



SPECIAL FEATURE REVIEW

Cardiovascular disease in SARS-CoV-2 infectionKei Sato^{1,2}, Jane E Sinclair³, Habib Sadeghirad⁴, John F Fraser^{1,2}, Kirsty R Short^{3,5†}  & Arutha Kulasinghe^{2,6†} ¹Critical Care Research Group, The Prince Charles Hospital, Brisbane, QLD, Australia²Faculty of Medicine, University of Queensland, Saint Lucia, QLD, Australia³School of Chemistry and Molecular Biosciences, The University of Queensland, Saint Lucia, QLD, Australia⁴Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia⁵Australian Infectious Diseases Research Centre, The University of Queensland, Saint Lucia, QLD, Australia⁶The University of Queensland Diamantina Institute, The University of Queensland, Brisbane, QLD, Australia**Correspondence**

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Abstract

Pre-existing cardiovascular disease (CVD) increases the morbidity and mortality of COVID-19 and is strongly associated with poor disease outcomes. However, SARS-CoV-2 infection can also trigger *de novo* acute and chronic cardiovascular disease. Acute cardiac complications include arrhythmia, myocarditis and heart failure, which are significantly associated with higher in-hospital mortality. The possible mechanisms by which SARS-CoV-2 causes this acute cardiac disease include direct damage caused by viral invasion of cardiomyocytes as well as indirect damage through systemic inflammation. The long-term cardiac complications associated with COVID-19 are incompletely characterised and thought to include hypertension, arrhythmia, coronary atherosclerosis and heart failure. Although some cardiac-related symptoms can last over 6 months, the effect of these complications on long-term patient health remains unclear. The risk factors associated with long-term cardiovascular disease remain poorly defined. Determining which patients are most at-risk of long-term cardiovascular disease is vital so that targeted follow-up and patient care can be provided. The aim of this review was to summarise the current evidence of the acute and long-term cardiovascular consequences of SARS-CoV-2 infection and the mechanisms by which SARS-CoV-2 may cause cardiovascular disease.

Keywords: cardiovascular disease, COVID-19, SARS-CoV-2**INTRODUCTION**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 and has caused the ongoing coronavirus disease 2019 (COVID-19) pandemic, infecting > 170 million people worldwide. SARS-CoV-2 causes a broad range of respiratory symptoms, ranging from

subclinical disease to viral pneumonia.¹ Despite the recent availability of vaccines, approximately 500 000 individuals are still infected daily with SARS-CoV-2. It is increasingly apparent that like other severe respiratory virus infections, SARS-CoV-2 causes a variety of extra-respiratory complications.^{1,2} Specifically, SARS-CoV-2 infection has been associated with acute myocardial injury,

myocarditis, arrhythmias, venous thromboembolism and other *de novo* cardiovascular complications.^{3–7} There is also now a growing body of evidence of increased cardiovascular disease in convalescent COVID-19 patients.⁸ Here, we review the current evidence of the acute and long-term cardiovascular consequences of SARS-CoV-2 infection and the mechanisms by which it may cause cardiovascular disease.

SARS-CoV-2 pathogenesis

The primary cellular receptor for SARS-CoV-2 is the membrane-bound aminopeptidase angiotensin-converting enzyme-2 (ACE-2). In addition to binding to ACE-2, the spike protein of SARS-CoV-2 must be cleaved at the S1/S2 boundary.⁹ This cleavage can be effected by host cell surface proteases, transmembrane protease, serine 2 (TMPRSS2) and endosomal cysteine proteases cathepsin B/L, which then primes the SARS-CoV-2 spike protein for entry.¹⁰ Additional cleavage by furin produces a sequence motif that binds to cell surface neuropilin-1, which enhances SARS-CoV-2 infection *in vitro*.¹¹ *In vivo* SARS-CoV-2 primarily targets epithelial cells within the respiratory tract, including type 2 pneumocytes in the lower respiratory tract. Whilst initial studies suggested that SARS-CoV-2 could also infect endothelial cells,¹² this has recently been called into question.¹³ Central to the pathogenesis of SARS-CoV-2 infection is the induction of a dysregulated pro-inflammatory response referred to as a cytokine storm. It is thought that this cytokine storm, and associated immunopathology, plays a significant role in both primary viral pneumonia and acute respiratory distress syndrome that is characteristic of severe COVID-19.¹⁴

Cardiovascular disease in acute COVID-19

The prevalence of myocardial injury and cardiovascular disease in the acute phase of COVID-19 varies dramatically between studies. This likely reflects the differing cardiovascular complications of SARS-CoV-2 infection, as well as hospital and laboratory facilities available across different countries.

Myocardial injury is defined as electrocardiogram abnormalities or an increase in cardiac enzyme and biomarker serum levels, such as troponin (cTnT), induced by ischaemia or non-

ischaemic causes.¹⁵ Myocardial injury, as defined by elevated cTnT, is found in 19.7–27.8% of COVID-19 patients requiring hospital admission.⁴ Abnormal findings in echocardiography are also found with 55% of COVID-19 patients during their initial hospital admission, including 39% of left ventricle (LV) and 33% of right ventricle (RV) abnormalities.¹⁶ In contrast, data from China suggest that approximately 7% of patients infected with SARS-CoV-2 develop cardiac injury, defined as elevated high-sensitivity cardiac troponin I or new echocardiographic, ECG abnormalities.¹⁷ This prevalence increases to 25% in those hospitalised with COVID-19¹⁸ and 22% in patients who required ICU admission.¹⁷ Following these myocardial injuries, various cardiac complications, such as cardiac arrhythmias, heart failure and myocarditis, may follow.

Cardiac arrhythmias are abnormal heartbeat rhythms that can manifest as tachycardia (an abnormally fast heartbeat), bradycardia (an abnormally slow heartbeat) or irregular heartbeat.¹⁹ Heart palpitations were the most common presenting symptom of arrhythmias in COVID-19 patients who did not have a fever or cough.²⁰ In a study of 137 patients infected with SARS-CoV-2, heart palpitations were reported in 10 (7.3%) cases.²¹ Amongst 138 hospitalised COVID-19 patients, cardiac arrhythmias were seen in 16.7% of all patients and were more prevalent in ICU admitted cases.¹⁷ In a study of 85 fatal cases with COVID-19, cardiac arrhythmias were found in 51 (60%) cases.²² Life-threatening arrhythmias were also reported in 11 (5.9%) of 187 COVID-19 patients.⁴

Myocarditis is a complication of COVID-19 that refers to inflammation of the heart muscle.²³ Segmental wall motion abnormalities or a reduced LV ejection fraction has been reported, although it is not specific for COVID-19, and also found in acute coronary syndrome. Amongst 68 fatal COVID-19 cases, 5 patients (7%) with myocarditis and circulatory failure were identified, whilst 22 patients (33%) had myocarditis and respiratory failure.²⁴ A systematic review of 14 cases of COVID-19-related myocarditis included 58% of male with the median age of 50.4 years and showed that the most prevalent comorbidity associated with myocarditis was hypertension (33%).²⁵ ECG findings varied from case to case, but troponin elevation was seen in 91% of cases. Of the patients who underwent echocardiography, 60% had a reduced ejection fraction. The overall

survival rate was 81%, and survival rate in those who received steroids was 85%.

Heart failure is a condition where cardiac output is insufficient to meet the oxygen demand for the body. Heart failure can be caused by SARS-CoV-2 as a result of acute coronary syndrome (following plaque rupture) or the mismatch between oxygen supply and demand because of hypoxic respiratory failure or viral cardiomyopathy.²⁶ This complication is characterised by an increase in serum NT-proBNP and a decrease in left ventricular ejection fraction.²⁷ In a study of 799 patients with COVID-19, heart failure was reported in 24% of all patients and in 49% of those who died.²² Amongst 191 COVID-19 patients, heart failure affected 23% of all patients and 52% of those who died.²⁸

Clinical consequences of cardiovascular disease in acute COVID-19

For the most part, the acute onset of cardiovascular injury because of COVID-19 is associated with a poor overall prognosis.^{17,18} For example, COVID-19 patients with cardiac injury had a higher mortality than those without cardiac injury during hospitalisation: 51.2% vs. 4.5%²⁹ or 59.6% vs. 8.9% respectively.⁴ Similarly, elevated cardiac biomarkers were associated with a poor COVID-19 prognosis. Amongst 41 COVID-19 patients, 5 (12%) had acute cardiac injury, of whom 4 were admitted to the intensive care unit (ICU).⁵ A study of 138 hospitalised patients infected with SARS-CoV-2 found cardiac injury in 10 patients (7.2%), almost all of whom required ICU care.¹⁷ A study of 191 COVID-19 patients reported that 33 (17%) cases developed acute myocardial injury, of which 32 patients died.²⁸ In another cohort of 416 COVID-19 patients, cardiac injury occurred in 19.7% of patients during hospitalisation, and cardiac injury was identified as an independent risk factor for in-hospital mortality.²⁹ These findings suggest that acute myocardial injury could be associated with severity and mortality for in-hospital COVID-19 patients.

At present, no specific treatment is available for COVID-19-induced cardiovascular disease. However, in the early stages of the COVID-19 pandemic there was significant concern that the use of ACE inhibitors (ACEi) and angiotensin

receptor blockers (ARB) for either *de novo* or pre-existing cardiovascular disease would increase COVID-19 severity. This was based on the suggestion that ACEi/ARB can increase the level of ACE-2 and thereby facilitate increased SARS-CoV-2 replication. However, when limited to a hypertensive subgroup, a recent meta-analysis showed a significant association between renin-angiotensin-aldosterone system (RAAS) inhibition and *reduced* risk of death.³⁰ This most likely reflects the vasodilation and anti-inflammatory effects associated with increased ACE-2 expression, which acts to counterbalance the renin-angiotensin system by degrading angiotensin II.^{31,32} However, this mechanism of action remains speculative and the exact role of RAAS inhibition in the pathogenesis of SARS-CoV-2 remains to be defined.

Mechanisms of cardiovascular disease in acute COVID-19

During acute COVID-19, cardiovascular disease may arise as the direct consequence of viral infection or as an indirect result of inflammation and respiratory distress (Figure 1). In terms of direct viral infection, *in vitro* studies have shown that SARS-CoV-2 can efficiently infect and replicate in human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) by binding to ACE-2.^{33–36} In contrast, human pluripotent stem cell-derived smooth muscle cells are refractory to infection.³⁴ SARS-CoV-2 infection of hPSC-CMs results in cessation of beating,³³ cell death,^{34,36} impaired electrophysiological function,³⁴ transcriptional and morphological signatures of damage³⁵ and impaired contractile function,^{34,36} all of which may contribute to cardiovascular disease *in vivo*. However, the *in vivo* evidence of SARS-CoV-2 infection in the heart remains equivocal. In autopsy and endomyocardial biopsy specimens from 4 COVID-19 patients, viral protein was detected by immunostaining in cardiomyocytes but not cardiac macrophages, fibroblasts or endothelial cells.³⁶ Similarly, in autopsies of 39 patients with COVID-19, SARS-CoV-2 RNA was detected in the myocardium of 24 patients, whilst negative sense RNA (indicative of active viral replication) was only detected in the myocardium of the 5 patients with the highest virus load.³⁷ An autopsy study of a further 41 patients showed that whilst SARS-CoV-2 RNA

could be detected in the hearts of a large number of patients ($n = 30$), SARS-CoV-2⁺ cells in the myocardium were rare.³⁸ In contrast to these findings, amongst autopsy specimens from five COVID-19 patients no viral antigens could be detected in the heart, although all patients displayed severe myofibrillar anomalies.³⁵ Similarly, in 8 COVID-19 autopsies SARS-CoV-2 could not be detected in the heart of any patient by *in situ* hybridisation, immunohistochemistry or qRT-PCR.³⁹ Therefore, the contribution of direct

viral infection of cardiomyocytes to *in vivo* pathogenesis remains unclear.

When considering the consequences of direct viral infection of the heart, it is important to recognise that the cellular receptor for SARS-CoV-2, ACE-2, plays an integral role in the renin-angiotensin system (RAS). In the RAS signalling pathway, ACE and ACE-2 play opposing roles. On the one hand, ACE converts Ang I to Ang II in order to induce vasoconstrictive, pro-oxidative and pro-inflammatory effects.^{31,32,40} On the other hand,

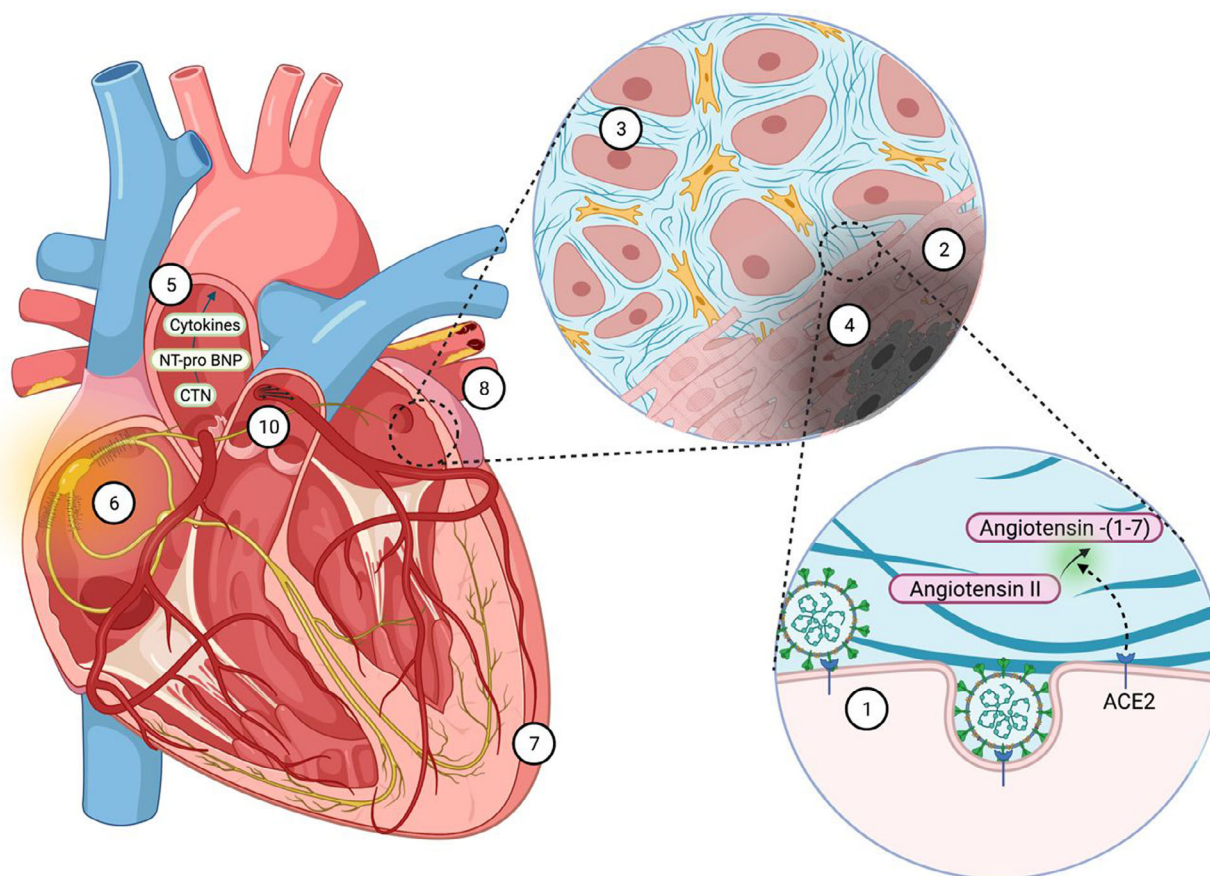


Figure 1. Schematic representation of the putative mechanisms by which SARS-CoV-2 causes cardiovascular disease. SARS-CoV-2 binds to ACE-2 in myocardium (1) to enter the target cell. This causes downregulation of ACE-2, which converts vasoconstricting/inflammatory angiotensin II into vasodilating/anti-inflammatory protein angiotensin 1–7. The concentration of angiotensin 1–7 decreases and that of angiotensin II increases, contributing to reduced coronary artery flow, myocardial ischaemia (2) and inflammation. Increased angiotensin II also cause vasoconstriction at the alveolar-capillary bed, leading specific increased strain on a right heart that is already struggling because of the hypoxic pulmonary vasoconstriction and micro vascular thromboses.⁵² Cell injury such as myocardial fibrosis (3) and apoptosis (4) is caused by both direct viral involvement and systemic inflammation from an imbalance of T helper 1 and 2 responses, denoted by elevated serum cytokines (5),⁵ facilitating long-term disease including arrhythmias (6) and hypercoagulability. Increased cardiometabolic demand leads to a reduced cardiac reserve, denoted by compensative left ventricular hypertrophy (7), further contributing to angiotensin-aldosterone system dysregulation. Therapies used during the acute phase of infection, such as high-dose steroid treatment, may increase plaque formation (8) and hypertension and decrease cardiac function. High-dose steroid also could work as a stress hormone, inducing excess catecholamine, leading to excess oxygen consumption of myocardium and decrease cardiac function.⁵³ Cardiac injury results in elevated cardiac troponin (CTN) and NT-pro BNP levels (5). All mechanisms promote plaque destabilisation and increase wall shear stress (10).⁵⁴ The image was created with Biorender.com.

ACE-2 degrades Ang II to Ang (1–7) resulting in the prevention of hypertension, fibrosis, inflammation, diabetes and cardiovascular disease.⁴¹ SARS-CoV-2 binds and internalises ACE-2 upon infection contributing to an increase in Ang II levels and, as a result, an increase in Ang II-induced biological effects, making COVID-19 patients more susceptible to cardiovascular diseases.²⁷ This dysregulation of the RAS may occur in conjunction with virus-induced cardiovascular damage and systemic inflammation, the combination of which may increase the development of *de novo* cardiovascular complications. Indeed, the role of ACE-2 in both viral replication and RAS may explain why SARS-CoV-2 induces a higher rate of cardiac complications than other pneumonia-inducing viral infections (which do not bind to ACE-2) such as seasonal influenza virus.^{42,43}

SARS-CoV-2 infection also induces a systemic inflammatory response, which may contribute to myocardial injury.⁵ Detection of SARS-CoV-2 pathogen association molecular patterns (PAMPS) and danger-associated molecular patterns (DAMPS) in the lung results in the induction of pro-inflammatory cytokines and interferons (IFNs) and induces the expression of IFN-stimulated genes (ISGs). Whilst serving to reduce viral replication and spread, a dysregulated pro-inflammatory response or 'cytokine storm' will itself culminate in tissue damage by attracting more cytokine-secreting cells to the lung and triggering epithelial cell apoptosis/necrosis. This pulmonary inflammatory response is further perpetuated in the vasculature where endothelial cells, although not directly infected with SARS-CoV-2, sense the viral infection in the adjacent epithelial cells and mount an inflammatory response.¹³ The local and systemic cytokine profile during COVID-19 includes IL-6, IL-10, IL-1 β , IL-18, tumor necrosis factor α (TNF- α), IFNs (IFN- α/β , IFN- γ) and C-X-C motif chemokine ligand 10 (CXCL10).^{5,44} This cytokine storm can cause acute cardiac injury through a variety of different mechanisms. Pro-inflammatory cytokines such as TNF- α , IL-1 and IL-6 have a negative inotropic effect on cardiac contractility.²³ Furthermore, TNF- α -induced continuous activation of inflammatory signalling can cause widespread cardiomyocyte apoptosis, leading to pathological remodelling of the left ventricle and, ultimately, acute heart failure.²³ Alternatively, in particular amongst patients with underlying comorbidities, inflammation may trigger cardiovascular disease

by triggering the rupture of the coronary atherosclerotic plaques.⁴⁵ Finally, this inflammatory response may not be independent of viral infection of the heart. SARS-CoV-2 infection of the heart would not only augment cardiovascular inflammation, but the resultant downregulation of ACE-2 would also serve to further perpetuate the inflammatory response.^{27,46,47}

In addition to systemic inflammation, it is possible that SARS-CoV-2 indirectly contributes to cardiovascular disease via the induction of respiratory distress, acute respiratory distress syndrome (ARDS) and systemic hypoxia, with resultant hypoxic pulmonary vasoconstriction.⁴⁸ Long-term hypoxia causes myocardial cell injuries and necrosis, as well as cardiac arrhythmias.^{4,49,50} Specifically, cardiomyocytes undergo cell membrane destruction as a result of intracellular acidosis and reactive oxygen species (ROS) production caused by decreased blood oxygen and energy supply (hypoxemia).⁵¹ Hypoxemia also induces an influx of calcium ions, which contributes to cardiomyocyte injury and apoptosis.⁵¹ Alternatively, it is possible that viral pneumonia and the often-associated pulmonary thromboembolisms result in RV abnormalities.

Long-term cardiovascular complications in COVID-19 patients

At present, it remains unclear how long the cardiovascular complications of COVID-19 can persist in convalescent individuals (Figure 2). Hospitalisation for bacterial pneumonia is associated with an increased long-term risk of cardiovascular disease.⁵⁵ In contrast, the cardiovascular complications associated with acute avian influenza (including tachycardia, atrial fibrillation and ST changes) resolve within 1 year of infection.⁵⁶ The limited number of studies performed on the long-term complications of COVID-19 suggests that the prevalence of cardiovascular disease may vary depending upon the patient population in question. Studies such as the long-term impact in intensive care survivors of coronavirus disease-19 (AFTERCOR study – ACTRN12620000799954p)⁵⁷ may shed light upon this.

Amongst individuals who experienced severe COVID-19 (i.e. hospitalised during the acute phase of disease), signs of persistent cardiovascular disease appear to be relatively common. For

Long-term Cardiovascular Complications in COVID-19 Patients

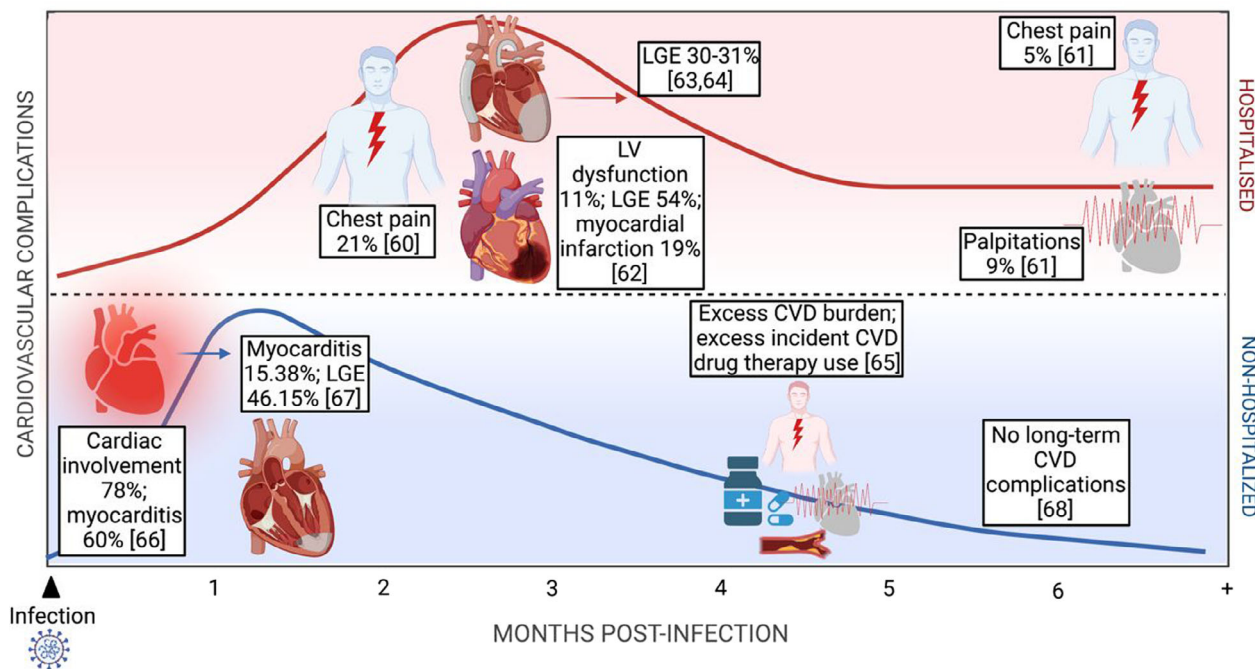


Figure 2. Schematic representation of the long-term cardiovascular complications of COVID-19. Amongst studies of patients initially hospitalised with severe COVID-19, signs of persistent cardiovascular disease appear to be relatively common, with patients continuing to suffer from chest pain, late gadolinium enhancement (LGE), LV dysfunction, myocardial infarction and palpitations 6 months post-infection. Cardiovascular complication incidence amongst convalescent COVID-19 patients who experienced mild illness is less well defined, with patients suffering from cardiac involvement, myocarditis and LGE earlier post-infection but seeming to recover by 6 months post-infection. Considering that some cases with mild illness still have cardiovascular complications at 6 months post-infection,⁶⁶ it cannot be concluded that mild cases of COVID-19 never cause chronic cardiac complications. The image was created with Biorender.com.

example, 21% of previously hospitalised COVID-19 patients still experienced chest pain 60 days post-symptom onset.⁵⁸ At 6 months post-infection, 9% of previously hospitalised COVID-19 patients continue to experience heart palpitations, whilst a further 5% experienced chest pain.⁵⁹ Cardiovascular magnetic resonance (CMR) showed that amongst 148 patients recovering from severe COVID-19 (median follow-up time post-symptom onset = 68 days), 11% of patients had abnormal left ventricular function, whilst 19% of patients had myocardial infarction and 54% of patients had late gadolinium enhancement (LGE) or ischaemia.⁶⁰ LGE indicates myocardial fibrosis, which is important because LGE may play a role in the pathophysiology of dilated cardiomyopathy,^{61,62} eventually leading to impaired cardiac contraction.⁶³ Of patients with ischaemic injury pattern, 66% (27/41) had no history of coronary disease. CMR of another COVID-19 patient cohort (where the average duration from hospital discharge was 102 days)

showed LGE in approximately 30% of convalescent COVID-19 patients.⁶⁴ These findings are consistent with smaller studies ($n = 26$) where 31% of patients with a history of COVID-19 hospitalisation displayed LGE.⁶⁵ The prevalence of LGE is of particular concern given that LGE is an independent predictor of all-cause mortality and cardiac mortality in myocarditis.⁶⁴

The incidence of cardiovascular complications amongst convalescent COVID-19 patients who experienced a mild illness is less well defined. Recently, the long-term complications of COVID-19 were investigated amongst 73 435 users of the Veteran Health Administration (VHA).⁶⁶ All convalescent COVID-19 patients experienced a mild, acute disease (i.e. patients were not hospitalised) with a median follow-up time of 126 days post-symptom onset.⁶⁶ Compared to approximately 4 million COVID-19-negative VHA users, a history of COVID-19 diagnosis was associated with an excess burden of hypertension, cardiac dysrhythmias, circulatory signs and

symptoms, chest pain, coronary atherosclerosis and heart failure.⁶⁶ Amongst COVID-19 convalescent patients, there was also evidence of excess use of beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics and antiarrhythmics.⁶⁶ These data suggest that (1) the cardiac risk and associated burden of post-acute sequelae are evident even among individuals who did not require hospitalisation at acute phase (representing the majority of people with COVID-19) and (2) the cardiac risk and associated burden increase across the severity spectrum of acute COVID-19 infection (from non-hospitalised to hospitalised individuals, to those admitted to intensive care).⁶⁶ These findings have been echoed in several smaller scale studies. Amongst 100 convalescent COVID-19 patients (follow-up time > 2 weeks post-symptom onset), cardiac magnetic resonance imaging showed that 78% of patients had cardiac involvement and 60% had ongoing myocardial inflammation.⁶⁷ Strikingly, the presence of cardiovascular disease was independent of time from the original diagnosis, pre-existing conditions and the severity and course of the acute illness, raising concerns that cardiovascular disease may emerge in patients who only experienced mild or even asymptomatic COVID-19.⁶⁷ Consistent with this notion, amongst 26 competitive college athletes who had recovered from mild COVID-19 (11–53 days post-symptom onset) four athletes had CMR findings consistent with myocarditis, whilst 12 athletes had LGE.⁶⁸ In contrast to these findings, no significant long-term cardiovascular complications were recorded in healthcare workers ($n = 74$) 6 months following a mild COVID-19 infection.⁶⁹ Specifically, compared with seronegative healthcare workers there was no significant changes in cardiac structure, function, tissue characterisation or biomarkers of individuals with a history of COVID-19 infection.

At present, the mechanisms by which COVID-19 may cause long-term cardiovascular disease remains purely speculative. Elevated cytokine levels have been detected in the sera of convalescent COVID-19 patients, including elevated levels of pro-angiogenic MIP-1b, BDNF and VEGF.^{70,71} Whether this is sufficient to drive cardiovascular dysfunction, or is indicative of other underlying inflammation that then plays a causative role in cardiovascular disease, remains to be determined. Alternatively, it is possible that therapies used during the acute phase of illness

(such as high-dose steroid treatment) have long-term consequences, as was previously observed with SARS-CoV-1.^{72,73} However, such a hypothesis would fail to explain the incidence of cardiovascular disease in convalescent individuals who had mild COVID-19. Recovered COVID-19 patients may have increased cardiometabolic demand, as previously described in SARS-CoV-1 survivors, resulting in reduced cardiac reserve and dysregulation of the angiotensin-aldosterone system.⁸ Myocardial fibrosis or scarring (resulting from the acute inflammatory response or viral infection) may also facilitate long-term disease, including re-entrant arrhythmias.⁸

The current clinical consensus is not to advise the routine use of advanced cardiac imaging in convalescent COVID-19 patients. It is vital that research in this field continues to define which patients are most at-risk of long-term cardiovascular disease so that targeted cardiovascular follow-up can be performed.

CONCLUSION

During SARS-CoV-2 infection, myocardial injury and cardiovascular complications are more common than other pneumonia-inducing viral infections and this often leads to poor outcomes. Acute cardiac complications include arrhythmia, myocarditis and heart failure. Direct myocardial injuries can be caused by the invasion of the virus itself in patients with underlying comorbidities. Indirect myocardial injuries can be caused by systemic inflammation because of the cytokine storm, causing a negative inotropic effect on cardiac contractility, cardiomyocyte apoptosis and acute heart failure. Long-term cardiac complications include hypertension, arrhythmia, coronary atherosclerosis and heart failure. As the mechanism of long-term complications, hypoxia, cytokines, increased cardiac metabolism and myocardial fibrosis might be related. Whilst the incidence of the long-term complications is independent of the severity of the acute illness, studies to determine which patients are most at-risk of long-term cardiovascular disease are vital so that targeted cardiovascular follow-up can be performed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Kei Sato: Conceptualization; Writing-original draft; Writing-review & editing. **Jane E Sinclair:** Writing-original draft; Writing-review & editing. **John F Fraser:** Conceptualization; Writing-review & editing. **Arutha Kulasinghe:** Conceptualization; Resources; Supervision; Writing-original draft; Writing-review & editing.

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