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Review

Cardiovascular abnormalities of long-COVID syndrome: Pathogenic basis and potential strategy for treatment and rehabilitation

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ABSTRACT

Cardiac injury and sustained cardiovascular abnormalities in long-COVID syndrome, i.e. post-acute sequelae of coronavirus disease 2019 (COVID-19) have emerged as a debilitating health burden that has posed challenges for management of pre-existing cardiovascular conditions and other associated chronic comorbidities in the most vulnerable group of patients recovered from acute COVID-19. A clear and evidence-based guideline for treating cardiac issues of long-COVID syndrome is still lacking. In this review, we have summarized the common cardiac symptoms reported in the months after acute COVID-19 illness and further evaluated the possible pathogenic factors underlying the pathophysiology process of long-COVID. The mechanistic understanding of how Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) damages the heart and vasculatures is critical in developing targeted therapy and preventive measures for limiting the viral attacks. Despite the currently available therapeutic interventions, a considerable portion of patients recovered from severe COVID-19 have reported a reduced functional reserve due to deconditioning. Therefore, a rigorous and comprehensive cardiac rehabilitation program with individualized exercise protocols would be instrumental for the patients with long-COVID to regain the physical fitness levels comparable to their pre-illness baseline.

1. Introduction

Few months after the first epidemiologic report of human-to-human transmission cases around December 2019, the World Health Organization (WHO) officially recognized the coronavirus disease 2019 (COVID-19) as a pandemic outbreak in March 2020. Since then, due to the highly contagious nature of its viral pathogen, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), COVID-19 rapidly spread within the next few months in 2020 to over 200 countries in each continent of the world. The formidable impact of COVID-19 on global public health has remained even in the present time in 2024 and its long-term health adversity continues to be revealed. This article intends to review and discuss the common symptoms and possible mechanisms underpinning cardiac injury in long-COVID syndrome as well as potential targeted therapies and rehabilitation strategies for clinical management of long-COVID. We have focused on cardiac-related symptoms or injuries persisting 3 months beyond the onset of acute COVID-19 that were not present prior to the SARS-CoV-2 infection.

The phenomenon of the so-called post-acute sequelae of COVID-19, or simply termed as "long-COVID," has increasingly gained closer attentions from healthcare communities (Table 1). Data reported in a 2021 study[1] suggested that 10%–30% of individuals in United States may experience prolonged symptoms following SARS-CoV-2 infection, including cardiovascular abnormalities.[1] Similarly, a retrospective cohort study[2] has shown that in 47 780 hospitalized patients with COVID-19 in England, the incidence of major adverse cardiovascular events, e.g. heart failure (HF), myocardial infarction (MI), ischemic stroke, and arrhythmia, was significantly elevated in the hospitalized post-COVID patients (3 times more than those in the matched general population) with a median follow-up period of 140 days. Accordingly, these authors suggested that the diagnosis, treatment, and prevention of post-COVID syndrome requires integrated rather than organ or disease specific approaches.[2]

The common acute COVID symptoms include fatigue, dyspnea, brain fog, muscle weakness, nausea, vomiting, and diarrhea without specific cardiovascular manifestation. Exclusive cardiac manifestation in acute COVID is rarely reported.[3] However, hypoxia-driven cardiac injury, worsening chronic disease, and major cardiac events are less infrequent. Cardiac symptoms of long-COVID are relatively common and manifest as chest pain, dyspnea, palpitations, and postural orthostatic tachycardia

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Abbreviation list

31 P-CMRS	31-phosphorus CMR spectroscopy
ACE2	Angiotensin converting enzyme 2
ADAM17	A disintegrin and metalloprotease 17
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
Cas	CRISPR associated protein
CD68	Cluster of differentiation 68
CMR	Cardiovascular magnetic resonance
COVID-19	Coronavirus disease 2019
CPET	Cardiopulmonary exercise testing
CRISPR	Clustered regularly interspaced short palindromic repeats
DIC	Disseminated intravascular coagulation
DLCO	Carbon monoxide diffusion capacity
EBV	Epstein-Barr virus
ECG	Electrocardiogram
GCO	Ground glass opacities
GDMT	Guideline-directed medical therapy
H1N1	Hemagglutinin 1 and neuraminidase 1
HbA1c	Glycated hemoglobin
HF	Heart failure
HPV	Human papillomavirus
HR	Hazard ratio
ICAM-1	Intercellular adhesion molecule 1
IL1	Interleukin 1
IL6	Interleukin 6
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
miRNA	Micro ribonucleic acid
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NFkB	Nuclear factor kappa B
NT-proBNP	N-terminal pro b-type natriuretic peptide
OR	Odds ratio
PEM	Postexertional malaise
POTS	Postural orthostatic tachycardia syndrome
RNAi	Ribocnucleic acid interference
ROS	Reactive oxygen species
RT-PCR	Reverse transcription polymerase chain reaction
RVEF	Right ventricular ejection fraction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ssRNA	Single stranded ribonucleic acid
TMPRSS2	Transmembrane serine protease 2
TNFα	Tumor necrosis factor α
VEGF	Vascular endothelial growth factor
$\dot{V}O_{2peak}$	Peak oxygen consumption
WHO	World Health Organization

syndrome (POTS), which is considered as a sign of cardiovascular autonomic dysfunction.[3,4] Patients with prior HF had two to four-fold higher risk of decompensation and mortality in the post-acute period of COVID-19. Another retrospective study[5] demonstrated that 58% of patients in China who recovered from COVID-19 and reported cardiac symptoms showed myocardial edema and/or LGE (late gadolinium enhancement) foci on cardiac magnetic resonance (CMR) imaging. None of these patients had known prior heart diseases. In a prospective study, 70% of the patients had abnormal CMR findings including 5% decrease in left ventricular ejection fraction (LVEF) and 10% drop in right ventricular ejection fraction (RVEF), which were associated with increased levels of circulating biomarkers such as D-dimer, C-reactive protein, or lymphopenia.[6] A pooled meta-analysis showed that up to 6 months after discharge the hospitalized patients with COVID-19 had lower than normal median 6-min walking distance, impaired carbon monoxide diffusion capacity (DLCO), anxiety and posttraumatic stress disorder.[7] In another retrospective study from France, 75% of patients were found to have ground glass opacities (GCO) in the lungs at 3-month follow-up. In addition, those with GCOs had lower FEV1 (forced expiratory volume in 1 second) and DLCO.[8] Fibrotic changes as a response to parenchymal damage could eventually strain right ventricle from increased afterload.[9]

To the contrary, a prospective case-control study[10] demonstrated that British patients with long-COVID syndrome and without prior history of cardiovascular disease, who underwent CMR at 3T and 31-phosphorus CMR spectroscopy (31 P-CMRS), found no differences between the long-COVID patients and healthy controls in myocardial energetics (phosphocreatine to ATP ratio), cardiac structure (biventricular volumes) and function (LVEF, RVEF, global longitudinal strain), tissue characterization (T1 mapping and LGE) or perfusion (myocardial rest and stress blood flow, myocardial perfusion reserve).[10] These findings indicated a possible discrepancy between the perceived long-COVID clinical symptoms and the measured cardiac imaging and functional parameters.

2. Prevalence and comorbidity characteristics of long-COVID

A more recent estimate in 2023 indicated that approximately 15% of adult Canadians with SARS-CoV-2 infection have developed lingering long-COVID symptoms beyond 12 weeks after acute infection.[11] Researchers from Czech Republic followed up 2 732 patients (45.7% males; a mean age of 54.6) in post-COVID outpatient clinic for 26 months (from March 2020 to May 2022) and found no significant dependence between the cardiopulmonary fitness parameter $\dot{V}O_{2peak}$ (peak oxygen consumption) and post-COVID disability.[12] The impact of COVID-19 on arterial stiffness was also studied in 225 Polish patients with long-COVID syndrome (mean age 58.98, 54.7% women), using photoplethysmography measurements.[13] Multiple linear regression analyses identified several factors that influenced arterial stiffness, i.e., sex, age, body mass index, smoking status, hypertension, diabetes, severity of acute COVID-19, and recovery time from the disease onset.[13] Another Polish study in 1 847 non-hospitalized patients with COVID-19 (median age 51; 637 men and 1 210 women) found that the long-COVID syndrome was independently related to female sex (Odds Ratio - *OR*: 1.42), history of MI (2.57), asthma (1.56), and severity of acute COVID-19 (2.27), whereas there was no independent relation between the lifestyle factors (e.g. stress or overworking, nightshift work) and long-COVID.[14]

A retrospective analysis[15] based on medical records of an Italian university hospital between June 2020 and June 2021 revealed that out of 428 patients with COVID-19 (40% women, median age 64), 76% patients reported at least one persistent symptom, including dyspnea (37%), chronic fatigue (36%), insomnia (16%), visual disorders (13%) and brain fog (13%). Female patients had higher risk of long-COVID symptoms than male patients (*OR* 1.8).[15] Interestingly, the symptomatic patients infected by the original strain of SARS-CoV-2 from March to December 2020, had different symptoms from those infected by B.1.1.7 Alpha variant during January–April 2021, which showed modified neurological and cognitive/emotional symptoms, suggesting different SARS-CoV-2 variants may induce different long-COVID phenotypes, possibly due to changes in cell tropism and differences in viral-host interaction.[15]

3. Pathogenic basis of cardiovascular sequelae of long-COVID syndrome

Pathophysiology of SARS-CoV-2 infection involves a maladaptive angiotensin converting enzyme 2 (ACE2) pathway either through direct

Table 1
List of representative clinical reports documenting Long-COVID Syndrome and its cardiovascular complications.

Study/Trial Information	Subject Characteristics	Key Clinical Findings	Publications
1. Single-center retrospective study: *Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging.* Huazhong University of Science and Technology, Wuhan, China	26 patients recovered from COVID-19 without prior history of myocarditis or other cardiac disease	15 patients had abnormal CMR findings including myocardial edema, fibrosis and impaired right ventricle function that are associated with significantly elevated global native T1 and T2	Huang L. et al., *JACC Cardiovasc Imaging.* 2020 PMID: 32763118 https://doi.org/10.1016/j.jcmg.2020.05.004
2. Multi-center Retrospective study: *Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: The post Covid M3 study.* University of Paris, France	137 COVID-19 survivors with confirmed infection and pneumonia on chest-CT	Majority of patients have altered PFT at 3 months follow-up with significantly lower function in patients with residual CT lesions	Frija-Masson J. et al., *Respir Med.* 2021 PMID: 34020126 https://doi.org/10.1016/j.rmed.2021.106435
3. Single-center prospective observational study: *Persistent Post–COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment.* Guy's and St. Thomas' NHS Foundation Trust, London, UK	837 patients with a diagnosis of SARS-CoV-2 pneumonitis 6 weeks after discharge from hospital	A cohort of patients are left with both radiological inflammatory lung disease and persistent physiological and functional deficit	Myall K. et *al.*, *Ann Am Thorac Soc.* 2021 PMID: 33433263 https://doi.org/10.1513/AnnalsATS.202008-1002OC
4. Single-center retrospective study: *Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia.* Huazhong University of Science and Technology, Wuhan, China	183 consecutive patients with confirmed novel coronavirus pneumonia	Elevated D-dimer and FDP are common in deaths with novel coronavirus pneumonia	Tang N. et al., *J Thromb Haemost.* 2020 PMID: 32073213 https://doi.org/10.1111/jth.14768
5. Meta-analysis study: *Long-term cardiovascular outcomes of COVID-19.* Saint Louis University, Saint Louis, USA	National healthcare databases from the US Department of Veterans Affairs to build a cohort of 153 760 individuals with COVID-19	Beyond the first 30 days after infection, individuals with COVID-19 are at increased risk of incident cardiovascular disease	Xie Y. et al., *Nat Med.* 2022 PMID: 35132265 https://doi.org/10.1038/s41591-022-01689-3
6. Meta-analysis study: *Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks.* Zhejiang Chinese Medical University, Hangzhou, China	4 131 717 participants who underwent SARS-CoV-2 testing retrieved from the US Collaborative Network in TriNetX	The COVID-19 survivors were associated with increased risks of cerebrovascular diseases	Wang W. et al., *eClinicalMedicine.* 2022 PMID: 35971425 https://doi.org/10.1016/j.eclinm.2022.101619
7. Meta-analysis study: *High-dimensional characterization of post-acute sequelae of COVID-19.* VA Saint Louis Health Care System, Saint Louis, USA	73 435 COVID-19 survivors from the national healthcare databases of the US Department of Veterans Affairs	Identified 6 months incident sequelae including cardiovascular disorders	Al-Aly Z. et al., *Nature.* 2021 PMID: 33887749 https://doi.org/10.1038/s41586-021-03553-9
8. Single-center retrospective study: *Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications.* Universitario La Paz, Spain	3 080 consecutive patients with confirmed COVID-19 infection and follow-up of at least 30 days were analyzed	Patients with COVID-19 have significant incidence of acute heart failure and those with prior history of congestive heart failure are more prone to decompensation	Rey J.R. et al., *Eur J Heart Fail.* 2020 PMID: 32833283 https://doi.org/10.1002/ejhf.1990
9. Longitudinal prospective study: *Sequelae in Adults at 6 Months After COVID-19 Infection.* University of Washington, Seattle, USA	234 participants with COVID-19 with persistent symptoms up to 9 months after illness onset	Persistent symptoms reported in 1/3 of participants with fatigue being the most common	Logue J.K. et al., *JAMA Netw Open.* 2021 PMID: 33606031 https://doi.org/10.1001/jamanetworkopen.2021.0830
10. Retrospective cohort study: *Post-covid syndrome in individuals admitted to hospital with covid-19.* Office for National Statistics, London, UK	47 780 individuals (mean age 65, 55% men) in hospital with covid-19 and discharged alive by August 31, 2020	Individuals discharged from hospital after covid-19 had increased rates of multiorgan dysfunction compared with the expected risk in the general population.	Ayoubkhani D. et al., *BMJ.* 2021 PMID: 33789877 https://doi.org/10.1136/bmj.n693
11. Prospective cohort study: *Cardiovascular magnetic resonance imaging and spectroscopy in clinical long-COVID-19*	20 patients with a clinical diagnosis of long COVID-19 syndrome and no prior underlying cardiovascular disease	Overwhelming majority of patients with a clinical long COVID-19 syndrome with no prior CVD did not exhibit any abnormalities in	Gorecka M. et al., *J Cardiovasc Magn Reson.* 2022 PMID: 36089591 https://doi.org/10.1186/s12968-022-00887-9

(*continued on next page*)

Table 1 (*continued*)

Study/Trial Information	Subject Characteristics	Key Clinical Findings	Publications
syndrome. University of Leeds, Leeds, UK		myocardial energetics, structure, function, blood flow or tissue characteristics.	
12. Prospective cohort study: *Infection with SARS-CoV-2 Variants Is Associated with Different Long COVID Phenotypes.* University of Florence, Florence, Italy	428 patients admitted to the post-COVID-19 outpatient service 4–12 weeks after hospital discharge	Shortness of breath and chronic fatigue as the most frequent long COVID manifestations	Spinicci M. et al., *Viruses.* 2022 PMID: 36366465 https://doi.org/10.3390/v14112367
13. Meta-analysis study: *Increased risk of acute myocardial infarction after COVID-19 recovery.* University of Ferrara, Ferrara, Italy	1 244 604 patients recovered from COVID-19 infection and followed up over 8.5 months	Increased risk of acute myocardial infarction in COVID-19 recovered patients	Zuin M. et al., *Int J Cardiol.* 2023 PMID: 36535564 https://doi.org/10.1016/j.ijcard.2022.12.032

viral toxicity or the subsequent endothelial injury, hypercoagulability, metabolic disorders, immune dysregulation, hypoxia, and immunoinflammatory syndrome.[16] In the following sections, we attempt to discuss several key pathogenic components responsible for cardiovascular injuries occurred during the development of long-COVID.

3.1. Maladaptive ACE2 pathway

The cell entry mechanism of SARS-CoV-2 is mediated by spike proteins comprised of two subunits: S1 contains the receptor binding domain to ACE2 and S2 undergoes cleavage by the host transmembrane serine protease 2 membrane (TMPRSS2) to all fusion of viral envelope and cell membrane.[6,17] This leads to clathrin-mediated endocytosis of viral genome and subsequent viral replication (Fig. 1). Since ACE2 catalyzes the breakdown of AngII which counteracts the deleterious effects of vasoconstriction, inflammation through generation of reactive oxygen species (ROS), and cell hypertrophy, it is thought that SARS-CoV-2 causes cardiovascular complications by hijacking of ACE2.[18]

Autopsy of 39 patients infected with SARS-CoV-2 found 61% with detected virus in heart tissue along with increased expression of pro-inflammatory molecules including tumor necrosis factor α (TNFα) and interleukin 6 (IL6).[19] CD68 was also found in cardiac tissues of the COVID-19 patients, whereas CD68 is a common phagocytic cell marker known to be involved in tissue remodeling and scar formation. This suggests inflammatory response to viral invasion leading to cardiomyocyte death and subsequent fibrous or fibrofatty formation compromising cardiac conduction system and structural integrity. One classic example is arrhythmogenic right ventricular cardiomyopathy (ARVC) where RV myocytes are replaced with fibrofatty material, with Coxsackie viruses being a well-known etiology.[20] Based on another database study of > 150 000 patients, higher incidence of dysrhythmia was detected 12 months after positive COVID-19 test. The increased hazard ratio (*HR*) of cardiac events includes atrial fibrillation (HR, 1.71), atrial flutter (1.80), ventricular arrhythmias (1.84), and sinus bradycardia (1.53).[21] In addition, inflammatory cytokines, particularly TNFα, have been shown to induce dysfunction of gap junctions in atrial myocytes which predisposes to atrial fibrillation.[22] The cytokines also inhibit depolarizing K currents through downregulation of channel expression known as inflammatory channelopathy.[23] Electrocardiogram (ECG) changes including prolonged QT have been described in young athletes who suffer from long-COVID with prevalence as high as 27.5%.[24]

There is a pathological clue to direct viral toxicity isolated from inflammatory response though this is less frequent. In autopsy of first 80 consecutive cases of COVID-19 in Hamburg, Germany, only one case showed a small lymphocytic infiltrate as a sign of myocarditis.[25] Data from 277 autopsied hearts of COVID-19 patients indicated myocarditis in 7.2% of the cases, though only < 2% demonstrated histological criteria for true myocarditis.[26] The other cases involved single cell ischemia, small vessel thrombi, immune cell responses and amyloid deposits, suggesting myocarditis is rare. In another autopsy study of 39 patients, 16 had more than 1 000 viral copies without demonstrating a difference in immunological cell infiltrates compared to other 15 cases without cardiac viral infection.[19] Epstein-Barr virus (EBV) among other herpesvirus that were previously dormant presented in many COVID-19 patients. Given growing evidence of correlation between EBV reactivation and long-COVID, perhaps it is reasonable to question the possibility of latent viral reactivation in SARS-CoV-2.[27] This would explain why onset of long-COVID can occur after a period of recovery.[27,28]

Endothelial cell inflammation was demonstrated by the increased arterial and venous thromboembolism and laboratory evidence of elevated von Willebrand Factor, fibrinogen, D-dimer, coagulation factor VIII (FVIII), decreased antithrombin and TEG in COVID-19 patients.[29,30] Endotheliitis is postulated to be an important mechanistic step underpinning long COVID-19.[31] Postmortem lung samples of patients with COVID-19 demonstrated higher levels of TNFα, IL6 and intercellular adhesion molecule 1 (ICAM-1) in alveolar-capillary cells than those in patients with H1N1 subtype 2009.[32] Although COVID-19 patients have increased inflammatory and cardiac biomarkers, e.g. IL1, IL6, TNFα, and N-terminal pro b-type natriuretic peptide (NT-proBNP), the underlying mechanism was not fully elucidated.[33] Interestingly, increased expression of IL6, NFkB activation and other inflammatory markers was observed on exposure of human endothelial cells to S1 subunit independent of ACE2 enzymatic activity and viral replication.[34] There are reported cases of persistent positive rapid antigen and RT-PCR tests days to months after the acute phase of COVID-19 despite negative viral culture.[35] Perhaps, this explains in part the progressive subclinical nature of long-COVID that may manifest as debilitating clinical syndrome, depending on the extent of inflammatory injury caused by SARS-CoV-2.

3.2. Systemic dysregulation

As illustrated in Fig. 2, aside from direct viral toxicity causing endotheliitis, the involvement of pathological complement activation inducing platelet and endothelial activation persisted at 6–12 months follow-up in long-COVID patients.[36] Proteomic analysis of > 6 500 proteins revealed that serum C7 level was reduced with associated increase in C5bC6. C7 is a membrane-bound molecule on endothelial cells that plays a key role in regulating and interacting with C5bC6 in the formation of membrane attack complex and subsequent target-cell activation or lysis.[37] Increased anti-CMV and anti-EBV IgG titers at 6-month follow-up, supporting the evidence of increased herpesvirus reactivation in long-COVID patients.[38] Complement mediated pathologies lead to disruption of platelet and endothelial function, which in turn causes a hypercoagulable state as demonstrated by the increased rates of thromboembolic disorders, ischemic stroke and ischemic heart disease.[21,39,40] A retrospective study from China showed that 71% of non-survivors had disseminated intravascular coagulation (DIC).[41] This indicates that the virus can directly affect endothelial cells through ACE2 or indirectly disrupt endothelial function through inflammatory mechanisms. Regardless, it may be beneficial for the patients to receive anti-platelet drug therapy, especially in those with severe coronary artery disease (CAD).

A database study of > 70 000 COVID-19 patients found a

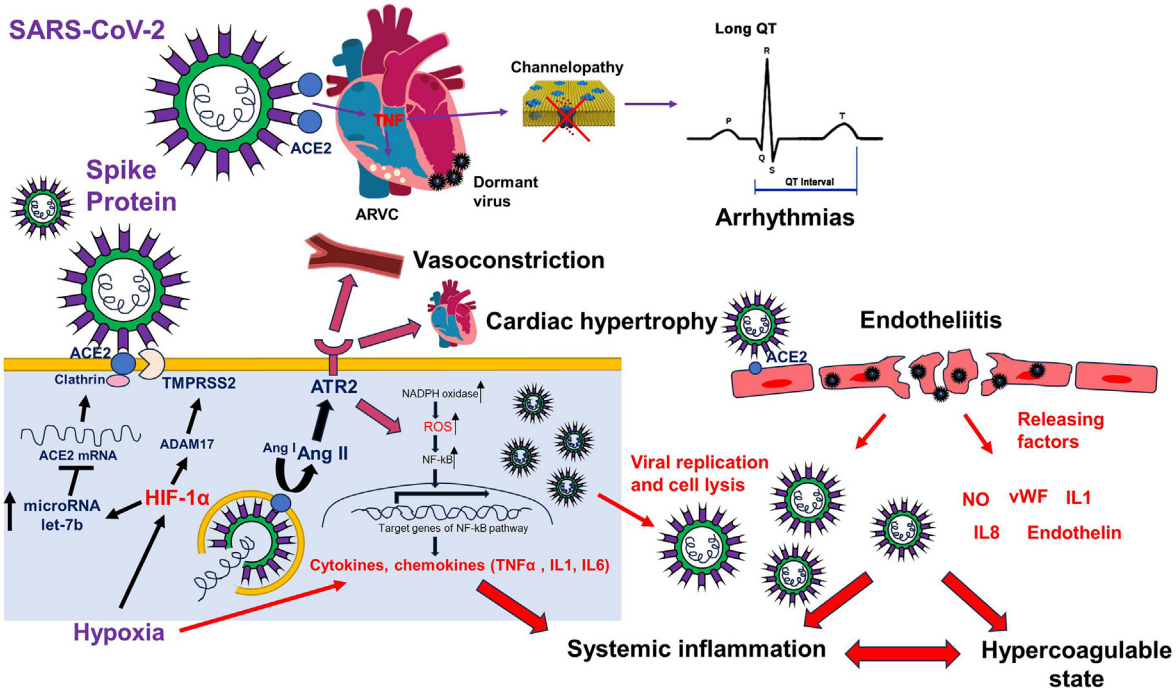

Fig. 1. Schematic summary of potential mechanisms involving direct viral toxicity and hypoxic injury underlying the cardiovascular sequelae of long-COVID syndrome

Abbreviations: ACE2, angiotensin converting enzyme 2; TMPRSS2, transmembrane serine protease 2; ADAM17, a disintegrin and metalloprotease 17; Ang I, angiotensin 1; Ang II, angiotensin 2; ARVC, arrhythmogenic right ventricular cardiomyopathy; ATR2, angiotensin 2 receptor; HIF-1α, hypoxia-inducible factor 1α; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; ROS, reactive oxygen species; NF-kB, nuclear factor kappa B; NO, nitric oxide; vWF, von Willebrand factor; IL1, interleukin 1; IL6, interleukin 6; IL8, interleukin 8; TNFα, tumor necrosis factor α; long-COVID, post-acute sequelae of coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

disproportional increase in metabolic disorders post-infection, including elevated low-density lipoprotein cholesterol, total cholesterol, triglycerides, glycated hemoglobin (HbAlc), diabetes mellitus and obesity,[42] which are known risk factors for coronary atherosclerosis and HF. In a study of 215 patients in Brazil, triglyceride, HbAlc and ferritin were abnormally high at 6-month follow-up especially in those who were

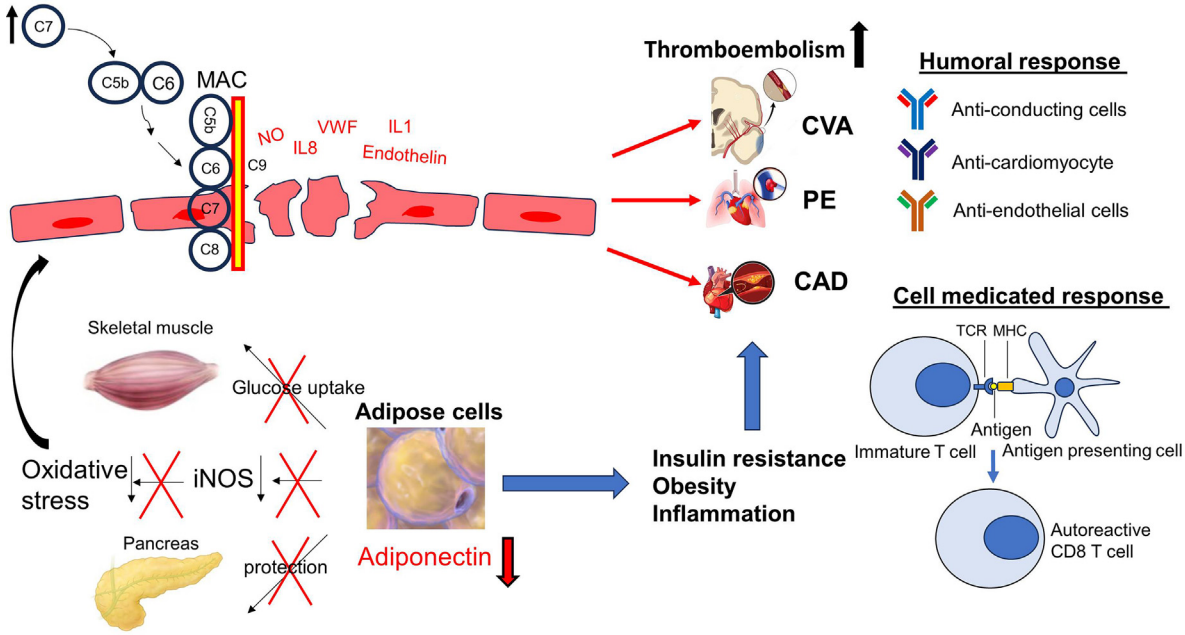

Fig. 2. Schematic summary of potential mechanisms involving metabolic, thromboembolic, and immunoinflammatory dysregulation underlying the cardiovascular sequelae of long-COVID syndrome

Abbreviations: C5b, Complement 5-b; C6, Complement 6; C7, Complement 7; C8, Complement 8; C9, Complement 9; MAC, membrane attack complex; NO, nitric oxide; iNOS, inducible nitric oxide synthase; vWF, von Willebrand factor; IL1, interleukin-1; IL8, interleukin-8; TCR, T cell receptor; MHC, major histocompatibility complex; long-COVID, post-acute sequelae of coronavirus disease 2019; CVA, cerebral vascular accident; PE, pulmonary embolism; CAD, coronary artery disease.

hospitalized during acute illness.[43] The involvement of elevated ferritin implicates the role of systemic inflammation in perpetuating cardiometabolic syndrome in long-COVID, and the impaired insulin signaling could play a role in the disease process.[44] Autopsy samples of infected individuals showed pancreatic islet cells were susceptible to SARS-CoV-2.[45] Upon viral entry, beta islet cells had decreased expression of insulin and higher expression of alpha and acinar cell proteins, glucagon, and trypsin-1. Adiponectin, produced by adipose tissue, regulates insulin sensitivity and protects pancreatic beta islet cells against oxidative stress, was found at lower levels in COVID-19 patients.[46,47] In patients with COVID-19 and acute respiratory distress syndrome (ARDS), insulin resistance was the prevalent cause of hyperglycemia as opposed to pancreatic beta cell failure in patients with ARDS without COVID-19. Furthermore, hamsters infected with SARS-CoV-2 had diminished adiponectin gene expression while launching an anti-viral response.[46]

Autoimmune response is another possible mechanism for cardiac injury in long-COVID as recent data identified 42% higher likelihood of acquiring autoimmune disease 3–15 months post-infection compared to non-COVID individuals matched for age, sex, and preexisting autoimmune diseases.[48] The observed increase in blood levels of antinuclear antibodies, anti-endothelial antibodies, cardiac conducting tissue antibodies and anti-cardiomyocyte antibodies was associated with syndromic manifestations such as chest pain, low QRS voltage, and atrial fibrillation.[49,50] High prevalence of immunomodulatory proteins that regulate interferon response and cell-mediated cytotoxicity was also evident.[51] Furthermore, they discovered correlations between the antibody titers and the severity of the clinical presentation. Although autoantibodies were not detected in long-COVID patients, researchers found persistent activation of $CD8^+$ T cells and higher level of non-class switched memory B cells for up to 6 months post-infection.[52] Taken together, aside from immunoinflammatory response, SARS-CoV-2 could possibly induce autoimmunity through unclear mechanisms of molecular mimicry involving humoral and/or cell-mediated response.

3.3. Hypoxia

Hypoxia is a critical etiology of mortality in patients with severe COVID-19 (Fig. 1). Apart from its progression to ARDS, ultimately resulting in multiorgan failure, hypoxemia also drives pulmonary vasoconstriction as a pulmonic physiological response and is involved in cytokine storm in systemic inflammatory response syndrome.[53,54] The accumulation of hypoxia inducible factor 1α (HIF-1α) was found after invasion of SARS-CoV-2. HIF-1α is believed to exert its inhibitory effect on ACE2 either through microRNA let-7b or direct cleavage of ACE2 from alveoli surface through upregulation of metalloproteinase domain-containing protein 17 (ADAM17).[55,56] HIF-1α is also thought to prime the coronavirus's spike-protein through suppression of TMPRSS2.[57] ADAM17 is also involved in the breakdown of TNFα, which suggests HIF-1α also serves multipurpose roles in stimulating and propagating a pro-inflammatory response to foreign invasion. ROS, generated mostly by macrophages and neutrophils as part of innate immunity, protects HIF-1α from degradation since pharmacologic inhibition of NADPH oxidase downregulates HIF expression.[58] HIF-1α subsequently stimulates vascular growth through vascular endothelial growth factor (VEGF) and disrupts neutrophil apoptosis. Since HIF-1α is a key molecule in oxygen sensing and hypoxic response, it plays a role in the induction of glycolysis through activation of multiple metabolic enzymes in starvation states.[59]

While HIF-1α has demonstrated anti-inflammatory effects such as through the activation of adenosine receptor-dependent pathway, current discourse concurs that the net consequence of HIF-1α activation under viral infection could be more harmful than beneficial.[60,61] The hijacking of HIF-1α signaling pathways for pathological destruction is also observed in other viral pathogens.[62] For example, there is an associated increase in HIF-1α protein level when human papillomavirus (HPV) oncogenes are present. HIF-1α also induces tumor angiogenesis through the VEGF pathways in non-small cell lung cancer.[62] In the dysregulated state such as systemic inflammatory response, HIF-1α may cause long-lasting tissue injury that contribute to prolonged clinical syndrome. Since evidence suggests that the severity of acute COVID-19 syndrome predicts the severity and duration of long-COVID, the syndromic spectrum of long-COVID may correlate with the level of accumulated HIF-1α.[63]

4. Clinical management of cardiovascular complications of long-COVID

It was recently summarized that there is still no evidence-based guideline available for the management of cardiovascular complications of long-COVID.[64] Accordingly, we hereby discuss a few existing or potentially useful treatment approaches and therapeutic agents for alleviating cardiac problems associated with long-COVID.

In 2022, the American College of Cardiology released its first expert consensus on the short-term and long-term cardiovascular sequelae of COVID-19.[65] The evaluation and management of cardiovascular sequelae of COVID-19 are currently carried out according to the corresponding general clinical guidelines for the purpose of reducing the discomfort and improving the quality of life of the patients with long-COVID (Fig. 3). The consensus endorses triad testing (ECG, serum troponin, echocardiogram) of patients with persistent cardiovascular symptoms including chest pain, dyspnea, palpitation, and syncope. Persistent dyspnea in the absence of cardiac workup should pursue further pulmonary evaluation to rule out other post-COVID related diseases such as interstitial lung disease, organizing pneumonia, and subsegmental pulmonary embolism.[66,67] Those with subclinical involvement do not need to undergo cardiac testing, however, the long-term consequence for this small group is unknown given the reported cases of subclinical CMR findings.[6] It remains debatable whether full cardiac evaluation as outlined by the Consensus is required before returning to normal activities, particularly for the patients with comorbid cardiovascular diseases. Perhaps a questionnaire or risk stratification template should be completed for patients following their acute recovery from COVID-19 so they could be followed up with appropriate intervention like those discharged for HF exacerbation.[68]

As stated, patients with exacerbated cardiovascular abnormalities should be managed according to the respective treatment guidelines for myocarditis, CAD, hypertension, atrial or ventricular arrhythmias, etc. to improve the patients' symptoms.[65] Because the pathophysiology of SARS-CoV-2 involves downregulation of the ACE2 receptor, in the early stage of the pandemic there were concerns of whether to continue using ACE inhibitors for blood pressure management in COVID-19 patients.[69–71] However, a 3 080-patient size retrospective analysis suggested that withdrawal of guideline-directed medical therapy (GDMT) was associated with higher mortality particularly in those with a history of HF.[72] Among COVID-19 recovered patients, acute MI occurred in 3.5 cases per 1 000 individuals.[73] Thus, continuing GDMT is paramount in the prevention of long-COVID cardiac sequelae.

Long-COVID patients often present common symptoms, such as POTS, exercise intolerance and cardiac deconditioning, should be carefully addressed since they are particularly difficult to manage. Recently, a panel of Canadian experts introduced some practical guidance for diagnostic and treatment approaches for adult patients with suspected long-COVID.[11] They emphasized the 4P-framework (pacing, prioritizing, positioning, planning) to educate people about energy conservation during post infection recovery.[11] Exercise intolerance is a phenomenon prevalent in long-COVID possibly related to cardiac deconditioning.[74] For example, in 5 healthy males, bedrest for 20 h led to their total blood volume reduced by 8%, central venous pressure by 14% and stroke volume by 19%. During upright exercise, stroke volume decreased by 30 mL and heart rate increased by 30 beats/minute at any workload compared to their pre-bedrest values.[75] This is likely because the decrease in preload from volume reduction resulted in stroke volume decrease and compensatory tachycardia. This orthostatic intolerance

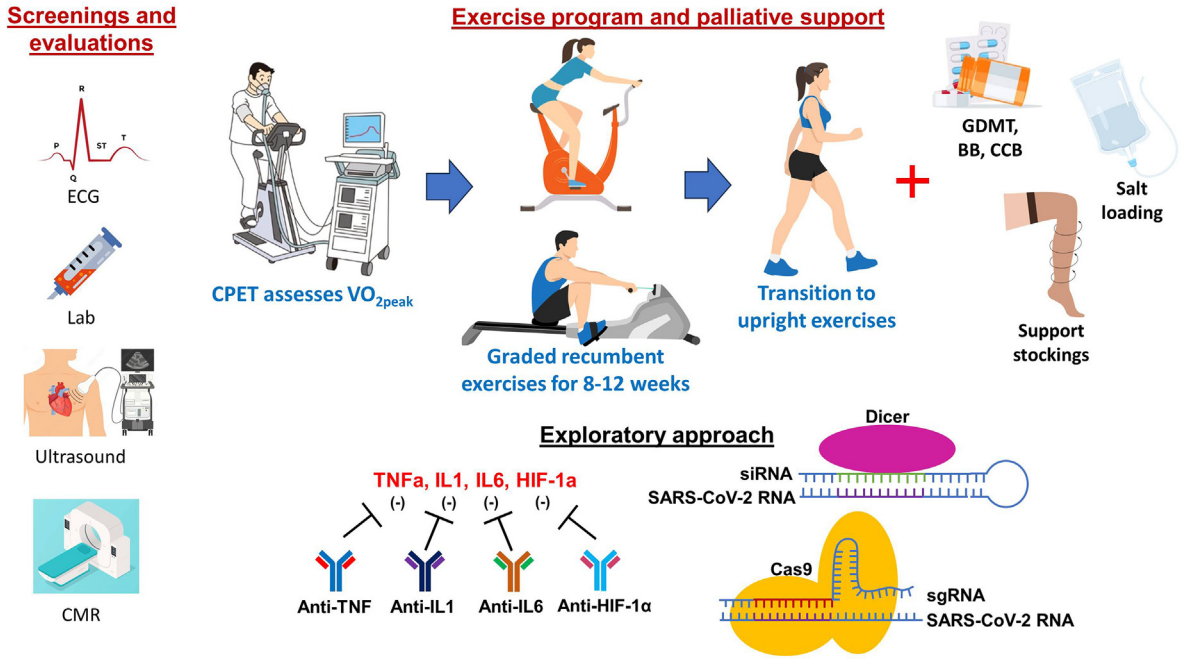

Fig. 3. Schematic summary of clinical management and exploratory approach to cardiac injury in long-COVID syndrome
Abbreviations: GDMT, guideline-directed medical therapy; BB, Beta blocker; Cas9, CRISPR associated protein 9; CCB, calcium channel blocker; CMR, cardiovascular magnetic resonance; CPET, cardiopulmonary exerciser testing; ECG, electrocardiogram; HIF-1α, hypoxia inducible factor 1α; IL1, interleukin 1; IL6, interleukin 6; SARS-CoV-2 RNA, Severe acute respiratory syndrome coronavirus 2 ribonucleic acid; sgRNA, single guided ribonucleic acid; siRNA, small interfering ribonucleic acid; TNFα, tumor necrosis factor α; long-COVID, post-acute sequelae of coronavirus disease 2019.

explains why upright activities after acute recovery from severe COVID-19 can paradoxically perpetuate bedrest deconditioning.[65,74] To avoid this problem, recumbent or semi-recumbent exercises such as rowing and cycling are recommended.[11,65,76] Out of 947 athletes recruited in a study to investigate LV hypertrophy in athletes, only 16 fulfilled criterion and 15 of them are rowers.[77] Furthermore, the dynamic nature of this exercise mode promotes strengthening of skeletal muscle groups, which could be a casual factor of decreased $\dot{V}O_{2peak}$ in long-COVID patients.[78]

There are also drug therapy options for treating common cardiac manifestations in long-COVID according to the abovementioned consensus.[65] POTS may be managed using the selective sinus node inhibitor – ivabradine, as well as low-dose beta-blockers or a non-dihydropyridine calcium channel blocker. Since plasma volume is reduced in cardiac deconditioning, non-pharmacological interventions including salt and fluid loading, head elevation, and support stocking can be administered. Fludrocortisone and midodrine can also be used to help orthostatic intolerance due to low blood volume.

5. Cardiac rehabilitation strategy for long-COVID: role of monitored exercise program

The long-term physical sequelae from SARS-CoV-2 infection were discussed by Serviente et al. who emphasized the need for the development of evidence-based rehabilitation guidelines.[78] The persistent multi-organ dysfunction induced by COVID-19 may set previously healthy individuals on a trajectory towards frailty and disease. Exercise intolerance, muscle weakness and fatigue are among the complaints and symptoms in the patients suffering long-COVID. A study in 11 middle-aged non-hospitalized patients with long-COVID symptoms, as compared with a control group of 12 patients who recovered from COVID without long-term symptoms,[78] reported that while pulmonary and cardiac function parameters were within normal range in all patients, $\dot{V}O_{2peak}$ was lower in the long-COVID group than Control group ([24.7 ± 5.0] mL·min^{-1}·kg^{-1} vs. [32.9 ± 7.4] mL·min^{-1}·kg^{-1}; $p < 0.05$), along with significantly slower $\dot{V}O_2$ kinetics. This muscle function decline was associated with substantial reductions in biomarkers of mitochondrial function, content, and biogenesis.[78] These findings justify a need for exercise training to regain the normal skeletal muscle function and mitochondria efficiency in patients with long-COVID.

A key benefit of physical exercise, when correctly guided, is to promote antioxidant defense, as previously shown in the patients with ischemic heart diseases underwent a cardio-rehabilitative program over 6 months,[79] and achieved a successive increase in antioxidant to oxidant ratio, which was correlated with increased $\dot{V}O_{2peak}$. Since the persistence of systemic inflammatory state is a key feature of long-COVID, a carefully structured individual-based exercise program should intervene this inflammatory state with enhanced antioxidant capacity.[79,80] Guided exercise training may also counteract long-COVID symptoms with improvement in cardiopulmonary fitness, functional status, and quality of life, and to allow the athletes' return to play in sports competitions,[81] whereas a balanced approach is recommended for safe sports practice, particularly after an asymptomatic SARS-CoV-2 infection representing the most common cases in children, considering the evidence on the cardiac sequelae of COVID-19 in children and young athletes remains inconclusive.[82]

The proposed exercise programs for post-COVID recovery should include 1) effective evaluation of symptom progression, 2) accurate diagnosis of symptom etiology, and 3) graded exercise intensity. Accurate evaluation of fitness level via cardiopulmonary exercise testing (CPET) is necessary to prepare individualized rehabilitation for each patient. Previous studies have demonstrated association of poor CPET results and severity of symptoms such as exercise intolerance and persistent dyspnea after recovery from COVID-19.[83–85] Notably, Canadian experts commented on the difference between exercise intolerance and postexertional malaise (PEM), which is present in 30% of patients with long-COVID.[86] Whereas exercise intolerance improves over time with appropriate physical exercise, PEM is characterized by worsening symptoms after physical activity that could last for days to weeks. In addition, the patients who underwent prolonged hospitalization can

suffer from critical illness polyneuropathy that confounds functional limitations pertaining to long-COVID syndrome.[76,87]

As discussed, patients undergoing rehabilitation should begin with recumbent exercises that can be gradually advanced based on tolerance. Successful cases were cited from a 12-week exercise program that targets cardiac deconditioning in long-COVID.[76] The program starts with rowing exercises at moderate intensity followed by gradually transitioning to upright exercises as tolerated. Similar frameworks are found in other programs and $\dot{V}O_{2peak}$ were used as a surrogate marker for progress monitoring.[88,89] If tolerated, patients could also benefit from concomitant pulmonary rehabilitation. A meta-analysis on 14 randomized clinical trials involving 1 244 patients revealed that the standardized rehabilitation intervention was associated with improved functional exercise capacity in patients with long-COVID.[90,91] Patients who successfully completed the 8-week supervised home-based respiratory muscle training program had improved quality of life measured, forced spirometry measurements, improved respiratory muscle function, and improved lower limb muscle strength. Regardless of the method, the exercise protocol should be individualized depending on patient's tolerance.

6. Exploratory approaches to long-COVID syndrome

Although the consensus recommends conservative management to long-COVID syndrome, innovative approach should be explored based on the above-proposed pathophysiological mechanisms. For example, since immunoinflammatory dysregulation is the cornerstone mechanism for both severe disease and persistent inflammation months after viral clearance, the use of cytokine-targeting monoclonal antibodies may be explored in long-COVID patients.[16,69,92,93] There are multiple clinical trials investigating antibody therapy against key pro-inflammatory cytokines such as TNFα, IL1, and IL6. The RECOVERY trial, an open label randomized control trail in UK ($n = 4\,116$), demonstrated that COVID-19 patients with hypoxia (oxygen saturation $< 92\%$) and systemic inflammation (CRP ≥ 75 mg·L^{-1}) who received tocilizumab had improved survivability (31%) and reduced symptom duration compared to the control group which received standard treatment including systemic corticosteroid.[94]

Timely treatment with HIF-1α inhibitors during acute illness may also prevent long-term consequences of COVID-19. There have been various pharmacological innovations including preventing HIF-1α mRNA expression, translation, and translocation between cellular compartments.[95] While HIF-1α is involved in stimulating the production of pro-inflammatory molecules especially in acute illness, the oxygen sensor is also implicated in cardioprotective mechanisms through the induction of inducible nitric oxide synthase, hemeoxygenase 1, and erythropoietin that alleviate ischemic injuries.[96] Severe hypoxia certainly is the trigger for the vicious cycle causing cell injury and death, but there is evidence that intermittent exposure to moderate hypoxia can induce an adaptive phenomenon called hypoxic conditioning.[97] For example, intermittent hypoxia training with brief exposures to 12% O_2 for 2–3 weeks can improve cardiovascular diseases outcomes including CAD.[98] This adaptive mechanism may be related to the induction of VEGF, which over time improves vascular supply and in turn diminish tissue hypoxia. Therefore, intermittent hypoxic conditioning may be a useful non-pharmacological modality that can prevent and treat long-COVID syndrome through improvement of tissue resistance to hypoxic injury.

Innovative ideas involve direct targeting viral genome through gene editing and use of RNAi. Wang et al. were among the first groups to use CRISPR-based technique called SHERLOCK to detect RNA of SARS-CoV-2.[99] Since the discovery of CRISPR-Cas9 technology a decade ago by Emmanuelle Carpentier and Jennifer Doudna, sequence-specific genome editing is possible with high success rate.[100] Recently CRISPR-Cas13 cassettes have been developed to directly target and inhibit ssRNA genome.[101,102] Similarly, non-coding RNA such as siRNA and miRNA can be used to target viral RNA through RNA interference mechanisms and invoke nucleotide degradation through Dicer-associated endonuclease activity.[103]

7. Remaining challenges and future perspectives

One of the challenges concerning the implementation of exercise intervention is correctly diagnosing long-COVID as the etiology of functional impairment. As mentioned, exercise intolerance can be confused with PEM. Patients that develop dysautonomics and/or POTS struggles may require more stringent graded exercise therapy along with pharmacological management to regain functionality, which can be a medical burden on patients. In addition, the diagnosis of long-COVID requires regular follow-up, a multitude of testing, and empirical exercise therapy that demand active engagement from patients and clinicians of various specialties. However, it was recently revealed that adherence to chronic treatment have declined since the COVID-19 pandemic despite the implementation of electronic-health tools.[104] This would impact patient registrations, interval follow-up appointments and patient outcomes.

Another challenge pertains to the evolved social practices and financial limitations since the start of the pandemic. A qualitative study by Roche et al. showed that aside from fear of contracting COVID-19 and governmental restrictions, people have developed new routines that allowed them to complete their responsibilities without going outside.[105] This includes physician visits where the use of telehealth and digital health platforms have been widely implemented,[106] which has made it difficult for patients to adhere to in-person visits. The pandemic-driven unemployment and economic downturn have also created financial limitations for patients to receive appropriate medical coverage. Although efforts are made to expand Medicaid coverage in multiple states in U.S., there is a persistent gap in coverage.[107] A study in 2018 linked cardiac rehabilitation dropout to depression and financial deficits among the top reasons for women aged 41 to 70.[108] The duration and commitment to exercise therapy for long-COVID is comparable to general cardiac rehabilitation, suggesting similar obstacles may be present.

Future direction should aim to establish diagnostic criteria and screening procedures for patients at increased risk to develop long-COVID. Just as the patients recently hospitalized for HF exacerbation would experience a vulnerable phase, known for poor outcomes at the first 3 months after discharge, the long-COVID patients may experience subclinical hemodynamic changes during a similar time period that drives future syndromic manifestation.[68] Therefore, COVID-19 patients, particularly those hospitalized for hypoxic failure during acute illness, should be considered for rehabilitation evaluation with appropriate exercise schedule. To address social work and financial needs, a framework for long-COVID management in Taiwan, China highlights a comprehensive approach that accounts coverage of the “National Health Insurance” and deliver appropriate reimbursement to establish case management system.[109] They also emphasized the designation of specialists to screen for potential candidates and establish a case registry system with standardized outcome measures. Future efforts should strive to integrate precise exercise protocols in conjunction with pharmacological pursuits and multidisciplinary effort that can target specific cardiac pathologies in long-COVID syndrome.

8. Summary

Tremendous global efforts and the advent of vaccine and SARS-CoV-2-targeted antivirals have seen success in controlling the spread of SARS-CoV-2. However, persistent symptoms, especially cardiovascular burden, remain major issues in healthcare settings. In this review we summarized the current understanding of pathological basis of long-COVID and attempted to postulate innovative gene-targeted therapeutic approaches to suppress the persistent inflammatory responses and associated symptoms despite the negative molecular testing results indicating clearance

of SARS-CoV-2 from body fluid samples. The role of spike proteins of SARS-CoV-2 is likely a critical determinant of its pathological progression and clinical outcomes in both short-term and long-term. This hints a possibility to use other novel treatments such as immunotherapies targeting the viral antigens, in addition to the pro-inflammatory molecules, to achieve better treatment outcomes for long-COVID. We further emphasized the importance of a monitored and individualized exercise program that can be instrumental for cardiac rehabilitation in the patients with cardiac problems of long-COVID to regain their physical fitness and quality of life at their pre-COVID levels. Finally, we also recognized the major challenges of implementing the above-described management protocols and the importance of integrated multidisciplinary approach to long-COVID syndrome.

Submission statement

All authors have read and agree with manuscript content. While this manuscript is being reviewed for this journal, the manuscript will not be submitted elsewhere for review and publication.

Conflict of interest

Lei Xi is an Editorial Board Member for Sports Medicine and Health Science and was not involved in the editorial review or the decision to publish this article. Otherwise, authors declare no conflict of interests in writing this review.

CRediT authorship contribution statement

Kainuo Wu: Writing – review & editing, Writing – original draft, Conceptualization. **Jonathan Van Name:** Writing – review & editing. **Lei Xi:** Writing – review & editing, Supervision, Conceptualization.

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