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Review article

LONG COVID-19 SYNDROME: AN OVERVIEW

LONG COVID-19 SINDROM

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Abstract

The Long COVID-19 syndrome has emerged as global epidemic, affecting individuals after an acute infection caused by the Severe acute respiratory syndrome coronavirus 2, impacting multiple organs, including the heart. The most common symptoms encompass fatigue and shortness of breath, which could persist for months after an acute COVID-19 infection. Numerous studies have researched the pathophysiology of Long COVID-19 syndrome, suggesting that local tissue damage and hyperinflation could be employed as possible mechanisms of Long COVID-19 syndrome. Many blood biomarkers (blood urea nitrogen, D-dimer, lymphopenia, troponin-1, interleukin-6, and CRP) and clinical risk factors (CRP female sex, a history of psychiatric disorders, and the presence of more than five symptoms during the first week of an acute illness) are shown to be associated with the development of Long COVID-19 syndrome. Currently, the evidence-based specific pharmacological treatments for the Long COVID-19 syndrome are lacking. Several studies have shown an association between antiviral drugs (such as nirmatrelvir, ensitrelvir, and molnupiravir) and vaccination against COVID-19 with a reduced risk of developing Long COVID-19 syndrome. This narrative review discusses the possible pathophysiology, risk factors, and treatments for Long COVID-19 syndrome with particular reference to the cardiovascular system.

Keywords:
COVID-19,
Long COVID,
viral infection,
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pandemic

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Sažetak

Long COVID-19 sindrom može nastati nakon preležane akutne infekcije SARS-CoV-2 virusom i može trajati mesecima. Najčešći simptomi uključuju malaksalost i nedostatak vazduha. Postoje različiti predloženi mehanizmi koji su dogovorni za nastanak Long COVID-19 sindroma kao što je produženo zapaljenje i oštećenje tkiva različitih organa, ali su neophodna dalja istraživanja da bi se ovo potvrdilo. Takođe, identifikovani su različiti biomarkeri (na primer urea, D-dimer, lymphopenia, troponin-1, interleukin-6, and C-reaktivni protein) kao i klinički faktori koji uključuju ženski pol, ranije prisustvo psihičkih poremećaja ili prisustvo 6 ili više simptoma u akutnoj fazi bolesti, koji su povezani sa povećanim rizikom od nastanka Long COVID-19 sindroma. Trenutno ne postoje specifični farmakološki tretmani za Long COVID-19 utemeljeni na dokazima. Neka istraživanja su pokazala povezanost između antivirusnih lekova (poput nirmatrelvira, ensitrelvira i molnupiravira) i vakcinacije protiv COVID-19 sa smanjenim rizikom od razvoja Long COVID-19 sindroma. Cilj ovog preglednog rada je diskusija o mogućoj patofiziologiji, faktorima rizika i terapiji za sindrom dugotrajnog COVID-19, sa posebnim osvrtom na kardiovaskularni sistem.

Ključne reči:
COVID-19,
Long COVID,
virusna infekcija,
SARS-CoV-2,
Korona virus,
pandemija

Introduction

Coronavirus disease 2019 (COVID-19) is an infection caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded positive-sense RNA virus infecting a range of host tissues and causing asymptomatic or symptomatic COVID-19 disease (1). Since the first registered case in December 2019 in Wuhan, China, over 770 million cases and over 6.9 million deaths worldwide have been documented until present (1,2).

Although COVID-19 infection often manifests as either asymptomatic or with mild symptoms, around 7 - 10% of patients with acute COVID-19 will attain the Long COVID-19 syndrome (also known as Post-COVID 19) (3,4). One study showed that as many as 76% of patients had Long COVID syndrome symptoms that included fatigue, hair loss and poor memory (5). The World Health Organization characterized the Long COVID-19 syndrome by symptoms such as fatigue, shortness of breath, cognitive dysfunction, etc, that usually occur three months from the onset of acute COVID-19, last for at least two months and cannot be explained by an alternative diagnosis (6). Nevertheless, the definition of the Long COVID-19 syndrome varies in published literature (see **table 1** and **figure 1**).

In this narrative review, we aimed to discuss the possible pathophysiology, risk factors, and treatments for the Long COVID-19 syndrome.

Pathophysiology of the Long COVID-19 syndrome

In general, there is a considerable gap in the understanding of the mechanisms underlying post-acute infection syndromes. There is a complex multi-factorial matrix linking acute SARS-CoV-2 infection with the Long COVID-19 syndrome. Proposed potential mechanisms underlying the Long COVID-19 syndrome include SARS-CoV-2 persistence and persistent activation of the immune system including various autoimmune reactions, the formation and persistence of microclots in various capillary beds, persistent central nervous dysfunction mediated by the SARS-CoV-2-induced inflammatory glial reaction, persistent vascular inflammation, residual organ damage caused by abnormal clotting and/or inflammation during acute COVID-19, reactivation of latent herpesviruses, persistent metabolic dysfunction owing to various immunopathological processes resulting in altered lipid metabolism and hypertriglyceridemia, liver disorders and/or altered glucose metabolism, gut microbiota alterations, amyloidogenesis, and so forth (12-16).

Table 1. Definitions of the Long COVID-19 syndrome in published literature.

WHO definition: Symptoms occurring three months from the onset of acute COVID-19, and lasting for at least two months provided that the symptoms cannot be explained by an alternative diagnosis (6)
Symptoms lasting for > 2 months (7)
Symptoms lasting for > 4 weeks after the initial infection or diagnosis (8)
Symptoms lasting for > 4 weeks after the first symptom onset (9)
Symptoms lasting for 5 - 12 weeks (Acute post-COVID symptoms) (10)
Symptoms lasting for 12 - 24 weeks (Long post-COVID symptoms) (10)
Symptoms lasting for > 24 weeks (Persistent post-COVID symptoms) (10)
Symptoms lasting for > 3 months from the first symptom onset (Post-COVID-19 syndrome) (11)

WHO - World Health Organisation; COVID-19 - Coronavirus disease 2019.

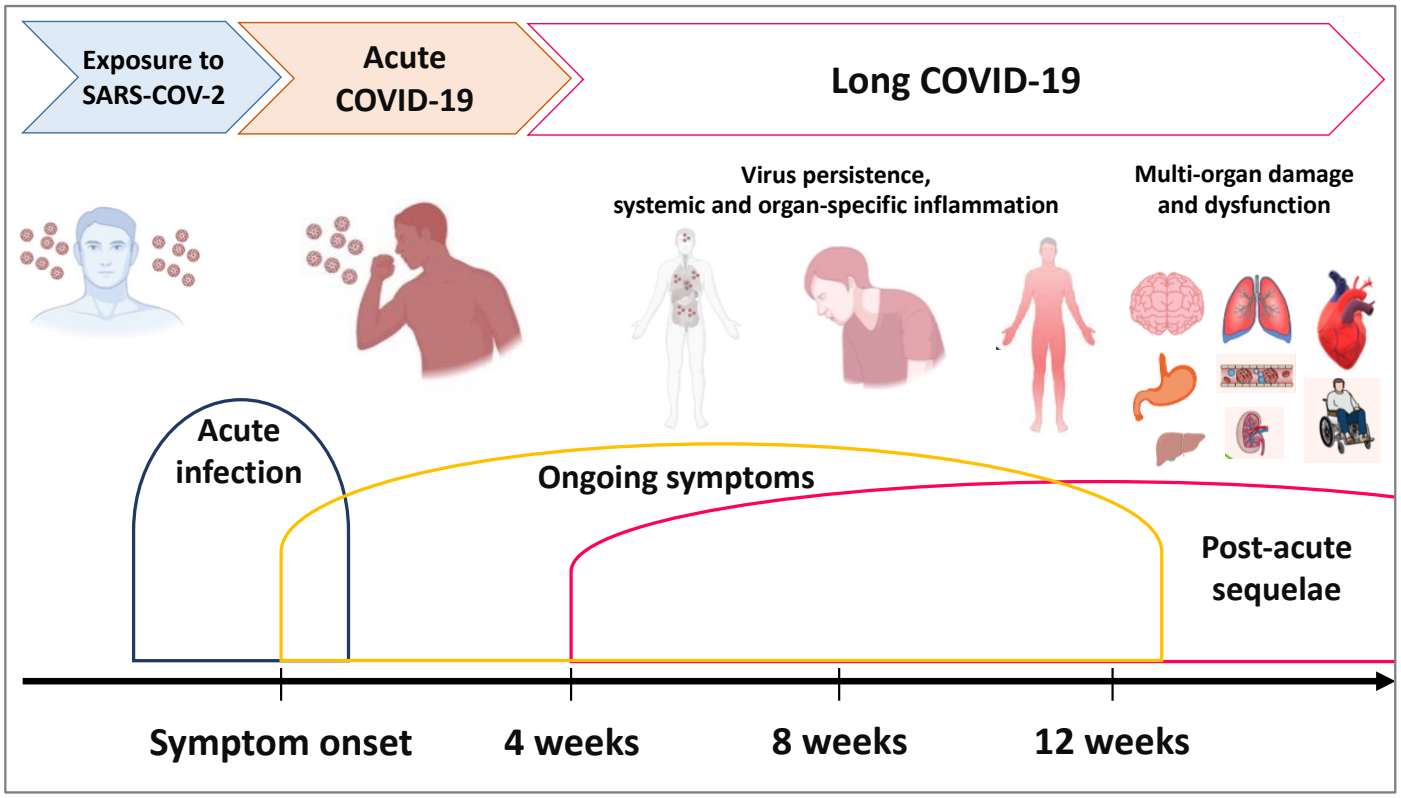

Figure 1. Long COVID-19 syndrome timeframe. SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2; COVID-19 - Coronavirus disease 2019.

The persistence of SARS-CoV-2, persistent activation of the immune system and autoimmune reactions

In certain individuals, the viral reservoir could persist for a prolonged time period, possibly contributing to development of the Long COVID-19 syndrome (17). Indeed, the presence of the whole virus, SARS-CoV-2 antigens and/or the viral RNA has been documented in various tissues and organs including the heart, brain, lungs, kidneys, adrenal glands, spleen, gut and lymph nodes (18), causing a direct damage of the cell, regional inflammation, exaggerated immune response and/or autoimmune reaction(s) (16). The immune response of individuals affected by the SARS-CoV-2 may be altered by a disturbance of the type I interferon pathway in the infected host cells, thus favouring viral persistence and SARS-CoV-2 variants production (19). While the SARS-CoV-2 may initially overstimulate T lymphocytes, thus causing a cytokine storm, such an exaggerated stimulation may ultimately exhaust T cells and attenuate the capacity for the clearance of SARS-CoV-2, which facilitates viral persistence (16, 19, 20).

The presence of autoantibodies is more common in patients with the Long COVID-19 syndrome than the general population, however, it is still unclear whether the autoimmune response to intracellular and non-protein autoantigens play a role in the development of the Long COVID-19 syndrome (16).

Amyloidogenesis and microclots

The SARS-CoV-2 spike protein has been shown to contain certain amyloidal sequences, and it has been hypothesized that its endoproteolytic cleavage would result in the formation of amyloid and its systemic deposition with a range of clinical manifestations (16, 21, 22). More specifically, amyloid fibrils generated by the cleavage of the SARS-CoV-2 spike protein would serve as a heterologous seed stimulating the accumulation of endogenous proteins and reactive thromboinflammation, ultimately resulting in the respective tissue degeneration and organ dysfunction (22).

Moreover, the presence and persistence of fibrin amyloid microclots in multiple capillary beds has been increasingly implicated in the pathogenesis of the Long COVID-19 syndrome (16). The occlusion of the microcirculation may result in tissue damage and ultimate clinically overt dysfunction of the respective organ(s). Additionally, microthrombi related to the SARS-CoV-2 infection have been shown to be resistant to fibrinolysis (16).

Central and autonomic nervous system dysfunction

By entering the axons or lymphatic system, SARS-CoV-2 may induce an inflammatory reaction of the glial tissue sometimes also accompanied with a central nervous system-targeted autoimmune reaction, which could underlie the 'general' central nervous system-related symptoms including abnormal tiredness, headache, and signs of cognitive impairment such as the lack of concentration, brain fog and/or the loss of memory (23).

Owing to a high density of the angiotensin converting enzyme 2 (ACE2) receptors in the brainstem compared with other regions of the brain, SARS-CoV-2 may enter the brainstem directly, via the ACE2 surface expression,

with consequent neuroinflammation and vascular damage-induced micro-thrombosis, ultimately resulting in altered function of the respiratory and cardiovascular control centres (24). Damage as such could underlie the symptoms of advanced cognitive and cardiorespiratory dysfunction (25).

Furthermore, the SARS-CoV-2-related amyloidogenesis and reactive pathological thromboinflammation may cause cerebral amyloid angiopathy and/or affect the autonomic nervous system, causing a variety of symptoms such as palpitations, nausea, blurred vision, lightheadedness, headache, tiredness, cognitive impairment and/or orthostatic intolerance, postural orthostatic tachycardia syndrome with or without syncope, all resulting from the COVID-19 infection-related dysfunction of autonomic nervous system (22).

Persistent vascular inflammation and residual tissue/organ damage

The SARS-CoV-2-related alterations of the coagulation, fibrinolytic and complement systems, in combination with endothelial cell damage and dysfunction, and impaired immune response, promote the onset of an acute inflammatory reaction, excessive thrombin production, inhibition of fibrinolysis and continuous activation of the complement pathways (26). These pathophysiological processes ultimately result in prolonged dysfunction of the microvasculature with increased risk of systemic micro-thrombosis which affects multiple organs, especially those with a high capillary density such as lungs, for example (27). Indeed, post-COVID-19 pulmonary fibrosis has been observed in more than a third of patients recovered from an acute SARS-CoV-2 infection (28), sometimes causing a considerable permanent pulmonary dysfunction.

An acute inflammatory reaction during SARS-CoV-2 infection may eventually result in myocardial injury, myocarditis, and thromboembolic events in the venous and/or arterial circulation (29). However, the association of the Long COVID-19 syndrome and development of a cardiovascular disease has not been fully elucidated yet. Various mechanisms including a prolonged damaging and cardiomyocyte death directly caused by the SARS-CoV-2 invasion, endothelial cell infection and resulting endotheliallitis, transcriptional changes in various types of cardiac cells, complement-mediated coagulopathy and microangiopathy, autonomic nervous system dysfunction, elevated pro-inflammatory cytokines and a transforming growth factor beta-mediated fibrosis in the cardiac tissue have all been proposed as underlying mechanisms of the development of cardiovascular disease in the Long COVID-19 syndrome setting (16, 26, 29-31). These pathophysiological mechanisms ultimately result in progressive fibrosis of the myocardium, compromised compliance and increased myocardial stiffness, decreased myocardial perfusion and increased risk of the initiation and maintenance of various cardiac arrhythmias (16).

Disorders of the gut microbiota

Persistence of the SARS-CoV-2 in the gastrointestinal tract, owing to the high expression of the ACE2 receptor (which is the binding receptor for SARS-CoV-2), could be responsible for gastrointestinal symptoms in the Long COVID-19 syndrome (32, 33). In addition, it has been proposed that a substantial rise in pathogenic bacteria with concomitant depletion of protective gut microbiota during the SARS-CoV-2 infection facilitates sustained gastrointestinal inflammation, thus postponing the recovery and promoting the development of Long COVID-19 syndrome (34). Increasing evidence suggests that the disruption of the gastrointestinal mucosal barrier may occur in the Long COVID-19 syndrome, resulting in translocation of microbiota into the systemic circulation (as an example, fungal translocation has been recently documented in 74% of patients with the Long COVID-19 syndrome) (16, 35).

Risk factors for Long -COVID-19 syndrome

Blood biomarkers

Numerous studies have demonstrated that certain blood biomarkers, such as blood urea nitrogen, D-dimer, lymphopenia, troponin-1, interleukin-6, and CRP were associated with sustained organ dysfunction including the lungs, heart, liver, and kidney, for an extended period of time after active COVID-19 infection (36). These blood biomarkers may serve as potential biomarkers for development of the Long COVID-19 syndrome (37, 38). Conversely, other studies reported contrasting findings, where no significant correlation has been observed between the investigated blood biomarkers (such as CRP, D-dimer, IL-6) and the occurrence of Long COVID-19 syndrome. These conflicting findings could result from the differences in respective study methodology and/or the involvement of multiple pathophysiology pathways in development of the Long COVID-19 syndrome (39, 40).

Clinical risk factors

Clinical risk factors implicated in the onset of Long COVID-19 syndrome include female sex, a history of psychiatric disorders, and the presence of more than five symptoms during the first week of COVID-19 infection (such as, for example, difficulty in focusing attention, memory loss, anosmia, ageusia, confusion, dyspnoea, chest pain, and pain with deep breaths) (39, 41).

In terms of the severity of acute COVID-19 infections, published research yielded conflicting results, with some studies indicating an association of the severity of acute COVID-19 infection and subsequent development of the Long COVID-19 syndrome, while other studies have not found this correlation (39, 42). In addition, available evidence shows that COVID-19 infection does not confer prolonged protection from reinfections with the SARS-CoV-2, and emerging evidence suggests that SARS-CoV-2 reinfection contributes to the development of the

higher severity of or de novo Long COVID-19 syndrome (43).

Clinical presentation of the Long COVID-19 syndrome

Despite the fact that COVID-19 is characterized as a respiratory infection, the illness may impact multiple organs. The variety of the Long COVID-19 syndrome clinical phenotypes is shown in **figure 2**. Patients affected with the Long COVID-19 syndrome may experience a wide range of symptoms with variable symptom intensity. Organ-specific symptoms in patients with the Long COVID-19 syndrome are shown in **figure 3**.

Cardiovascular complications of the Long COVID-19 syndrome

A study of over 150 000 individuals with documented COVID-19 infection, assessing cardiovascular complications one year after acute COVID-19 infection, showed that patients who have been afflicted with an acute COVID-19 infection are at increased risk of stroke, pulmonary embolism, the onset of atrial fibrillation and atrial flutter, ventricular arrhythmias, as well as pericarditis, myocarditis, heart failure, and acute coronary syndrome - **figure 4**. This elevated risk was observed regardless of age, sex, presence of comorbidities, or severity of acute COVID-19 infection (44). In another study involving patients with a history of prior COVID-19 infection, the use of cardiac magnetic resonance imaging (MRI) showed cardiac abnormalities (such as left or right ventricular dysfunction/dilatation and/or abnormal T1 mapping) in 58% of patients with Long COVID-19 syndrome at 12 months after an acute COVID-19 infection. Notably, in the same study, biomarkers such as troponin I and B-type natriuretic peptide were not predictors of these MRI findings (45). Noteworthy, the MRI abnormalities identified in patients with COVID-19 infection were found not to be related to the severity of the acute COVID-19 infection, pre-existing comorbidities, or the presence of symptoms (46).

The potential mechanisms underlying the occurrence of cardiovascular complications after an acute COVID-19 infection include direct viral invasion of cardiomyocytes, endothelial dysfunction, autonomic dysfunction, elevated levels of pro-inflammatory mediators leading to the development of tissue fibrosis, and scaring (26, 30, 47). In addition, the high expression of angiotensin-converting enzyme 2 receptors on cardiomyocytes serves as a pathway for the entry of SARS-CoV-2 into these cells, inducing a direct cardiotoxic effects (48). In patients with ischaemic cardiovascular complications, it has been shown that the systemic inflammatory response may cause coronary plaque rupture (49). Moreover, in patients experiencing severe COVID-19 infection, an imbalance between oxygen supply to the heart, due to acute respiratory distress syndrome, and increased myocardial oxygen demand, due to cytokine storm, could lead to myocardial injury, which could be clinically manifested after an acute COVID-19 infection (50). On the other hand, the mechanisms of thromboembolic events in Long COVID-19 syndrome could be attributed to the endothelial dysfunction

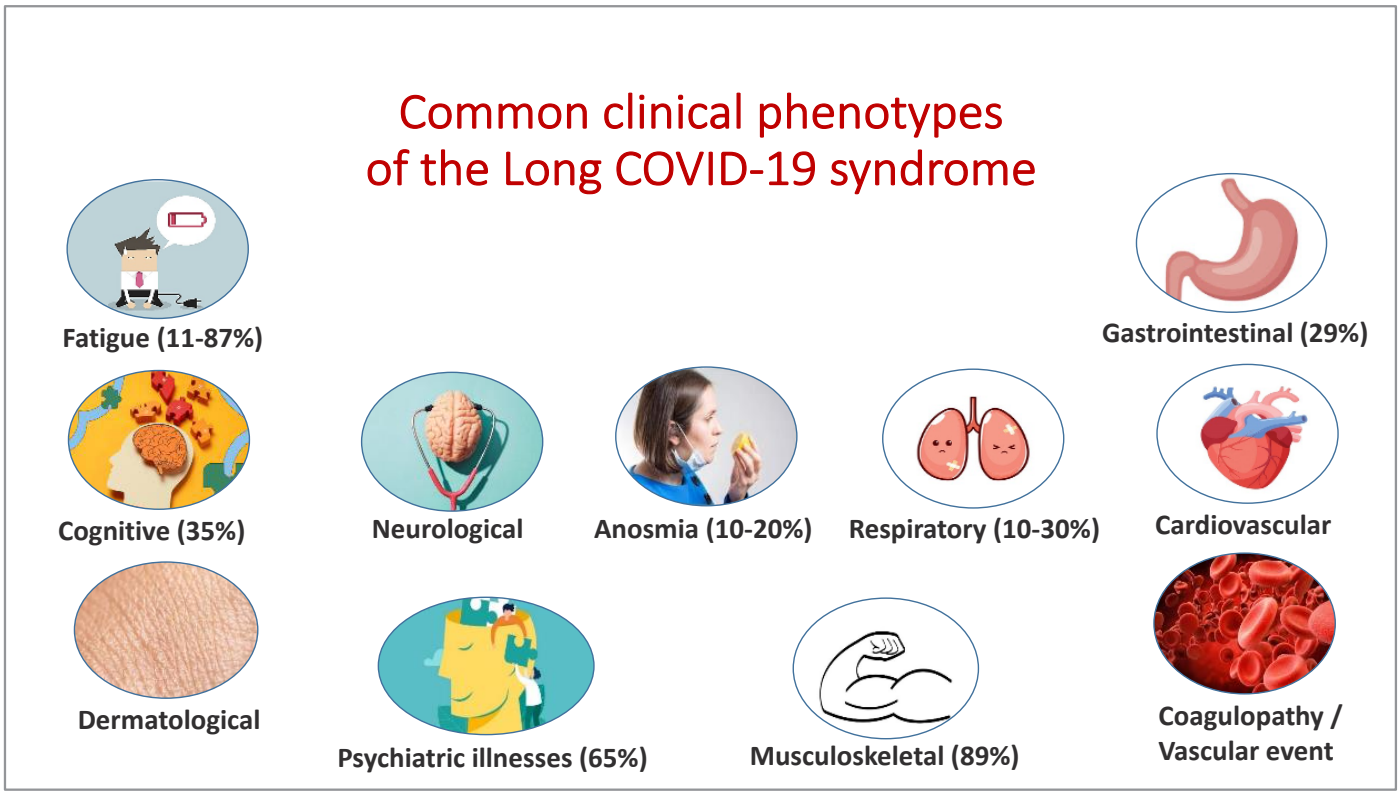

Figure 2. Common clinical phenotypes of the Long COVID-19 syndrome (the prevalence of specific phenotype is shown in brackets, where reported) (16). COVID-19 - Coronavirus disease 2019.

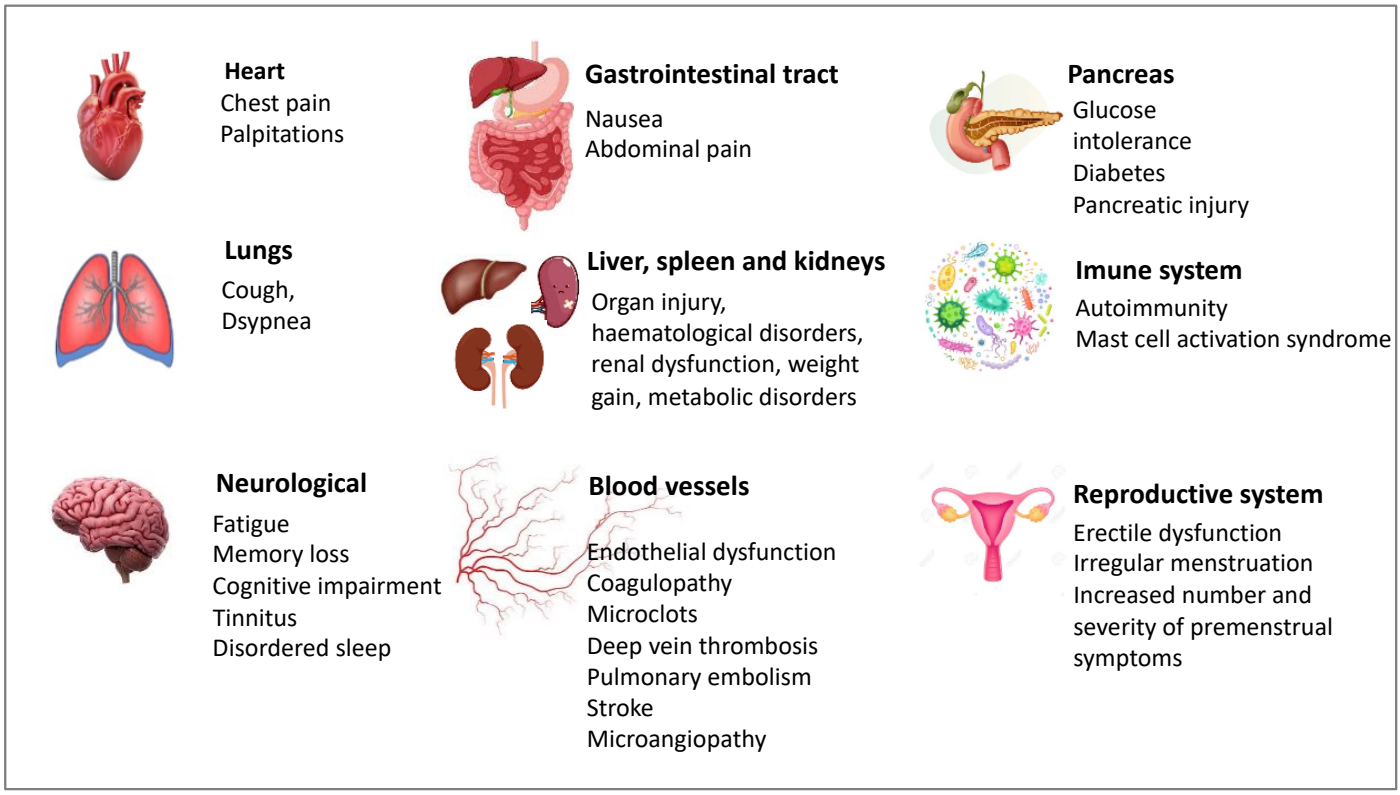

Figure 3. Organ-specific symptoms in patients with the Long COVID-19 syndrome.

resulting from SARS-CoV-2 infection, which is the consequence of inflammation in the walls of blood vessels, vasoconstriction, as well as the pro-inflammatory and pro-thrombotic effects of angiotensin II (26, 51). Overall, myocardial injury during the acute phase of COVID-19 infection is identified as an independent risk factor for the severity and mortality of COVID-19 infection (52).

Treatment of the Long COVID-19 syndrome

Currently, there are no evidence-based specific pharmacological treatments for the Long COVID-19 syndrome. Consequently, the therapy for cardiovascular complications primarily consists of cardiac-specific and symptomatic treatment. Specifically, the management of recent or incident thromboembolic events in COVID-19 patients should not be significantly distinct from the usual management of these major adverse cardiovascular events (53).

Physical exercise is important in patients with cardiovascular diseases and is an integral part of a post-cardiovascular event rehabilitation program aimed at improving mortality, cardiopulmonary fitness, and quality of life (54, 55). Emerging evidence suggests that personalized, multi-disciplinary supervised exercise programmes (encompassing activities such as breathing and physical exercises, along with psychological interventions) could be effective in the mitigation of long-term COVID-19 symptoms (56).

Prevention of the Long -COVID-19 syndrome

Several studies have shown an association between antiviral drugs and a reduced risk of development of Long COVID-19 syndrome. One cohort study involving over 180 000 patients with COVID-19 infection and at least one risk factor for progression to severe COVID-19 illness, treatment with nirmatrelvir during the acute phase of COVID-19 infection resulted in a 26% reduced risk for development of the Long COVID-19 syndrome (57). Similarly, studies with ensitrelvir and molnupiravir also showed a reduction of risk for the development of Long COVID-19 syndrome, but as with nirmatrelvir, the reduction risk was modest (58, 59). However, in clinical trials, these antiviral drugs are researched in patients with COVID-19 infection and risk factors for the development of a severe form of COVID-19 and thus the findings cannot be generalized to patients with low risk of progression. Additionally, a sub-analysis of one randomized controlled study has shown that outpatient treatment with metformin in patients with COVID-19 infections reduced the incidence of Long COVID-19 syndrome with an absolute risk reduction of 4.1% compared to placebo, but this result needs to be confirmed by further research (60).

Published research has also indicated a protective effect of COVID-19 vaccination against the development of the Long COVID-19 syndrome, owing to the reduction of the risk of development of new infection, as well as a mitigation of the course of new infection and reinfection, thus reducing the risk of the Long COVID-19 syndrome. The research conducted by the Office for National Statistics in the United Kingdom, including one million individuals aged 18 to 69 years vaccinated with two doses of COVID-19 vaccines, at least two weeks before contracting the COVID-19 infection, has shown a 41% reduction of the Long COVID-19 symptoms (61). Additionally, there was no statistical difference in the incidence of the Long

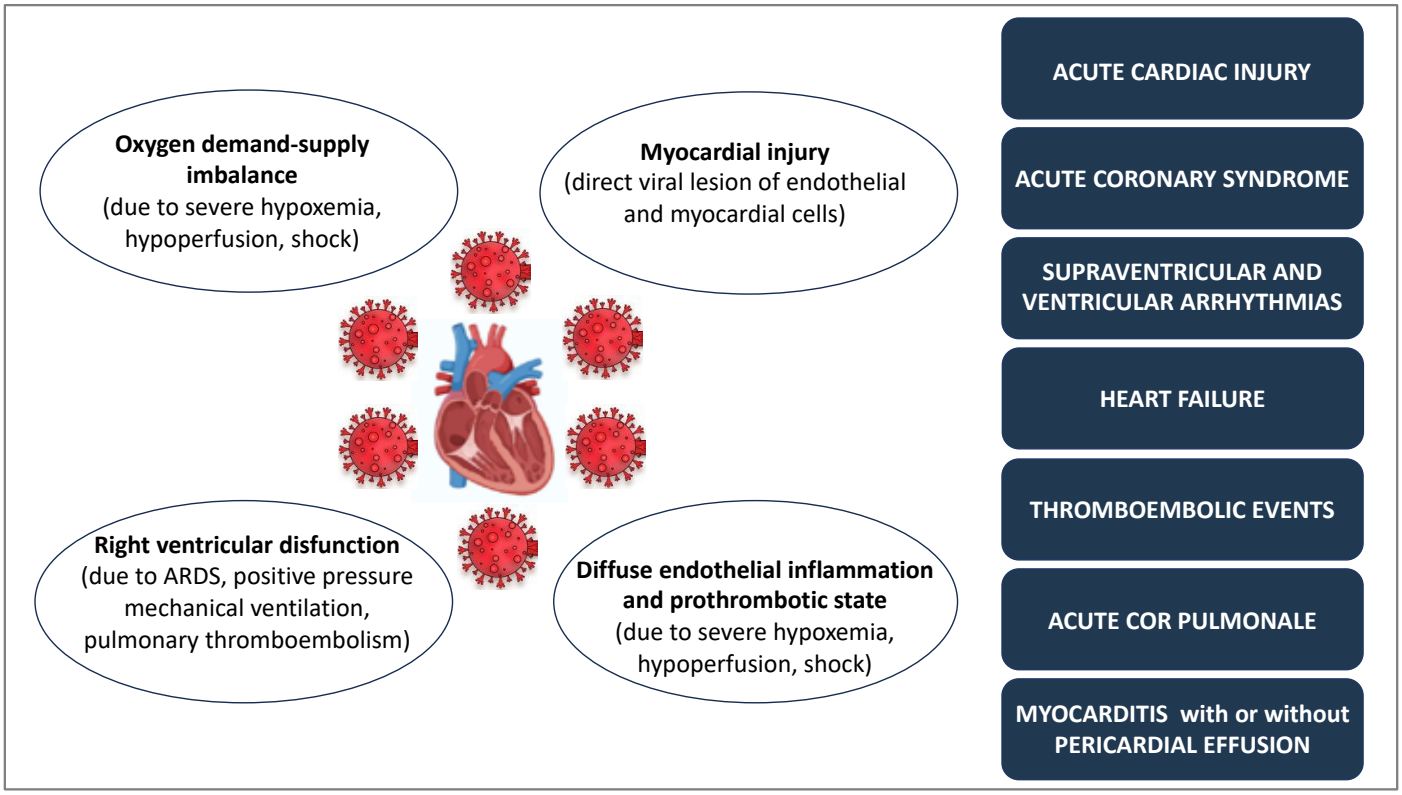

Figure 4. Cardiovascular manifestations of the Long COVID-19 syndrome. ARDS - Acute respiratory distress syndrome.

COVID-19 symptoms between patients receiving adenovirus vector (Oxford/AstraZeneca) or mRNA (Pfizer/BioNTech or Moderna) vaccines (61). Another community-based cohort study that included over 6700 patients vaccinated against COVID-19 after the COVID-19 infections showed a reduction of the risk for development of the Long COVID-19 symptoms by 13% after one dose and an additional 9% after two vaccine doses (62).

Conclusion

Given that many people have been infected with COVID-19, and the fact that the infection does not provide long-term protection from reinfection, the Long COVID-19 syndrome will likely affect many individuals after the acute infection. Even though the symptoms of the Long COVID-19 syndrome could regress over time, the long-term prognosis is challenging, and there is no evidence that damage to the CV system would also regress over time. Currently, the treatment of Long COVID-19 syndrome is symptomatic and specific to complications of COVID-19 infection, including multidisciplinary rehabilitation. What is certain is that the prevention of COVID-19 infection would prevent the development of Long COVID-19 syndrome and thus epidemiological measures and vaccination should be implemented where indicated by the current guidelines. Further research on the mechanisms, treatment and prevention of the Long COVID-19 syndrome is needed to inform optimal management strategies for the management of patients with COVID-19 infection.

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