Cardiovascular disease as part of Long COVID: A systematic review

Vasiliki Tsampasian[1], Maria Bäck[2,3], Marco Bernardi[4], Elena Cavarretta[5,6], Maciej Dębski[1], Sabiha Gati[7], Dominique Hansen[8], Nicolle Kränkel[9], Konstantinos Koskinas[10], Josef Niebauer[11], Luigi Spadafora[4], Manuel Frias Vargas[12,13], Giuseppe Biondi-Zoccai*[6,14], Vassilios S Vassiliou*[1, 15]

[1] Norwich Medical School, University of East Anglia, Norwich, UK

[2] Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3] Department of Medical and Health Sciences, Division of Physiotherapy, Linköping University, Linköping, Sweden

[4] Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

[5] Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

[6] Mediterranea Cardiocentro, Naples, Italy

[7] Royal Brompton Hospital, UK and Imperial College London, UK

[8] Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium

[9] Deutsches Herzzentrum der Charité, Klinik für Kardiologie, Angiologie und Intensivmedizin, Campus Benjamin-Franklin (CBF), Charité University Medicine Berlin, 12203 Berlin, Germany

[10] Department of Cardiology, Bern University Hospital – INSELSPITAL, University of Bern, Switzerland

[11] University Institute of Sports Medicine, Prevention and Rehabilitation and Research Institute of Molecular Sports Medicine and Rehabilitation, Paracelsus Medical University, Salzburg, Austria

[12] Department of Medicine, Faculty of Medicine, Complutense University of Madrid, Spain

[13] San Andres Primary Care Health Centre, Madrid, Spain

[14] Department of Medical – Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

[15] Department of Cardiology, Norfolk and Norwich University Hospital, UK

*Authors GBZ and VSV have contributed equally and are joint senior authors

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Authorship

GBZ, VT and VSV contributed to the conception or design of the work. All authors contributed to the data collection, abstract and full text screening. VT drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Abstract

Background: Long COVID syndrome has had a major impact on million patients' lives worldwide. The cardiovascular system is an important aspect of this multifaceted disease that may manifest in many ways. We have hereby performed a narrative review in order to identify the extent of the cardiovascular manifestations of the Long COVID syndrome.

Methods and Results: An in-depth systematic search of the literature has been conducted for this narrative review. The systematic search of PubMed and Cochrane databases yielded 3,993, of which 629 underwent full text screening. A total of 78 studies were included in the final qualitative synthesis and data evaluation. The pathophysiology of the cardiovascular sequelae of Long COVID syndrome and the cardiac manifestations and complications of Long COVID syndrome are critically evaluated. In addition, potential cardiovascular risk factors are assessed, and preventive methods and treatment options are examined in this review.

Conclusions: This systematic review poignantly summarises the evidence from the available literature regarding the cardiovascular manifestations of Long COVID syndrome and reviews potential mechanistic pathways, diagnostic approaches, preventive measures and treatment options.

Introduction

The post-acute sequelae of coronavirus disease 2019 (COVID-19) infection has become the focus of attention of the public, patients, clinicians, and researchers worldwide. After facing the immediate consequences of infection with the severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) strain, millions of people are confronted with persistent post viral symptoms that may have a major impact in their daily lives.

'Long COVID' or 'Post COVID-19 condition', as officially named by the World Health Organization, has been defined as the 'continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with the symptoms lasting for at least 2 months with no other explanation' [1]. These symptoms may affect any body system and may fluctuate or change over time [1,2]. Evidence suggests that up to 45% of COVID-19 survivors are experiencing persistent symptoms at 4 months post the acute infection [3]. In the United Kingdom, it is reported that Long COVID has resulted in limitation of the day-to-day activities of 1.7 million people [4]. These 'long haulers' may encounter a variety of symptoms, such as fatigue, shortness of breath, cough, aches and cognitive dysfunction, to name but a few [3,5].

Cardiovascular (CV) disease is part of this post-acute infection sequelae with many patients having symptoms or complications indicative of arrhythmias, ischaemic or thrombotic events, inflammation and some even suffering cardiac arrest and sudden death [6]. Undeniably, the Long COVID syndrome has a multifaceted interplay with the CV system, with the latter having an important role not only in the presentation but also in the pathophysiology and risk stratification of Long COVID.

We have conducted a systematic search of the published literature in order to critically assess how Long COVID syndrome may impact the CV system. More particularly, the aim of this systematic review was to evaluate the possible pathophysiological mechanisms that lead to CV symptoms and complications of Long COVID syndrome. In addition, we evaluated the potential risk factors, preventative mechanisms and treatment options of Long COVID related CV disease.

Methodology

The methodology for the conduct of the systematic search for this narrative review is provided in full in Supplementary Table 1. In brief, Cochrane and PubMed databases were searched for clinical studies on cardiovascular disease as part of Long Covid-19 from inception to July 9, 2022. Search results were imported for abstract screening. After removal of the duplicates, each record was screened by two any independent co-authors of this manuscript. Disagreements were resolved by discussion with the senior authors VSV and GZB, after which consensus was achieved.

The study has been registered to PROSPERO (registration number CRD42023478892) and has been reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Figure 1).

Results

The full Results are included in the supplementary material (Supplementary table 1, supplementary table 2, supplementary figure 1). In brief, a total of 3993 studies were identified. After removing the duplicates and title/abstract screening, 629 articles underwent full-text evaluation. Out of these, a total of 78 studies were included in this systematic synthesis which guided the review.

Cardiovascular disease and Long COVID

Pathophysiology of cardiovascular sequelae of Long COVID syndrome

The mechanisms perpetuating the post-acute COVID-19 sequelae in the CV system are complex and remain incompletely understood. After direct viral invasion, SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) receptor to enter the host cell and replicate. Despite the fact that imbalance of the renin-angiotensin system (RAS) has a central role in the pathophysiology of the acute infection, neither the serum levels of ACE2 nor the medications affecting the RAS axis have been shown to have an effect on the presentation or severity of COVID-19 infection [7–11]. Similarly, there is no definitive evidence to suggest that RAS imbalance or ACE2 dysregulation are implicated in the pathogenesis of Long COVID and its CV complications [12].

While there is data implying a link between genetic predisposition and acute COVID-19 severity [13–15], less is known about the genetics of Long COVID syndrome. Global collaborations have been established to ascertain if there are genetic determinants of Long COVID. The Long COVID Host Genetics Initiative with data from 23 countries have conducted genome-wide association studies (GWAS) of individual cohorts and have suggested potential variants associated with Long COVID but without genome-wide statistical significance [16–18]. Nevertheless, this is ongoing work with the study sizes in each cohort gradually increasing, therefore this could change in the future. As such, it remains unclear whether there is genetic predisposition to Long COVID and its CV manifestations. Continuing work from research groups internationally aim to shed more light in this matter and determine if gene mutations affect the immune response to COVID-19 infection and predispose individuals to lingering symptoms [19].

Immunity and its response to infection with SARS-CoV-2 has a key role in the development of Long COVID, with multi-omic profiling revealing significant association of specific Long COVID

endotypes and immunological profiles [20,21]. Re-activation of other viruses, exacerbation of pre-existing co-morbidities and significant organ injury are some of the factors that may be contributing to an unheralded immunological response [22]. Prolonged symptoms post the acute infection have been shown to be aligned with a persistently augmented antigen-specific T cell response and raised antibody level [23]. A specific immune response for the SARS-CoV-2 virus has been found to persist for 9 or more months after the acute infection, with elevated B and T cells [24,25]. However, antibodies and T cells have been found to be elevated in the majority of the patients 3 months after the acute COVID-19 infection [26].

While it remains unclear if certain immunological phenotypes translate to increased susceptibility to Long COVID syndrome, it is established that the immune system is implicated in the pathogenesis of cardiac arrhythmias. Auto-immune and inflammatory cardiac channelopathies may promote arrhythmias via auto-antibodies and cytokines respectively [27]. Inflammatory cytokines, such as tumour necrosis factor alpha (TNF-a), interleukin-1 (IL-1) and interleukin-6 (IL-6) can be arrhythmogenic and this phenomenon is observed after a systemic inflammatory response to a pathogen, including SARS-CoV-2. Indeed, the levels of the cytokine triad of TNF-a, IL-1 and IL-6 have been shown to be substantially elevated for prolonged periods in patients with Long COVID [28–31]. TNF-a and IL-6 are known to be implicated in the pathophysiology of myocardial infarction, inflammation and heart failure regardless of acute infection with extrinsic pathogens [32–34]. In addition, patients with Long COVID have been shown to have auto-antibodies specifically against components of the cardiovascular system, including anti-cardiolipin and anti-apolipoprotein A-1 antibodies, both of which are linked with cardiovascular events and worse outcomes [35]. However, it remains to be clarified if they have

a significant or a different role in the mechanistic pathways of cardiovascular disease in the setting of Long COVID.

The combination of viral toxicity with the patient's immune and inflammatory response contributes to the presentation of the CV sequelae in Long COVID syndrome. While the role of genetic vulnerability remains to be determined some studies have identified specific loci and predisposition to Long COVID [14,15,18] (Figure 1).

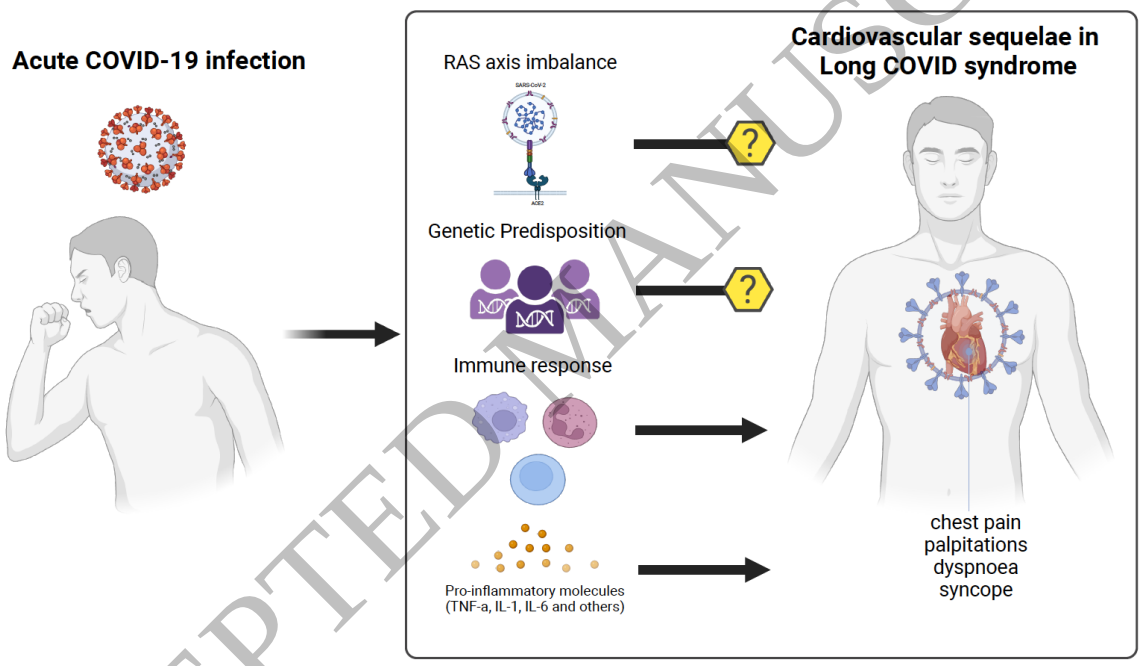

Figure 1 Following the acute infection, inflammatory and immune response may contribute to the development of Long COVID syndrome. Imbalance of the RAS axis and genetic predisposition may also have a role, however this has not been confirmed from current evidence (Image created with BioRender.com).

Cardiovascular disease as risk factor for Long COVID syndrome

Certain cardiac pathologies have been shown to increase the risk of Long COVID syndrome. In a study that included 198,601 patients with Long COVID, Ioannou et al. showed that patients with

pre-existing congestive heart failure have 34% higher risk of developing Long COVID compared to those who did not have pre-established heart failure [36]. In the same study, it was found that patients with ischaemic heart disease and previous myocardial infarction had a significantly higher risk of suffering with the persistent symptomatology of the post-acute COVID-19 condition [36]. Furthermore, a recent meta-analysis of 860,783 patients demonstrated that patients with ischaemic heart disease have 28% higher risk of developing Long COVID syndrome [37].

There is, however, conflicting evidence regarding other pre-existing cardiac conditions and their contribution in the development of Long COVID syndrome. Two studies showed that pre-existing hypertension is not linked with the development of the post-acute COVID-19 sequelae [38,39]. In a meta-analysis of 10 longitudinal studies in the United Kingdom, it was shown that neither hypertension nor hypercholesterolaemia were significant predictors of Long COVID [40]. However, these data contradict the results of a cross-sectional study of 442 patients, which showed that the risk of developing – specifically cardiac-related – Long COVID symptoms were two-times higher in those with underlying CV diseases or risk factors, including hypertension, dyslipidaemia, atrial fibrillation, heart failure and valvular heart disease [41].

Obesity has been shown by several studies to be an important independent risk factor for the development of Long COVID syndrome [37,42–44]. In the Post-hospitalisation COVID-19 (PHOSP-COVID) study, which included 2,320 patients, it was shown that obese patients were 50% less likely to recover fully 12 months after their acute COVID-19 infection [45]. This observation could be explained by the immunological role the adipose tissue has in its ability to

become a reservoir for viruses, including the SARS-CoV-2, and the promotion of persistent systemic inflammation and endothelial dysfunction [44,46].

Pre-existing diabetes has also been shown to be a significant risk factor for Long COVID syndrome, although this has not been confirmed by all studies in the field [47]. In a meta-analysis of 10 longitudinal cohorts, diabetes was not shown to be a significant risk factor for Long COVID [40], a finding which was in agreement with other studies [39,48,49]. However, a larger meta-analysis of 18 studies and 259,978 patients showed that patients with diabetes are 6% more likely to develop Long COVID syndrome, a risk significant although small [37].

In conclusion, there is strong evidence demonstrating that pre-existing obesity, heart failure and ischaemic heart disease are significant risk factors for the development of long COVID syndrome. However, there is conflicting data in literature about other CV diseases such as hypertension, cholesterol, atrial fibrillation and diabetes mellitus.

Table 1 provides a summary of studies that have examined cardiovascular diseases as risk factors for Long COVID.

Table 1 Summary of studies investigating the cardiovascular diseases that increase the risk of Long COVID

Study	Study design	Population	Follow-up	Main findings
Abdelrahman et al. [50]	Prospective cohort study	172 patients	8-10 months	Hypertension and ischaemic heart disease were not significant predictors of Long COVID
Adler et al. [51]	Prospective cohort study	2,755 patients	1-6 months	Obesity and dyslipidaemia are significant risk factors for Long COVID
Belkacemi et al. [52]	Prospective cohort study	216 patients on renal replacement therapy	6 months	Obesity, diabetes and previous MI were significantly associated with Long COVID syndrome
Bellan et al.	Prospective	238 patients	4 months	No significant association between

[53]	cohort study			diabetes, CAD, obesity and Long COVID
Blomberg et al. [38]	Prospective cohort study	312 patients	6 months	Hypertension and chronic heart disease were associated with post COVID-19 fatigue
Chudzik et al [54]	Retrospective observational study (STOP COVID registry, Poland)	2,218 patients	3 months	Obesity was a significant predictor of Long COVID, whereas hypertension, CAD and heart failure were not
Cuomo et al. [55]	Retrospective observational study	394 patients	≥3 months	Hypertension was a risk factor for development of cardiovascular complications
Daitch et al. [56]	Multicentre prospective cohort study	2,333 patients	5 months	Obesity and hypertension are risk factors for Long COVID
de Oliveira et al. [57]	Cross sectional study	439 patients	138 days (median)	Obesity, hypertension, diabetes, heart failure, coronary artery disease not significant risk factors for Long COVID
Dias et al. [58]	Prospective cohort study	1,042 hospitalised patients	≥3 months	Cardiovascular disease was not a significant predictor of Long covid
Fernández-de-las-Peñas et al. [59]	Multicentre case-control study (2:1)	88 patients with obesity and 176 controls hospitalised with COVID-19 (age- and sex-matched individuals)	8.4 months (mean)	Obesity was independently associated with a greater number of post-COVID symptoms and poor sleep quality
Fernández-de-las-Peñas et al. [60]	Case-control Study	287 patients	7.2 months	Hypertension is associated with greater number of post-COVID symptoms and poor sleep quality
Ioannou et al. [36]	Retrospective cohort study	198610 patients	≥3 months after acute infection	Diabetes, heart failure and previous MI correlated significantly with the presence of Long COVID syndrome
Jones et al. [49]	Observational study	310 patients	Collection of data for 4 months	Heart failure and ischaemic heart disease were not significant predictors of Long COVID

Kisiel et al. [61]	Prospective cohort study	366 patients	1 year	Hypertension and obesity were significant predictors of persistent symptoms
Kostev et al. [62]	Retrospective cohort study	51,630 patients	≥3 months	Heart disease was not significant predictor of Long COVID
Legrand et al. [63]	Prospective observational study	2,187 patients	2 months	Congestive heart failure was a risk factor associated with an increased number of persistent symptoms.
Menezes et al. [64]	Retrospective cohort study	108 patients	12 weeks	Obesity is a significant predictor of Long COVID, but dyslipidaemia and diabetes are not.
Munblit et al. [39]	Longitudinal cohort study	2649 patients	218 days (median)	Hypertension and ischaemic heart disease were not significant predictors of Long COVID
Ogungbe et al. [41]	Prospective cohort study	442 patients	≥3 weeks	The presence of cardiovascular disease doubled the risk of Long COVID syndrome
Pazukhina et al. [48]	Prospective cohort study	1,013 patients	≥6 months	Hypertension is a risk factor for Long COVID
Peghin et al. [65]	Bidirectional cohort study	599 patients	≥6 months	Cardiovascular disease is not a significant risk factor for Long COVID
Samannodi et al. [66]	Cross-sectional, nationwide study	2,737 patients	6 weeks – 6 months	Cardiovascular disease is not a significant risk factor for Long COVID
Schulze et al. [67]	Cross-sectional study	101 patients	≥2 months	Cardiovascular disease is not a significant risk factor for Long COVID
Thompson et al.[40]	Analyses of survey data from 10 UK established population based longitudinal studies (LS) and records electronic healthcare records (EHR)	6,907 patients from LS and 4189 from EHR	≥12 weeks	Hypertension, hypercholesterolaemia and diabetes were not significant risk factors for Long COVID. Obesity was significantly associated with Long COVID.
Tleyjeh et al. [68]	Prospective cohort study	222 patients	122 days (median)	Pre-existing hypertension was associated with an increased risk of

				persistent symptoms
Whitaker et al. [69]	Cross-sectional survey	55,730 patients	12 weeks	Obesity was significantly associated with Long COVID.
Wu et al. [70]	Cross-sectional survey	308 patients	12 weeks	Heart disease is not a significant risk factor for Long COVID. Obesity was significantly associated with Long COVID.

Diagnosis and Cardiac manifestations of Long COVID

Being a multi-organ disease, Long COVID manifests itself with a variety of symptoms that may present simultaneously or sequentially during or after the acute infection. The diagnosis of Long COVID remains a clinical one, with no established diagnostic laboratory testing available so far. Recent evidence has shown that there is a potential for use of certain complement fragments and components (Ba, iC3b, C5a and Terminal Complex Component) to identify and diagnose the disease [71], large trials and evidence from population studies are currently lacking and therefore their use is not implemented in clinical practice. Another laboratory blood test that identifies non-classical monocytes and cytokines, has also shown promise in identifying patients with Long COVID syndrome and has recently gained approval for use in Europe [72,73]. The CV symptoms of Long COVID might reflect the complex pathophysiological mechanisms occurring during the course of the disease. Common causes that lead to symptom occurrence may include left or right ventricular dysfunction, pulmonary hypertension, arrhythmias or autonomic dysfunction [74–76]. On these occasions, relevant diagnostic tests and clinical examination will enable the identification of the complication – provoked by Long COVID – and the appropriate management steps will be followed for treatment. Importantly, however, many Long COVID patients exhibit cardiac symptoms without objective evidence of cardiovascular

disease [77]. Establishing the diagnosis of Long COVID in these patients can be extremely challenging, as on some occasions there may inevitably be significant overlap with other conditions, such as postural orthostatic tachycardia syndrome and myalgic encephalomyelitis/chronic fatigue syndrome [74,77]. Nevertheless, however difficult it may be, it is imperative to appreciate that Long COVID and its accompanied symptomatology do not require abnormal or pathological evidence on clinical, radiological or biochemical assessment for the diagnosis to be established. Still, it is imperative that common CV diseases are not missed, and for this reason, thorough assessment of the patient is required to ensure appropriate risk stratification and management plans.

Cardiac symptoms are very common amongst patients with Long COVID, representing the third most common clinical manifestation of the disease [74]. A systematic review of 9 studies that reported cardiac manifestations in patients with Long COVID showed that palpitations and chest tightness were very frequently reported from the patients [78]. In a systematic review of 25 studies, chest pain was found to be the most prevalent clinical manifestation of Long COVID, with 89% of the participants reporting it in their follow-up assessment [79]. The COVID Symptoms Study demonstrated that cardiac symptoms were prevalent amongst patients with Long COVID, the majority of whom experienced these symptoms for the first time 3-4 weeks after the onset of Long COVID [42].

Our systematic review confirms that chest pain, palpitations, dyspnoea and syncope are the most commonly reported symptoms among patients with Long COVID syndrome. Supplementary Table 2 summarises all the studies identified from our systematic search that reported cardiac symptomatology in patients with long COVID.

Cardiovascular disease as complication of Long COVID

Long COVID has also been implicated in the development of new onset CV diseases in subjects without pre-existing co-morbidities. In a study of 153,760 patients, it was shown that patients with Long COVID syndrome have 1.6 times higher risk of new onset CV disease of any type, including dysrhythmias, non-ischaemic and ischaemic cardiomyopathies, cerebrovascular and thrombotic disorders [6]. This was evident for a variety of diseases including ischaemic heart disease, heart failure, dysrhythmias, inflammatory cardiac diseases and thromboembolic disease. This finding is in agreement with another study of 47,780 patients, which demonstrated thatmajor adverse cardiovascular events were more 1.5 times more frequently encountered in patients with Long COVID compared to controls [105]. New onset diabetes mellitus type 2 and hypertension have also been commonly noted in patients with Long COVID [106–108] (table 3).

Table 3 Summary of studies that reported new incidence of cardiac diseases in the course of Long COVID syndrome

Study	Study design	Population	Follow-up	Main findings
Ayoubkhani et al. [105]	Case control study	47780 patients	140 days (mean)	New incidence of diabetes and major adverse cardiovascular events were diagnosed more frequently (3.0 and 1.5 times respectively) in Long COVID patients compared to controls
Chowdhury et al. [106]	Prospective cross-sectional study	313 patients	20 weeks	New incidence diabetes and hypertension observed in 0.64% and 1.28% and post-COVID uncontrolled diabetes and hypertension in 54.55% and 34.78% respectively.
Cuomo et al. [55]	Retrospective observational study	394 patients	≥3 months	Cardiovascular event developed in 15.7% of the subjects. These were mainly pulmonary embolism (9.4%), followed by

				arrhythmias (3.3%), myocardial infarction (2.3%), and myocarditis (0.8%).
Maestre-Muñiz et al. [88]	Cross-sectional study	543 patients	12 months	1.3% and 2% of patients developed new onset diabetes and heart failure respectively.
Ogungbe et al. [41]	Prospective cohort study	442 patients	≥3 weeks	26.9% (119/442) of individuals reported a new cardiac condition; 20% had newly diagnosed hypertension, 24% had tachycardia and 13% had postural orthostatic tachycardia syndrome (POTS)
Senjam et al. [94]	Cross-sectional study	773 patients	≥2 months	3.1% of patients with Long COVID developed new onset hypertension
Vyas et al. [109]	Prospective observational study	248 patients	12 months	New onset of hypertension was detected in 32.3% of patients at one-year follow-up post-COVID-19 disease recovery
Xie et al. [6]	Case control study	153760 patients	12 months	Patients with Long COVID had increased risk of incident cardiovascular disease spanning several categories, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease
Xie et al. [108]	Case control study	181 280 patients	12 months	People with Long COVID exhibited an increased risk (HR 1·40, 95% CI 1·36–1·44) and excess burden of incident diabetes

Furthermore, Long COVID may have a direct impact on the myocardium. This can usually be evidenced by pathological findings on examination and diagnostic tests. Our systematic search revealed twenty studies that evaluated the impact of Long COVID syndrome on the

myocardium through imaging evaluation with echocardiography and/or cardiac magnetic resonance (CMR) (table 4).

Several echocardiographic studies have confirmed that the most commonly encountered findings in patients 2-3 months after the acute infection are impaired GLS, with the findings more commonly encountered in patients that had severe infection during the acute phase [110–116].

Myocardial involvement was shown to be a feature of Long COVID syndrome from the early months of the COVID-19 pandemic, with CMR imaging being the gold standard for the detection of myocardial oedema, inflammation and fibrosis. Several patients that presented with 'atypical' cardiac symptoms, such as chest pain and palpitations, were found to have abnormal CMR imaging [117]. Notably, the presence of symptoms is not a prerequisite for myocardial involvement and vice versa. However, individuals with persistent symptoms are more likely to have abnormal findings in the CMR [90]. Interesting features include the presence of myocardial oedema and/or fibrosis, various patterns of late gadolinium enhancement (LGE) in the myocardium, interstitial fibrosis and pericardial involvement [82,91,95,117–120].

All the above findings have to be interpreted with caution, acknowledging that they are derived from observational – albeit large – studies. Inevitably, it is impossible to know if all the abnormalities and diseases are truly attributed to Long COVID alone or if they were pre-existing, as baseline (pre-COVID) assessments of the patients was not performed. In addition, while cardiac involvement in the acute phase is a well-recognised phenomenon that may accompany patients suffering with acute COVID-19 infection [11,121,122], the impact of Long

COVID syndrome on the myocardium follows pathways and mechanisms that are not fully understood yet. It is difficult therefore to ascertain if the aforementioned complications are truly associated with Long COVID solely or if they are persistent features of the acute infection. Nonetheless, regardless if they are features of the acute infection or the post COVID sequelae, their clinical relevance and prognostic significance is important. Therefore, further studies with longer follow-up of the patients affected are needed to explore these aspects and understand their impact on patients' lives.

Table 4 Summary of studies that investigated the impact of Long COVID on the myocardium through advanced imaging (Echocardiography or cardiac magnetic resonance, CMR)

Study	Study design	Population	Follow-up	Main findings
Akbulut et al. [123]	Prospective cohort study	58 patients	6 months	The LVESD was significantly lower in patients with COVID-19 compared to healthy controls. TAPSE was significantly higher in COVID-19 patients compared to the control group. LV and RV GLS values and both atrial peak systolic strains did not differ between the groups.
Akkaya et al. [114]	Cross-sectional study	105 patients	3 months	TAPSE, RV fractional area change, RV S' and RV GLS were significantly lower in the COVID-19 group compared to control group ($p < 0.05$).
Baruch et al. [116]	Prospective cohort study	80 patients	3 months	In patients recovering from COVID-19 infection most LV routine echocardiographic, haemodynamic, and STE parameters did not improve in the months following acute infection. RV routine echocardiographic, haemodynamic and RV STE parameters improved in the majority of patients.
Breitbart et al. [82]	Prospective cohort study	56 patients	71 days	Acute myocarditis was confirmed by T1/ T2-weighed CMR and elevated NTpro-BNP levels in 1 patient.

				Additional eight patients (14%) showed suspicious CMR findings, including myocardial oedema without fibrosis (n = 3), or non-ischemic myocardial injury suggesting previous inflammation (n= 5)
Cannata et al. [124]	Prospective cohort study	110 patients	7 months	Impaired LV GLS was found in 37 patients (34%) and was associated with an increased risk of Long-term MACE with a good discriminative power (area under the curve: 0.73)
Cecchetto et al. [125]	Prospective cohort study	229 patients	5 months	LV GLS and RV free wall strain were reduced in 36% (n=81) and 7.2% (n=16) of the patients at 5 months. The presence of at least one cardiovascular risk factor was a significant predictor of impaired LV GLS. Subclinical myocardial dysfunction did not improve at the 12-month follow-up.
De et al. [126]	Prospective observational study	472 patients	12 weeks (median)	As compared to controls, the post-COVID subjects had impaired LV systolic and diastolic function. The patients in the lowest GLS tertile were older, had higher burden of co-morbidities, and had had more severe initial infection with greater need for hospitalization, oxygen therapy and steroids. The need for hospitalization was independently associated with lower GLS at the time of current presentation.
Filipetti et al. [127]	Prospective observational study	19 patients	3 & 11 months	At the 3-month follow-up CMR study the findings included LV concentric remodelling (12 patients), myocardial tissue abnormalities (11 patients) and increased myocardial ECV (9 patients). At the 11-month follow-up CMR study, LV function and remodelling were unchanged but ECV returned to normal or below the normal range.

Garcia-Zamora et al. [110]	Prospective observational cohort study	595 patients	2 months	Cardiovascular abnormalities after COVID-19 infection were rare (8.2%) and usually mild, especially following mild infection, with a low GLS of left and right ventricle being the most common ones in this registry.
González et al. [128]	Prospective observational study	31 patients	5 months	LGE lesions indicative of residual myocardial injury were encountered in 15 of the 31 patients. Intraindividual comparison with the pre-COVID-19 CMR revealed all of these lesions as pre-existing and thus not COVID-19-related. Quantitative analyses detected no increase in the size of individual LGE lesions nor in the global left ventricular LGE extent. Comparison of pre- and post-COVID-19 cine imaging sequences did not show any differences in ventricular functional or structural parameters.
Gorecka et al. [129]	Prospective case-control study	20 patients	3 months	Between the Long COVID-19 syndrome patients and matched contemporary healthy controls there were no differences in myocardial energetics (phosphocreatine to ATP ratio), in cardiac structure (biventricular volumes), function (biventricular EF, GLS), tissue characterization (T1 mapping and LGE) or perfusion (myocardial rest and stress blood flow, myocardial perfusion reserve).
Huang et al. [117]	Retrospective observational study	26 patients	Not defined	Myocardial oedema was found in 14 (54%) patients and LGE in 8 (31%) patients. Significantly elevated global native T1, T2, and ECV and RV impairment were found in patients with positive conventional CMR findings, compared with patients without positive findings and controls.

Joy et al. [130]	Prospective case-control study	149 patients	6 months	In this population, mild COVID-19 left no measurable cardiovascular impact on LV structure, function, scar burden, aortic stiffness, or serum biomarkers. CMR abnormalities included reduced ejection fraction (n = 2), T1 elevation (n = 6), T2 elevation (n = 9), late gadolinium enhancement (n = 13). These were distributed equally between seropositive and seronegative individuals.
Kotecha et al. [131]	Prospective cohort study	148 patients	68 days (median)	LGE and/or ischaemia was found in 54% (80/148). This comprised myocarditis-like scar in 26% (39/148), infarction and/or ischaemia in 22% (32/148) and dual pathology in 6% (9/148). Of patients with ischaemic injury pattern, 66% (27/41) had no past history of coronary disease. There was no evidence of diffuse fibrosis or oedema in the remote myocardium.
Kunal et al. [132]	Prospective observational study	30 patients	6 months	All participants had abnormal LV GLS during acute infection and 16 patients had abnormal CMR at baseline. Follow-up CMR was abnormal in 4/16 (25%) with LGE persisting in three patients (who had severe COVID-19). Subjects with severe COVID-19 had a greater frequency of LGE (53.8%) and myocardial oedema (61.5%) as compared to mild and moderate cases. Myocardial T1 and T2 values were significantly higher in post COVID-19 subjects compared to healthy controls and mild and moderate cases.
Moody et al. [111]	Prospective observational cohort study	79 patients	3 months	At 3 months, 56 (71%) patients had a normal TTE. In those with any abnormality, 16 had only RV adverse remodeling, 5 had only adverse LV remodeling, and 2 had biventricular

				involvement. Of the 16 patients with persisting RV changes at 3 months, 7 had pulmonary embolism diagnosed during hospital admission.
Niebauer et al. [113]	Prospective cohort study	150 patients	6 months	Echocardiography detected reduced GLS in 11% and diastolic dysfunction in 4%. CMR imaging revealed traces of pericardial effusion in 18% and signs of former pericarditis or myocarditis in 4%. Exertional dyspnoea was associated with impaired pulmonary function, reduced GLS and/or left ventricular diastolic dysfunction.
Puntmann et al. [90]	Prospective observational cohort study	346 patients	109 days (median)	Diffuse myocardial oedema was more pronounced in participants who remained symptomatic at follow-up as compared to those who improved. Female gender and higher baseline native T1 predicted the symptomatic status at follow-up.
Raman et al. [91]	Prospective observational cohort study	58 patients	2-3 months	LV and RV function were normal and comparable between groups. Slice-averaged basal and mid-ventricular native T1 were significantly elevated in patients. Native T2 was not different between patients and controls. Focal fibrosis burden was mildly increased in patients.
Roca-Fernandez et al. [119]	Prospective cohort study	534 patients	12 months	CMR abnormalities were common (one in five individuals at 6 months) and commonly persisted (three out of five individuals at 12 months). Low LVEF at baseline was associated with persistent CMR abnormality, abnormal GLS was associated with low quality of life and abnormal T1 in at least three segments was associated with better clinical outcomes at 12 months.
Tangen et al. [112]	Prospective observational cohort study	92 patients	3 months	All patients had normal LV function by LVEF 3 months after hospitalisation. However, LV GLS,

				was reduced in 15% of the patients. There was no significant relationship between reduced GLS and disease severity (treatment at intensive care unit) or elevated high sensitivity cardiac troponin after 3 months.
Wang et al. [120]	Prospective cohort study	47 patients	3 months	LGE was found in 13 (30%) of COVID-19 patients. LGE-positive patients had significantly decreased LV and RV peak global circumferential strain, RV peak global longitudinal strain (GLS) as compared to non-LGE patients ($p < 0.05$), while no difference was found between the non-LGE patients and healthy controls.
Wojtowicz et al. [95]	Cross-sectional study	121 patients	41 days (median)	Non-ischemic cardiac injury (defined as the presence of LGE lesion and/or active myocarditis in CMR) was detected in over half of post-COVID-19 patients (52.9%). RV EF was reduced in patients that were hospitalised during the acute phase.

ATP, adenosine triphosphate; CMR, Cardiac Magnetic Resonance; ECV, Extracellular volume; EF, Ejection Fraction; GLS, Global longitudinal strain; LGE, Late gadolinium enhancement; LV, Left ventricle; LVESD, Left ventricular systolic dimension; MACE, Major adverse cardiac events; RV, Right ventricle; TAPSE, Tricuspid annular plane systolic excursion; TTE, Transthoracic echocardiography

Prevention of cardiovascular disease as part of Long COVID

Although there is no established or proven method of preventing Long COVID syndrome, optimal control of the modifiable risk factors may help the management of Long COVID symptoms and complications. For example, a healthy nutrition is rich in antioxidants, fibre and polyphenols and contains minimum amounts of saturated fat and pro-inflammatory molecules, which is beneficial in achieving a normal body mass index (BMI) and sleep pattern and contributes towards a positive mental health [133,134]. Therefore, lifestyle changes that

include a healthy dietary pattern and regular exercise have invaluable advantages that enhance the natural immunity and make the body less vulnerable to Long COVID and its complications [134]. While there is some evidence to suggest that plant-based and pescatarian diets are associated with reduced risk of severe acute COVID-19 infection [135], there is no study yet investigating the potential impact of such diets in Long COVID syndrome.

On the other hand, vaccines have been shown to be an effective way of preventing Long COVID syndrome. A meta-analysis has already shown that vaccinated individuals have 40% less risk to develop Long COVID compared to unvaccinated people [37]. A case-control UK study of 1.2 million people showed that the risk of symptoms persisting for more than 28 days was almost 50% lower in those who were vaccinated compared to unvaccinated individuals [136]. Another systematic review and meta-analysis of six studies and 629,093 patients showed that patients with two-dose vaccination had 36% and 40% less risk of Long COVID compared to those with no or one-dose vaccination [137]. Vaccination has also been shown to reduce the risk of cardiac injury. In an observational prospective study of 1,883 patients, vaccinated patients had significantly lower prevalence of cardiac injury as evidenced by echocardiography than unvaccinated patients [138]. However, further research needs to be done on this field to investigate the impact of vaccination on the different variants and to determine the optimal number of booster doses.

Medications may also have a role in the prevention of Long COVID syndrome. In a recent randomised placebo-controlled study that included 1,126 overweight and obese patients, it was shown that metformin during the acute infection reduces the incidence of Long COVID by 41.3% compared with placebo [81]. While this is a very promising result, it remains to be

determined if the benefit would be evident in a wider population of patients with normal BMI. It is also unclear whether the incidence of Long COVID was reduced because of a direct antiviral mechanism that prevents the presentation of the syndrome or because it significantly reduces the viral load during the acute infection and the risk of severe acute COVID-19 infection [139,140]. Antivirals that are recommended for the acute COVID-19 infection in patients with high-risk features have also been shown to be beneficial. Large cohort studies demonstrated that the use of nirmatrelvir and molnupiravir during the acute illness significantly reduced the incidence of long COVID syndrome and the post-acute COVID-19 sequalae [141,142]. Notably, this effect was shown regardless of the patients' baseline vaccination status [141]. Other medications such as ivermectin and fluvoxamine were not shown to have similar effect as they did not reduce the risk of neither Long COVID not severe acute COVID-19 infection [81,139].

Despite all the above, prevention of Long COVID and its related CV manifestations has been particularly challenging. Prevention requires adequate risk stratification at a population level and tackling of all potential factors that may increase an individual's risk of developing Long COVID syndrome. However, in the case of Long COVID, the quest for identification of the risk factors is still ongoing as outlined above. Whereas some co-morbidities have been shown to significantly increase the risk of Long COVID, there is lack of evidence regarding their pre-morbid status and Long COVID. For example, it is unclear if someone with well-controlled diabetes is at higher risk of developing Long COVID compared with a person with poorly controlled diabetes. In addition, up to this day, there is a lack of clinical and/or laboratory tests with the ability to establish early diagnosis. By definition, Long COVID syndrome is diagnosed after 3 months of persistent symptoms, which, for many other diseases is considered 'late'. As

such, although it may be suspected, it is not possible to diagnose early the condition and plan the appropriate management promptly.

Figure 2 summarises the potential ways of preventing the cardiovascular manifestations of Long COVID syndrome.

Treatment and prognosis of cardiovascular disease as part of Long COVID

Currently there is no specific treatment recommended by the guidelines for patients with Long COVID syndrome. This may not come as a surprise considering the existing gaps in the understanding of the causal pathophysiological mechanisms of Long COVID syndrome. Management is focused primarily on the relief from symptoms and/or complications that may accompany them. However, this may soon change as hundreds of researchers worldwide have set out to identify therapeutic targets and develop medications that can treat the lingering symptoms of Long COVID.

This step involves the development of a treatment that would tackle the hyperinflammatory state that dominates the Long COVID pathophysiology. The antiviral drug, nirmatrelvir, inhibits viral replication by targeting the chymotrypsin–like cysteine protease enzyme (M^{pro}) [143]. Its use has been approved for patients with acute COVID-19 infection who are at high risk of progressing to severe disease [144]. However, apart from its positive impact in the acute phase, it was quickly shown that it has a substantial benefit for the post-acute lingering symptomatology of COVID-19 infection. A recent retrospective cohort study that included 281,793 participants, showed that nirmatrelvir reduced the risk of Long COVID syndrome by

26% and the risk of post-acute death and hospitalisation by 47% and 24% respectively [145]. Based on this, a randomised placebo-controlled trial investigating nirmatrelvir in adults with Long COVID has started (NCT05668091) and its results are highly anticipated. Other antivirals have been shown to be efficient in the acute phase of the infection [141], however their impact on the Long COVID incidence is yet to be determined.

The next achievement would be to identify effective treatments for symptom specific Long COVID symptoms. Understandably, there are several studies that are investigating different pathways that are implicated in the pathogenesis of certain Long COVID symptoms. A few of them are focused on the CV manifestations of Long COVID. Three trials are investigating the role of medications for patients with tachycardia or postural orthostatic tachycardia syndrome, including ivabradine (NCT05481177) and efgartigimod (NCT05918978), while another trial is investigating the impact of early intervention on the myocardium with immunosuppression and anti-remodelling therapy in the form of prednisolone and losartan in patients with post-acute COVID-19 inflammatory cardiac involvement (NCT05619653). Other trials are exploring the value of cardiac rehabilitation and behavioural interventions on the cardiac manifestations of Long COVID (NCT05530317, NCT05035628, NCT05228665, NCT05566483, NCT05629884, NCT05539950, NCT05877534). Of these, only one study, the HEARTLOC (HEART Rate Variability Biofeedback for Long COVID Dysautonomia) study, has been completed (NCT05228665). This feasibility study comprised of 13 participants showed that a heart rate variability biofeedback programme via a standardised slow diaphragmatic breathing was not a feasible intervention that improved the symptomatology of patients with Long COVID [146].

Supplementary Table 3 provides a summary of all the ongoing studies with a focus on cardiovascular disease as part of Long COVID syndrome.

More than 3 years on since the beginning of the pandemic, it has been evident that some patients have fully recovered from Long COVID, with their cardiac related symptoms settling with time. However, a proportion of patients have ongoing debilitating symptoms that impacts their quality of life and everyday activities. Whilst the short term prognosis appears to be good for the majority of the patients, the future course and long-term prognosis of the disease and its manifestations remain uncertain [147].

The results of the currently running randomised trials are highly anticipated not only to elucidate the progression of Long COVID syndrome with time but also to guide management and improve patients' quality of life.

Unmet clinical need and Evolving concepts in Long COVID

Although a lot of progress has been achieved in understanding the pathways by which the disease affects the cardiovascular system and vice versa, the dynamic and rapidly evolving field of Long COVID syndrome remains perplexed and challenging.

Further research is needed to understand the pathophysiology and exact mechanisms by which Long COVID unfolds itself. While it is known that the immune response has a major role in the presentation of Long COVID syndrome, further research is needed to determine whether this is influenced by certain pre-existing conditions or if there is a genetic predisposition that makes some individuals more prone to lingering symptomatology. Furthermore, at the moment the diagnosis of Long COVID remains a clinical one, and the use of diagnostic testing has been of

limited value. Identifying a blood biomarker that associates closely with Long COVID, will facilitate earlier diagnosis but also potentially targeted therapy. This, in combination with a deeper understanding of the Long COVID phenotyping, would allow the development of a targeted therapy that would alleviate patients from the associated prolonged symptoms of the disease.

In addition, it remains yet to be fully understood if and in what ways vaccination will affect the incidence of Long COVID syndrome in the future. Vaccination may also change the disease phenotype and future studies may establish if vaccination results in 'milder' Long COVID phenotypes, with less severe or reduced number of symptoms. Furthermore, the scenery of Long COVID syndrome may change as new variants appear. The past history of coronavirus would suggest that new variants will be less damaging and lead to milder acute infection, however it remains unknown how this will affect the risk of developing Long COVID syndrome or the severity of Long COVID syndrome. Finally, healthcare systems need to adapt to the increasing number of people with Long COVID, and support individuals with psychological strain, as well as their families, and provide wholistic therapies where possible and appropriate quickly.

Limitations

All the studies conducted so far are observational and therefore carry unavoidable limitations and bias that prohibit the application of their results in a wider or a different population. In addition, the existing evidence comes from studies at different time points in the pandemic, which in turn means different variants, vaccination status, immunity status and even different

Long COVID definitions. These factors have substantially changed in a very short period of time, which has perhaps made the observations of some studies of this systematic review already outdated.

Conclusions

Long COVID syndrome represents a highly evolving and dynamic field that is yet to be explored in its entire entity. The individual's immune and inflammatory response are key mechanisms in the pathophysiology of Long COVID syndrome, with cytokines and pro-inflammatory molecules potentially triggering cardiac symptomatology. While there is evidence suggesting that patients with pre-existing obesity, heart failure or ischaemic heart disease are at higher risk of suffering with Long COVID, there is no strong evidence about the risk that patients with other types of CV diseases may have. On the other hand, patients with Long COVID may be confronted with new onset CV diseases such as diabetes, arrhythmias, heart failure and others. The most commonly encountered cardiac-related symptoms include chest pain, palpitations, shortness of breath and syncope. These could be present in isolation or in combination with pathological evidence of myocardial impairment on echocardiography or CMR imaging. Vaccination and certain medications, including antivirals, have been shown to reduce the risk of Long COVID syndrome, however further studies are needed to assess this potentially protective effect in a large population taking into account the new variants of the virus. Although treatment remains supportive, ongoing studies may enable the identification of beneficial treatment strategies that will improve the patients' quality of life and reduce their symptom burden.

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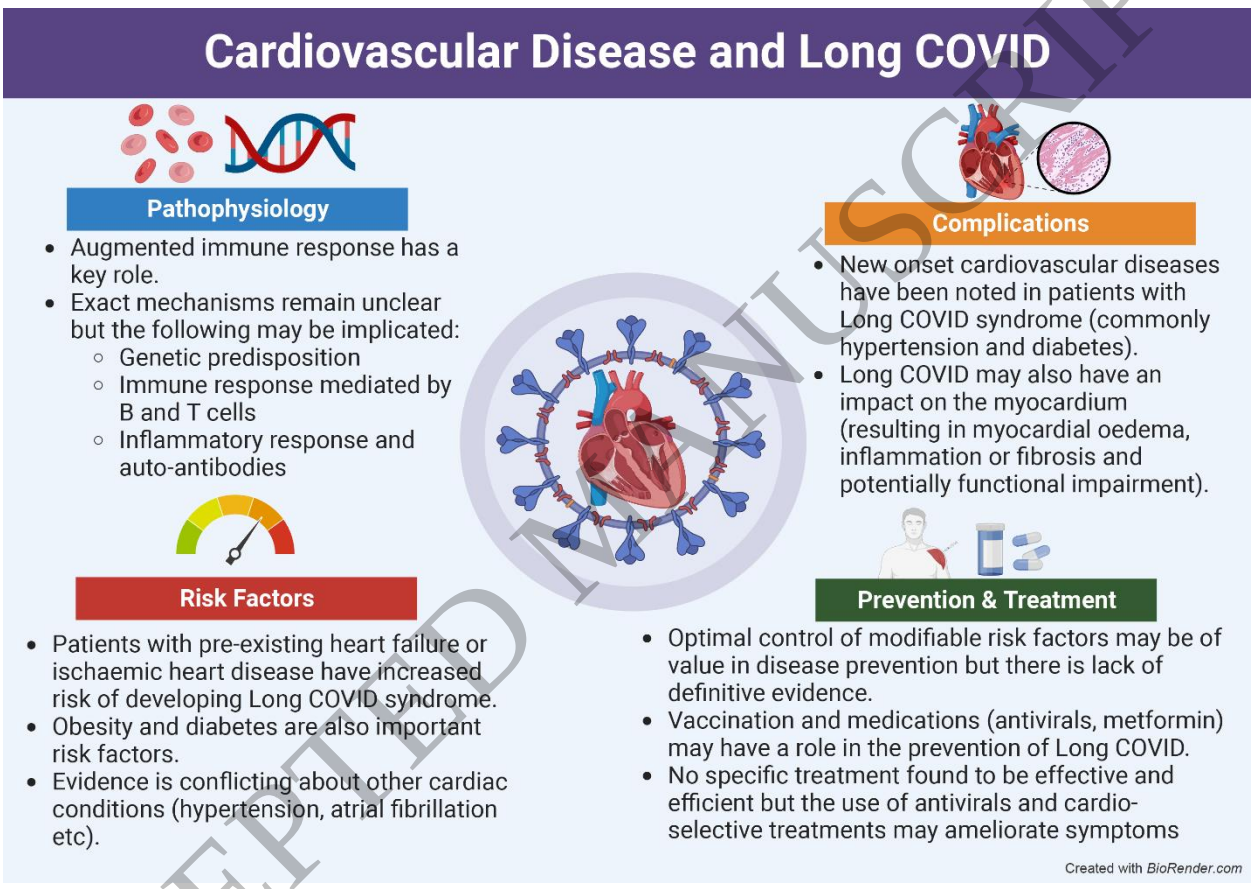

Graphical Abstract
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