoxin exposure, hypoxia, a cytokine storm, rhabdomyolysis, and secondary infections (*176*). The presence of SARS-CoV-2 in the kidneys of patients with COVID-19 further verified the possibility of direct viral toxicity (*188*).

Microcirculatory disturbances are also observed in many organs of patients with COVID-19 (*189*). Su *et al*. reported microvascular obstruction and segmental fibrin microthrombi in the glomeruli of patients with COVID-19 (*190*). The action of thrombocytes plays a key role in microvascular injury and disseminated intravascular coagulation in COVID-19 because SARS-CoV-2 might bind the ACE2 in the thrombocytes and activate them (*191*). In addition, activation of inflammatory pathways and complements *via* molecules (release of a pathogen-associated molecular pattern and damage-associated molecular pattern) may lead to the release of pro-coagulant substances and tissue factors involved in the activation of the extrinsic pathway of coagulation in COVID-19 (*192*). Emerging evidence suggests that excessive formation of neutrophil extracellular traps plays a key role in the pathophysiology of endothelial injury and immune-thrombosis in severe cases of COVID-19 (*193,194*).

Collapsing glomerulopathy is the most commonly reported glomerular disease in COVID-19 patients and is associated with polymorphisms of the APOL1 gene particularly in patients of African ancestry (*195*). A previous study indicated that viral infection may cause upregulation of the APOL1 gene, subsequent activation of interferon and toll-like receptors, and induce dysregulation of podocytes and glomeruli (*196*). However, evidence of SARS-CoV-2 infection is not available so far. Commonly signs of COVID-19-related collapsing glomerulopathy are AKI, heavy proteinuria, and hypoalbuminemia (*197-199*). Moreover, biopsy findings of no collapsing features in some patients with focal segmental glomerulosclerosis suggest the involvement of podocytopathy in COVID-19-related glomerulopathy, a topic that requires further investigation.

In addition to the aforementioned pathogenic mechanisms, other hypotheses such as involvement of COVID-19-related tubulointerstitial fibrosis (*176*) warrant further investigation.

6.3. Insights into clinical practice

6.3.1. Biomarkers to predict prognosis

The aforementioned decrease in eGFR is regarded as a predictor of a worse prognosis for LC-related AKI. Chaudhri *et al*. reported that proteinuria and hematuria at admission and during hospitalization are associated with a worse prognosis in hospitalized patients with COVID-19 (*200*). In addition, many biomarkers, and particularly inflammation-related biomarkers, have been found to be closely associated with the prognosis for COVID-19 (*201*). In a meta-analysis evaluating the relationship between available biomarkers and the prognosis for hospitalized patients with COVID-19, the severity of COVID-19 was found to be associated with an increase in CRP, PCT, LDH, and D-dimer (*202*). More specific biomarkers of COVID-related AKI were evaluated, including urinary nephrin (*203*), IL-18 (*204,205*), neutrophil gelatinase-associated lipocalin (NGAL) (*203,204,206*), monocyte chemoattractant protein (MCP-1) (*203,205*), kidney injury molecule 1 (KIM-1) (*203,205*), epidermal growth factor (EGF) (*205*), plasma NGAL (*204*), NFα receptors in their soluble form (sTNFR 1 and 2) (*207*), YKL-40, KIM-1, IL-2, IL-10, IL-18, sFTL1, TNF-α, and Ang2 (*208*). The plasma sTNFR1 level was identified as a predictive factor of COVID-19 prognosis (*207,208*); high urinary levels of NGAL (*203,204,206*), KIM-1 (*205*), and MCP-1 (*205*) and a low urinary level of EGF (*205*) were associated with a worse prognosis for COVID-19-related AKI (*203*). However, these biomarkers require further investigation due to the limited available evidence.

6.3.2. Treatment for COVID-19-related renal dysfunction

A comprehensive strategy to treat COVID-19-related renal dysfunction should be promptly selected to avoid deterioration of the situation. Treatment for COVID-19-related AKI should include management of AKI along with treatment of COVID-19. The KDIGO guideline for AKI includes fluids and vasopressors, nutrition and glycemic control, diuretics, vasodilator therapy (such as dopamine, fenoldopam, and natriuretic peptides), and avoiding nephrotoxins (*169*). Available evidence in the context of COVID-19, however, is limited, so lung-kidney interactions should be seriously considered

(*209*). Several issues should be taken into account depending on the pathophysiological state of a given patient: *i*) Selection of appropriate ventilation (lung protective ventilation, or prone ventilation, or lung protective ventilation with a neuromuscular blockade, or spontaneous breathing during airway pressure release ventilation); *ii*) Fluid management (conservative fluid management, albumin, and diuretics); *iii*) Medications (antivirals, anti-inflammatory treatments such as glucocorticoids±mineralocorticoid, immunosuppressors such as cyclosporine, and antibiotics). Once all conservative treatments are unsuccessful, KRT and renal transplant should be considered for patients with volume overload and/or refractory hypoxemia.

6.4. Paths for future exploration

Thus far, insights into and understanding of COVID-19-related renal dysfunction are insufficient. Evidence regarding diagnosis and treatment remains limited. To better manage COVID-19-related renal dysfunction, several issues should be addressed:

i) Well-designed large-scale, multicenter RCTs on diagnostic and therapeutic strategies need to be conducted to obtain compelling evidence. Accordingly, a mechanism of transnational cooperation, an international surveillance system, and a databank of COVID-19-related renal dysfunction need to be established to promote international collaborative research and sharing of information.

ii) Renal dysfunction in LC lacks specific symptoms, so a renal function test should be performed routinely during follow-up for patients who recovered from acute COVID-19, and particularly for asymptomatic patients.

iii) A long-term follow-up prospective study should be conducted.

iv) Treatments for special populations, such as pregnant women, patients with diabetes, the elderly, children, and those who are undergoing surgery, should be considered.

7. The endocrine system

The endocrine system including the hypothalamus, pituitary, thyroid, pancreas, adrenal and reproductive glands plays a vital role in regulation of the physiological functions of the whole body. The nature of a wide distribution of ACE2 in endocrinal organs/glands indicates that such structures seem to be targeted by SARS-CoV-2 infection (*210*). Several known clinical characteristics of COVID-9, such as the relationship between susceptibility (and severity) of COVID-19 and diabetes/obesity, as well as the fact that males are likelier to develop a severe/life-threating illness, confirm the involvement of the endocrine system. Accordingly, exploring the impacts of SARS-CoV-2 infection on the endocrine system, and particularly the functioning of the endocrine glands, is extremely important in clinical practice. Unfortunately, due to the *status quo* of medical care during the pandemic, many indispensable tests of the functioning of the endocrine glands were not available, and this has been a stumbling block to better understanding the actual physiological state of the endocrine system. The mechanisms of endocrinal involvement, along with the long-term effects of COVID-19, have not been fully investigated and understood. Although direct viral invasion and viral toxicity to each organ might play a role, complicated systemic COVID-19-related mechanisms, such as abnormal immune-inflammatory reactions, dysautonomia, an abnormal hypothalamic-pituitary-glands axis, and particularly complex interactions among organs (glands) and among pathophysiological factors, might play a more crucial role in endocrinal involvement in the context of SARS-CoV-2 infection. The relationship between endocrine disorders and SARS-CoV-2 infection is reported to be bidirectional: On the one hand, preexisting endocrine disorders such as diabetes and obesity are known to negatively impact the severity and mortality of COVID-19. On the other hand, SARS-CoV-2 infection might trigger new endocrine disorders, such as diabetes, hypopituitarism, and primary adrenal insufficiency (*22*). Importantly, some endocrinal symptoms trigged by acute infection do not resolve with recovery from acute infection and might be persistent or even lifelong (*22*). This issue warrants particular concern and further investigation.

7.1. Pituitary involvement

Due to the uncommon nature of pituitary disorders, recognition of and knowledge regarding pituitary involvement is still limited and uncertain. COVID-19 related hypopituitarism might be a result of pituitary apoplexy and/or hypophysitis (*22*). A number of risk factors, such as hypertension, hyperglycemia, obesity, vertebral fractures, and preexisting pituitary disorders, are reported to be associated with COVID-19-related hypopituitarism (*211,212*). However, ACE2 expression in pituitary is reported to be low in a healthy pituitary gland (*213*). Hence, some authors have contended that the involvement of the pituitary might be attributed to an emerging endocrine phenotype that is closely associated with the severity of and prognosis for COVID-19 (*211,214*). Thus far, available evidence remains limited. Carosi *et al*. found that pituitary hormonal deficiencies were present in 85.8% of patients with adrenal insufficiency and that hypopituitarism did not seem to significantly affect COVID-19 outcomes (*215*). Urhan *et al*. found that cortisol and growth hormone (GH) measured in a pituitary function test were lower in patients who recovered from acute COVID-19. They concluded that pituitary function, and particularly the HPA and GH axes, might be influenced

by SARS-CoV-2 infection (*216*). Yoshimura *et al*. reported a 65-year male patient with COVID-19 but with no history of endocrinopathy who suffered from multiple endocrine deficiencies affecting the HPA axis, GH-IGF-I axis, and testes (*217*). Acute respiratory symptoms improved, but the patient suddenly developed hypotension and a decrease in circulating ACTH and cortisol levels. After administration of hydrocortisone, hypotension was alleviated but the pituitary hormonal deficiencies persisted. An insulin tolerance test three months later indicated combined hypopituitarism. The GH response recovered completely, whereas the ACTH response recovered partly at 12 months after discharge. At 15 months after discharge, the basal ACTH and cortisol levels returned to normal, and hydrocortisone replacement was discontinued without a deterioration in symptoms. However, hypogonadism persisted. The GH and ACTH deficiency lasted for more than a year and finally disappeared, but hypogonadism did not disappear during the 15-month follow-up. This case indicates the existence of COVID-19-related hypopituitarism. All of the above findings suggest that hypopituitarism might be triggered by the initial SARS-CoV-2 infection and persist for a long time after recovery from acute infection. Some of the hormonal deficiencies may disappear during a long follow-up whereas some may not, and this topic requires further investigation. Hyponatremia is the most common electrolyte abnormality in patients with COVID-19. It occurs in approximately 20-60% of hospitalized patients (*218*). However, the *status quo* of hyponatremia in LC remains unclear. Oguz and Yildiz commented that hypopituitarism seems to not be associated with development of severe illness, whereas hyponatremia and hypocalcemia seem to be associated with the severity of COVID-19 (*22*).

7.2. Adrenal involvement

The abundant expression of ACE2 in the adrenal glands indicates that the adrenal glands are targets of SARS-CoV-2 infection. Adrenal dysfunction may be a comprehensive effect of direct viral toxicity, an abnormal HPA axis, microthrombi in small adrenal vessels (*219*), and adrenalitis (*219,220*). The involvement of the adrenal glands has been well-documented in acute COVID-19 (*215,221,222*), but a study has reported that adrenal involvement, and particularly adrenal insufficiency (AI), seldom affects the clinical outcomes of COVID-19 (*22*). Several previous studies have indicated that most adrenal dysfunction commonly occurs in the acute stage of SARS-CoV-2 infection, it lasts several months, and then it finally disappears after a long follow-up (*217,223*). Thus far, limited available data seem to imply that SARS-CoV-2 infection does not have long-term effects on the adrenal glands (*22*), though this topic requires further investigation.

7.3. Thyroid involvement

Thyroid involvement is quite analogous to adrenal involvement. The abundant expression of ACE2 in the thyroid gland indicates that both the thyroid gland and the hypothalamic-pituitary-thyroid (HPT) axis are targets of SARS-CoV-2 infection (*224*). The underlying mechanisms are direct viral effects, an abnormal HPT axis, and abnormal immune-inflammatory reactions (*17*). Thyroid impairment, such as abnormal thyroid function test results (*225*), non-thyroidal illness syndrome (NTIS) (*226*), and subacute thyroiditis (*227*), might develop both in the acute phase and recovery phase (*17*). NTIS is common in hospitalized patients with COVID-19, but it tends to resolve upon recovery (*22*). Lisco *et al*. indicated that COVID-19 might be associated with short-term and reversible thyroid impairment (*228*). Available evidence does not indicate the long-term effects of COVID-19 on the thyroid (*22*).

7.4. Obesity and COVID-19

The prominent role of obesity in COVID-19 has been well-documented. The close association between obesity and the worse clinical outcomes of COVID-19 is widely recognized. Obese people are susceptible to SARS-CoV-2 infection. Abdominal obesity is regarded as a risk factor for COVID-19, and a high body mass index (BMI) and increased visceral adipose tissue have been cited as predictors of COVID-19 severity (*229*). Another study based on the American Heart Association COVID-19 Cardiovascular Disease Registry indicated that obesity is an independent risk factor for the severity and mortality of COVID-19 (*230*).

The effects of obesity on SARS-CoV-2 infection are still not fully understood. Several hypotheses were put forth based on the available findings. As direct effects, *i*) Obesity may cause respiratory difficulties (such as atelectasis or a ventilation-perfusion mismatch) and subsequently cause hypoxemia (*231*); *ii*) Obesity is prone to cause a microcirculatory disturbance, such as increased blood viscosity, elevated prothrombotic markers, and suppressed fibrinolytic activity (*232*), and *iii*) Obese patients have more adipocytes and enlarged adipose tissue that abundantly express ACE2 and that might serve as a SARS-CoV-2 reservoir (*232,233*). As indirect effects, *i*) Obesity may induce immune dysfunction. Cytokines and adipokine secreted by adipose tissues induce a pro-inflammatory state in obese people (*232*) that might be associated with systemic abnormal immune-inflammatory reactions in the context of COVID-19, *ii*) Obesity is closely associated with a battery of metabolic-related comorbidities, such as hypertension, insulin resistance, and type 2 diabetes (T2B, see the next section), and secondarily affect the clinical outcomes of COVID-19, and *iii*) Obesity can induce mood disorders (depression, anxiety, and

stress) (*234*), which are also associated with the clinical outcomes of COVID-19. Accordingly, obesity results in a worse clinical outcome for COVID-19, in males and females of all ages.

Available findings and knowledge regarding LC sequelae are limited. Evidence in children and adolescents has indicated that obesity is associated with the severity of LC sequelae (*235*). LC-related symptoms were associated with a change in body weight that was independent of the patient's initial COVID-19 status (*236*). Hedin *et al*. found that obese patients infected with SARS-CoV-2 took twice as much time (*vs*. non-obesity patients) to return to usual health (*5*). A recent study analyzed the risk of post-acute sequelae of COVID-19 associated with the continuous spectrum of BMI in 11,296 patients with COVID-19 and found that a BMI of 22.1 in men and 21.6 in women may result in the best recovery (*237*). A higher BMI was associated with fatigue, neurocognitive impairment, and chest symptoms. Both high and low BMIs are associated with impaired recovery after COVID-19. Those findings seem to indicate that obesity and emaciation are not beneficial for recovery from COVID-19. The underlying mechanisms and the roles of exercise in recovery from LC sequelae need to be investigated further.

7.5. Diabetes and COVID-19

Diabetes, and particularly T2D, is the most significant endocrine/metabolic disease. It is also the most significant COVID-19-related disease, playing a comprehensive role (risk factor for/predictor of infection, severe illness, and death; a comorbidity; a sign of the effects of many diseases, *etc*.) in the pathophysiological mechanisms of COVID-19. The complicated association between diabetes and COVID-19 has been well-documented. In the past, the association between T2D and COVID-19 was considered to be bidirectional (*238*). On the one hand, once glycemic control in pre-existing T2D is inappropriate, it can render the patient susceptible to infection, enhance the severity of COVID-19, or be independently associated with many adverse outcomes (*238*). On the other hand, SARS-CoV-2 infection *per se* can trigger a battery of metabolic abnormalities, including insulin resistance and hyperglycemia, finally inducing the onset of T2D (*239*). Many individuals with prediabetes that progressed to diabetes during the pandemic can be partly attributed to the viral infection (certainly, epidemic control measures such as "lockdowns" and "isolation at home" may have changed the lifestyles of some people, which might be an indirect cause of this issue). However, the association between T2D and COVID-19 appears to be multidirectional (Figure 2). First, both T2D and SARS-CoV-2 infection may affect the whole body. Second, almost all of the pathophysiological factors involved in SARS-CoV-2 infection are also associated/interact with T2D. Hence, rather than being "bidirectional," the

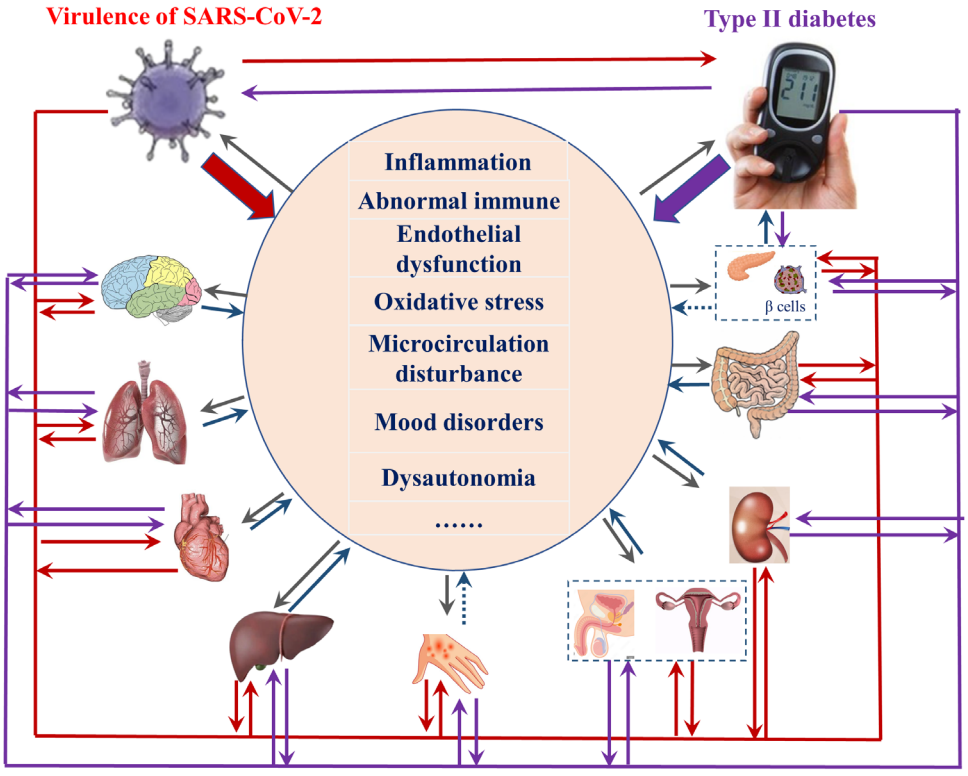

Figure 2. The multidirectional interactions between SARS-CoV-2 and type 2 diabetes. Red arrows/lines represent the influence of a SARS-CoV-2 infection. Purple arrows/lines represent the influence of type 2 diabetes. Gray arrows represent the influence of pathophysiological factors. Blue arrows represent the direct influence of the organs on pathophysiological factors, and a dotted line represents an uncertain influence.

association/interaction between T2D and COVID-19 is extremely complicated and intricate, and almost all organs and all pathophysiological factors might be involved (Figure 2). Thus, mechanisms between T2D and COVID-19 are far from clarified. ACE2 is expressed in the pancreas, so direct invasion of SARS-CoV-2 might be a plausible explanation for impaired insulin secretion. In addition to pancreatic injury, the essential question is whether beta cells are destroyed by the viral infection. Several clinical (*154*) and experimental (*240*) studies have found that rather than direct damage to beta cells, hyperstimulation of the beta cells by viral infection-related insulin resistance may cause exhaustion of beta cells and worsen diabetes (*241*). Alternatively, abnormal immune-inflammatory reactions (*241*), endothelial dysfunction (*240*), and other pathophysiological factors like dysautonomia and mood disorders more or less contribute to COVID-related insulin resistance and beta cell dysfunction (*242*). Nonetheless, T2D certainly appears to "connive" with SARS-CoV-2 to induce a worse clinical outcome. This contention is supported by a study in India, which indicated that T2D patients diagnosed during the COVID-19 pandemic had more severe glycemia than those diagnosed before the pandemic (*154*). What should be kept in mind is that impaired beta cell function and insulin resistance cannot recover as soon as the body recovers from acute infection. Those effects might be persistent (*241*) and even lifelong sequelae of COVID-19.

7.5.1. Diabetes in LC

Box 3. Particular concerns regarding diabetes in LC
- The prognosis for COVID-19-related hyperglycemia or diabetes
- Whether the incidence of diabetes remains higher in patients with LC
- What is the difference between T2D patients with and without a history of SARS-CoV-2 infection during a long-term follow-up?

Several particular concerns regarding diabetes in LC are listed in Box 3.

The available evidence is inadequate, but several clinical studies have helped to address these concerns. Montefusco *et al*. found that 46% of patients with COVID-19-related hyperglycemia were still hyperglycemic whereas 27% were normoglycemic (*241*). Even in those normoglycemic patients, abnormal glycometabolic control and a cytokine profile, along with insulin resistance, were still observed. Glycemic abnormalities can persist at least two months after recovery from acute infection. However, a study in Italy obtained the opposite results. The study observed 589 patients with COVID-19; 19.6% had preexisting T2D, 6.7% had new-onset T2D, 43.7% had hyperglycemia not in the diabetes range, and 30% were normoglycemic (*243*). After recovery from acute infection, the incidence of dysglycemia returned to its level pre-admission. The study therefore ruled out COVID-19-related disruption of glycometabolic control as a long-term sequela. Accordingly, more rigorous trials need to be conducted to observe the long-term prognosis for COVID-19-related hyperglycemia or diabetes.

Xie and Al-Aly conducted a cohort study to observe the risks and burdens of incident diabetes in people with LC, and they found that patients with COVID-19 had a higher risk and excess burden of incident T2D and antihyperglycemic agent use during a 12-month follow-up (*11*). Another large cohort study investigating the long-term effects of COVID-19 on cardiometabolic outcomes found that the net incidence of T2D increased in the first four weeks after COVID-19 and remained high for 5-12 weeks but did not increase for 13-52 weeks. Hence, the incidence of T2D increased for at least 12 weeks after COVID-19 (*244*). These findings indicate that patients with COVID-19 had an increased risk of developing T2D during a long-term follow-up.

Fernández-de-Las-Peñas *et al*. conducted a case-control study to compare LC sequelae between COVID-19 patients with and without T2D and they found that the most common LC symptoms were fatigue, dyspnea on exertion, and pain (*245*). There were no differences in LC symptoms and reduction of ADL between COVID-19 patients with and without T2D. They wondered if T2D might be not a risk factor for developing LC symptoms. In another case-control study, Mittal *et al*. found that COVID-19 patients with T2D had more fatigue than those without T2D during an average 92-day follow-up (*246*).

Altogether, the heterogeneity of the limited available literature cannot provide compelling evidence to address the concerns in Box 3. The effects of diabetes in LC warrants further investigation because it may greatly impact the QOL of and prognosis for these patients.

7.5.2. Prospects for the future

In light of the limitations of the available studies and based on the authors' clinical experience, there are several recommendations to improve the management, diagnosis, and treatment of LC-related diabetes.

Management: T2D is a lifestyle-related disease, which means that it is associated with many unhealthy lifestyles. Indeed, T2D and COVID-19 share many common risk factors. Management of risk factors such as blood pressure, dyslipidemia and glucose, along with lifestyle improvements, can benefit T2D as well as LC. There is robust evidence regarding the beneficial effects of multifactorial-risk-factor-interventions on T2D (*247*). A future study should focus on verification of these multifactorial-risk-factor-interventions in LC, and particularly for controversial interventions such as exercise.

Diagnosis: Standardization of the diagnostic protocol

for T2D in the context of LC, including laboratory tests and timing, is important. Other than simple fasting blood glucose, more specific examinations such as oral glucose tolerance tests, multiple point insulin, C-peptides, pancreatic and hepatic ectopic fat, body composition, and a hyperglycemic clamp test should be considered and conducted (*248*). This will help to explore the association between LC and T2D (insulin resistance). Moreover, attention should be paid to the timing of the examination. Thus far, there is no robust evidence on the optimal timing for a T2D examination. In light of the authors' experience, three months after recovery from acute COVID-19 might be a good time given glycosylated hemoglobin levels and exclusion of hyperglycemia caused by steroids or stress. This topic needs to be investigated further.

Treatment: Several studies evaluated the efficacy/safety of mainstream anti-diabetic agents for treatment of patients with T2D and COVID-19 (*249-252*). One of those studies reported that dipeptidyl peptidase-4 inhibitor (DPP-4i) was related to increased mortality (*249*) and two reported adverse reactions to insulin (*249,250*). No study reported adverse reactions to glucagon-like peptide-1 receptor agonists (GLP1RA), sodium-glucose cotransporter-2 inhibitors (SGLT2i), or metformin. Moreover, GLP1RA, followed by SGLT2i and metformin, exhibited the best protective effects against death (*250*). GLP1RA and SGLT2i are also reported to help reduce body weight, facilitate glycemic control, reduce cardiovascular events, and improve renal outcomes (*253*). Administration of GLP1RA and SGLT2i is also associated with a better prognosis for COVID-19. Accordingly, GLP1RA and SGLT2i are most likely to be recommended for treating diabetes in LC, and this topic requires further verification by rigorously designed RCTs.

8. The reproductive system

SARS-CoV-2 infection may cause long-term sequelae in the reproductive systems of both males and females. ACE2 is widely expressed in the testes (*254*) and ovarian and endometrial tissue (*255*), hence unsurprisingly, SARS-CoV-2 infection can involve the male and female reproductive systems. Impairment of the HPA axis in the context of COVID-19 (described in the neurological section) also contributes to disorders in the reproductive system due to the dysfunction of the neuroendocrine system. Moreover, the abnormal immune-inflammation-related changes due to COVID-19, such as dysautonomia (*100*), ME/CFS (*7,256*), and mood disorders (*257,258*), may indirectly affect the reproductive system, thereby inducing many specific and non-specific symptoms. However, available studies regarding the long-term effects of SARS-CoV-2 infection on the reproductive system are quite limited thus far.

8.1. Involvement of the male reproductive system

Erectile dysfunction (ED) is the most common reported reproductive symptom in male patients with COVID-19. A study in Italy reported that the prevalence of ED was 28% in patients with COVID-19, which was significantly higher than that in individuals without COVID-19 (9.33%) (*259*). In an observational study in Thailand, Harirugsakul *et al*. reported that the prevalence of COVID-19-related ED was 64.7%; most ED was milt in severity (*257*). ED in these patients was associated with mental disorders. ED is affected by many factors. In addition to pathological factors, it is also influenced by other factors such as culture, education, religion, and attitude towards sex. This is understandable given the great heterogeneity among different countries. However, what is clear is that the prevalence of ED is higher in patients with COVID-19. Kresch *et al*. noted the prolonged presence of SARS-CoV-2 in penile tissue, which can induce vascular dysfunction or endothelial dysfunction and obstruct the blood supply to penile tissues thereby causing ED (*260*). In addition, direct testicular injury and COVID-19-related mood disorders (such as depression and anxiety due to SARS-CoV-2 infection) may also contribute to the development of ED (*261*).

Maleki *et al*. noted problems with sperm count, semen volume, motility, sperm morphology and sperm concentration in patients with LC and found that they were associated with increased cytokines and the presence of caspase 8, caspase 9 and caspase 3 in seminal fluid (*262*). These findings confirmed testicular injury in LC. Due to the abundance of ACE2 in the testes, testicular injury might be induced by SARS-CoV-2 infection-related oxidative stress and inflammation and further cause abnormal sperm motility, DNA breakage, and male infertility (*263*). Moreover, invasion by SARS-CoV-2 might cause orchitis and epididymitis of the testis (*264*). However, this hypothesis is controversial since no inflammatory markers associated with predicting testicular pain or orchitis were found in patients with COVID-19 (*265*). In addition, more cases of testicular torsion were reported during the COVID-19 pandemic, and those mechanisms remain unclear (*266*).

8.2. Involvement of the female reproductive system

ACE2 is well distributed in ovarian and endometrial tissue (*267*). A plausible hypothesis is that SARS-CoV-2 infection could greatly influence the production of ovarian hormones and endometrial response during menses (*255*). Ding *et al.* reported that ovarian damage, including diminished ovarian reserve and a reproductive endocrine disorder, were observed in female patients with COVID-19 (*268*). Menstrual changes are commonly reported during the COVID-19 pandemic. Li *et al*. found that in 237 female patients with COVID-19, frequent

menstrual dysfunctions were changes in menstrual volume (25%), changes in the menstrual cycle (28%), decreased volume (20%), and a prolonged cycle (19%). Concentrations of sex hormones and ovarian reserve did not change. These changes might be associated with systemic dysfunction rather than specific to the female reproductive system. The endocrine and ovarian systems seem not to be seriously affected by SARS-CoV-2 infection (*269*). Takmaz *et al*. found that the prevalence of a menstrual cycle irregularity increased due to COVID-19 pandemic-induced depression, anxiety, and stress in healthy female caregivers (*258*). In a large-scale retrospective cohort study involving 18,076 smartphone app users, Nguyen *et al*. found that the COVID-19 pandemic did not affect population-level changes in ovulation and menstruation in the women who participated (*270*). The results of these studies seem to imply that menstrual changes in COVID-19 are more associated with secondary changes in COVID-19 (*e.g.*, mood disorders) rather than the direct impact of SARS-CoV-2 infection. Many researchers have argued that the problem of menstrual changes in COVID-19 seems to be "neglected" or "underestimated" so that long-term sequelae involving the female reproductive system are not well investigated (*271-273*). Medina-Perucha *et al*. conducted a cross-sectional online survey study investigating menstrual changes in LC and found that patients with LC had a higher risk of developing menstrual changes in comparison to those who did not have COVID-19 or those who had COVID-19 but not LC (*273*).

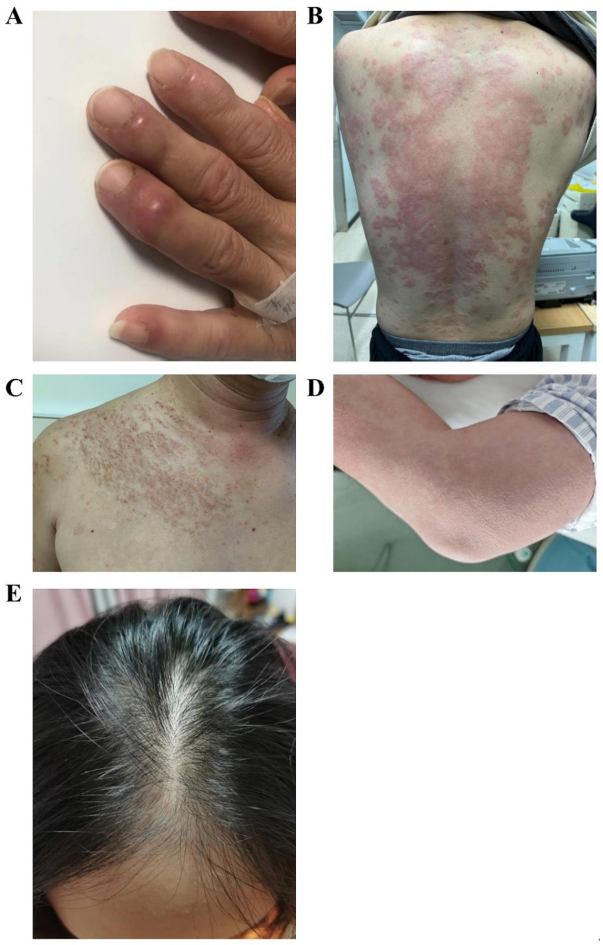

Figure 3. Common dermatologic manifestations of long COVID. **A**, pernio-like lesions; **B**, urticaria; **C**, papulosquamous eruptions; **D**, morbilliform-like eruptions; **E**, hair loss.

8.3. Paths for future exploration

In light of the available literature, the long-term effects of COVID-19 on the reproductive system, either male or female, remain uncertain. Other than the possible direct influence of viral invasion, interactions between the reproductive organs and other systems might be important, and particularly bidirectional interaction with mood disorders (*4*). This means that dysfunction of the reproductive system might adversely affect other systems and increase their dysfunction. Davis *et al*. reported that menstruation and the week before menstruation might play an inciting role in the relapse of LC symptoms (*4*). Hence, reproductive involvement in the context of COVID-19, and especially long-term effects, cannot be ignored. Aspects of reproductive involvement should be included in future follow-up studies.

9. Dermatologic involvement

Many dermatologic manifestations are reported in patients with COVID-19. Of those, acral chilblain-like or pernio-like lesions ("COVID toes," Figure 3A) are reportedly the most common dermatologic symptoms in acute COVID-19. The other commonly reported skin findings include morbilliform-like eruptions, papulosquamous eruptions, urticaria, and livedo reticularis (Figure 3). Most of these lesions spontaneously resolve within two weeks after onset (*20*). However, some authors reported persistent lesions such as chilblain lesions (*274*), pernio, and papulosquamous eruptions (*275*) that might fall under dermatologic sequelae of LC. In a meta-analysis, Mirza *et al*. found that the prevalence of chilblains/pernio-like lesions was 51.5%, that of an erythematous maculopapular rash was 13.3%, and that of viral exanthem was 7.7%. Latency from initiation of respiratory symptoms to dermatologic manifestations was an average of 1.5 days in children and 7.9 days in adults, ranging from -3-38 days. Approximately 10% of patients have only dermatologic manifestations, and 5.3-13.3% of patients initially developed cutaneous symptoms (*276*). An important study observed dermatologic involvement in patients with COVID-19 and found that the median duration of skin findings was 13 days (IQR 7-21) for all patients, and seven days (IQR 5-14) for patients with laboratory-confirmed COVID-19. Chilblains/pernio-like lesions persisted a median of 15 days (IQR 10-30) in patients with suspected COVID-19 and 12 days

(IQR 7-23) in confirmed cases. Morbilliform persisted a median of 7 days (IQR 5-10) and urticarial eruptions persisted a median of 4 days (IQR 2-10) in patients with confirmed COVID-19; the longest duration was 28 days. Papulosquamous eruptions persisted 20 days (IQR 14-28) in confirmed cases; one patient had a confirmed "long-hauler" eruption persisting 70 days. Seven of 103 patients (6.8%) with pernio were long-haulers whose pernio persisted over 60 days (*275*). This observational study drew a useful picture of common COVID-19-related skin findings. The mechanisms of these skin findings are not clear. Tammaro *et al*. hypothesized that these dermatologic manifestations in LC might be induced by prolonged abnormal immune-inflammatory reactions, along with psychological stress, and this topic requires further investigation (*274*). Nailfold capillaroscopy has therefore been recommended for identification of potential microcirculatory morphological alterations in these patients (*20*).

In addition to the aforementioned skin findings, hair loss was reported in approximately 20-25% of patients 3-6 months after recovery from COVID-19 (*6,28,277*). This is also regarded as an LC sequela (Figure 3E). However, a study in South Korean involving 226,737 patients with COVID-19 found no evidence of an association between COVID-19 and the development of alopecia areata (*278*). Lopez-Leon *et al*. believe that hair loss after COVID-19 might be regarded as a form of telogen effluvium that results from the transition of premature follicles from the anagen phase to the telogen phase due to systemic stress and/or infection (*6*).

However, due to the complex nature of SARS-CoV-2 infection, there is no compelling evidence whether these dermatologic manifestations are caused by or related to COVID-19. The underlying causal relationship should be determined.

10. Concluding Remarks

The current study comprehensively reviewed the sequelae of LC in main organ systems on the basis of the latest available literature prior to February 2023. This work has attempted to provide updated information to all COVID-19 researchers. The take-home messages should help to improve the insights into and understanding of the long-term effects of COVID-19. Based on the aforementioned knowledge and limitations of the available studies so far, several considerations/suggestions can be offered for future investigation:

i) Over three years have passed since the COVID-19 pandemic started. A study with a longer follow-up (over two years) would help to better understand LC sequelae. That said, the possible inadequacy of medical examinations during the pandemic might limit our understanding of the effects of SARS-CoV-2 infection on each organ as well as related pathophysiological states. This might be partly compensated for with a well-designed follow-up. Indeed, we are now conducting a two-year follow-up investigating the risk factors for COVID-19-related pulmonary fibrosis. More studies with a longer follow-up should be conducted.

ii) Most of the included studies did not report the variant infecting patients (Table 1, onlin data: *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=140*). Due to the heterogeneous nature of the different variants (epidemiological and clinical features), future studies should clearly report the variant involved. In addition, rigorous comparison of LC sequelae by variant might be interesting.

iii) Findings have revealed that many LC sequelae developed independently of the initial severity of COVID-19. This means many LC sequelae can develop in mild and even asymptomatic patients. Moreover, some LC sequelae, such as dysfunction of the kidneys and liver, potentially develop into severe illness and even life-threatening syndromes. However, such conditions often lack specific symptoms and might be ignored in the early stage. We therefore strongly recommend that patients with a history of SARS-CoV-2 infection, no matter the severity of the initial infection (including asymptomatic patients), should undergo a periodic physical examination to identify possible hepatic and/or renal damage.

iv) An abnormal immune-inflammation reaction and a mood disorder (anxiety, depression, and stress) might be common mechanisms involved in the dysfunction of organs throughout the body (Figure 2). Hence, anti-inflammatory agents and antivirals and treatments for mood disorders should be developed and verified in future clinical trials, and particularly their long-term effects on LC sequelae and adverse reactions they might cause.

v) Interactions of symptoms might be bidirectional or even multidirectional (Figure 2). A typical example is the interaction between the ED and a mood disorder. ED might develop from depression, while conversely ED can also lead to depression. The interaction between ED and depression may constitute a vicious cycle and finally lead to a worse outcome. Clinicians should investigate the potential formation of a vicious cycle and attempt to break this vicious cycle to achieve a better clinical outcome. Accordingly, future studies should be conducted with full consideration of the interaction/crosstalk among organs and symptoms (Figure 2).

vi) The latest computer technology, such as artificial intelligence, big data, and machine learning, should be used in future LC studies.

Taken together, COVID-19 is a complicated disease involving the whole body. We propose establishing mechanisms for multidisciplinary collaboration to fight against LC. These should include not only the medical disciplines but also a large spectrum of disciplines including chemistry, engineering, materials science, and computer science in order to combat LC.

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