Pathogenesis and management of myocardial injury in coronavirus disease 2019

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The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a major health crisis and a worldwide pandemic. COVID-19 is characterized by high infectivity, long incubation period, diverse clinical presentations, and strong transmission intensity. COVID-19 can cause myocardial injury as well as other cardiovascular complications, particularly in senior patients with pre-existing medical conditions. The current review summarizes the epidemiological characteristics, potential mechanisms, clinical manifestations, and recent progress in the management of COVID-19 cardiovascular complications.

Keywords COVID-19 • SARS-CoV-2 • Heart • Blood vessels • Inflammation

Introduction

In December 2019, a virus-associated disease, predominately characterized by pneumonia, emerged and quickly spread around the world. The disease outbreak has triggered a major health crisis in many countries throughout the world and is now named coronavirus disease 2019 (COVID-19) officially by the World Health Organization.1 The pathogen causing COVID-19 has been attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus closely related to severe acute respiratory syndrome coronavirus (SARS-CoV).2 SARS-CoV-2 is the third member of coronaviruses family known to cause life-threatening disease, following SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).3 SARS-CoV-2 attack the respiratory system, mainly characterized by the rapidly progressive pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome.5 While much of the focus has been on pulmonary manifestations, it is essential to be aware of cardiovascular complications, which increase the severity and mortality of COVID-19. Cardiovascular manifestations are previously reported in the setting of SARS and MERS. Acute myocarditis has been reported in MERS patients without pre-existing cardiac conditions.6 About 10% of SARS patients have reversible cardiomegaly without any sign of heart failure.7 Some SARS patients who died from cardiac arrest exhibited elevated levels of myocardial biomarkers, also indicative of myocardial damage.8 Compared with SARS and MERS, COVID-19 exerts more adverse impacts on the cardiovascular system, leading to an elevated incidence of cardiovascular events, most notably myocardial injury (Table 1).9,10,11 In the current review, we summarize the epidemiological features, underlying mechanisms, and clinical characteristics of COVID-19-related myocardial injury. We also review and discuss recent progress in management and therapeutic strategies for COVID-19 cardiovascular complications.

COVID-19-associated myocardial injury

The cardiovascular system is highly vulnerable to the tissue injury caused by COVID-19. The pathogenesis of myocardial injury has been demonstrated by recent autopsy reports from different...
investigators.9,35 The exact mechanism for the development of COVID-19 cardiovascular complications has not been fully understood. COVID-19 may damage the heart directly or indirectly or both (Figure 1). The occurrence of myocardial injury is generally diagnosed when the serum levels of troponin I/T (TnI/T) increase above the 99th percentile upper reference limit after excluding TnI/T elevation related to obstructive coronary artery disease, according to the fourth universal definition of myocardial infarction.35 The incidence of myocardial injury in COVID-19 ranges from 7.2% to 40.9% in general cohorts.5,9,11–14,17,20,21,33 TnI/T elevation appears much more striking in severe patients and non-survivors.10,18,19 Recent reports on the prevalence and description of myocardial injury are summarized in Table 2.5,9–21 In a recent study enrolling 191 patients, myocardial injury occurred in 46% of non-survivors, compared with only about 1% of discharged patients.11 Myocardial injury appears to serve as an independent risk factor for the severity and mortality of COVID-19, with reported hazard ratio ranging from 4.3 to 8.9,12,13,16 and odds ratio from 6.6 to 26.9.14,15,36 in different studies. Furthermore, some of the deceased patients show dynamic elevation of TnT levels during hospitalization, whereas discharged patients or survivors showed no change in TnT levels, suggesting that aggravated myocardial injury is associated with adverse COVID-19 prognosis.17,18

Electrocardiographic and echocardiographic findings for COVID-19 patients with myocardial injury are generally normal.13 Specific electrocardiographic and imaging abnormalities are usually diagnosed as acute myocarditis.22–25 Inciardi et al.23 reported a case of COVID-19 with myocarditis in the absence of respiratory symptoms. Magnetic resonance imaging (MRI) revealed typical changes of myocarditis, such as diffuse myocardial oedema and late gadolinium enhancement. The patient had severe systolic dysfunction, indicated by refractory hypotension and diffuse biventricular hypokinesis (left ventricular ejection fraction of 35%) on MRI. The pathological evidence for acute myocarditis has been obtained from another COVID-19 patient25 who also presented with typical manifestations of fulminant myocarditis.

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### Table 1 Cardiovascular complications of COVID-19

| Manifestations in COVID-19 patients | Ref. |
|-----------------------------------|------|
| Elevation of myocardial biomarker levels (e.g. TnI/T) Non-specific changes on electrocardiography and echocardiography | (Table 2) 5,9–21 |
| Elevation of myocardial biomarker levels (e.g. TnI/T) Diffuse or focal ST-segment elevation on electrocardiography Myocardial oedema, ventricular hypokinesia and late gadolinium enhancement on echocardiography or magnetic resonance imaging Myocardial inflammation and SARS-CoV-2 genome confirmed by autopsy or biopsy | 22–26 |
| Elevation of D-dimer levels Acute pulmonary embolism on computed tomography pulmonary angiography Deep vein thrombosis on ultrasonography | 27–30 |
| Haemorrhagic tendency and microcirculation disturbance Elevation of D-dimer and fibrin degradation product levels Decrease in platelet counts and fibrinogen levels Prolonged activated partial thromboplastin time and prothrombin time | 29,31 |
| Hemiplegia, dysarthria gaze preference and facial weakness Infarct lesion on computed tomography | 16,29,32 |
| Elevation of NT-proBNP levels Pulmonary oedema on chest radiography Enlarged ventricle and reduced left ventricular ejection fraction on echocardiography | 11,16,33 |
| Rapid ventricular tachycardia lasting >30 s or ventricular fibrillation on electrocardiography Haemodynamic instability Syncope Sudden death | 17,34 |

COVID-19, coronavirus disease 2019; NT-proBNP, N-terminal pro B-type natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TnI/T, troponin I/T.

aNo incidence data available.
bOnly patients suspected of having pulmonary embolism underwent computed tomography pulmonary angiography, so the real incidence may be lower.
cIncidence in severe or deceased cohorts.
Myocardial inflammation was confirmed, and coronavirus particles were detected in the patient’s endomyocardial biopsy specimens, although in macrophages and not in myocardial or endothelial cells.

**Other adverse cardiovascular events in COVID-19**

In addition to the direct myocardial injury caused by viral infection, other cardiovascular complications may occur in COVID-19, in particular acute vascular events, which may contribute to the development of myocardial injury and dysfunction.

**Thromboembolic complications**

In a study of 184 intensive care unit patients with COVID-19, up to 31% of them presented with thromboembolic complications, including 27% with venous thromboembolism and 3.7% with arterial thrombotic events, even though all patients had received standard doses of thromboprophylaxis. In a New York hospital, reportedly, several young and previously healthy COVID-19 patients were found to suffer from an abnormally high incidence of stroke. In another study, patients diagnosed as disseminated intravascular coagulation (DIC) accounted for 71.4% of non-survivors but occurred only in 0.6% of survivors. Activated partial thromboplastin time and prothrombin time were decreased in 16% and 30% of COVID-19 patients. Moreover, levels of D-dimer were significantly higher among those who died of COVID-19 vs. those who survived and a subsequent study identified an abnormal D-dimer level (>1 μg/L) as a major risk factor for death, also suggesting that coagulation abnormality contributes to mortality. The above findings reveal a high prevalence of thromboembolic events during the development of COVID-19, and support the necessity of closely monitoring the status of coagulation and thrombosis in hospitalized patients.

**Acute heart failure**

Acute heart failure represents another common cardiovascular complication of COVID-19, especially in patients undergoing clinical deterioration. In the history of deceased patients, plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) levels often showed dynamic elevation during hospitalization, revealing the close relationship between cardiac dysfunction and disease severity. The new-onset myocardial injury is partly responsible for acute cardiac failure, described by several case reports as discussed above. Clearly, with COVID-19 progression, there is a positive correlation between the levels of NT-proBNP and TnT ($R^2 = 0.376$, $P < 0.001$). Nearly 50% of COVID-19 patients developing heart failure had a history of CVD, suggesting that...
| Cohort                          | Myocardial injury                                      | Severity/prognosis                                      | Troponin and other evidence                                                                 | Ref. |
|--------------------------------|--------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------|------|
| Wuhan, China Mortality: 15.0%  | 5/41 (12.2%)                                           | 30.8% ICU vs. 3.6% non-ICU patients with myocardial injury | • hs-TnI levels (pg/mL): 3.3 (IQR 3.0–163.0) vs. 3.5 (IQR 0.7–5.4) in ICU and non-ICU patients (reference: <28 pg/mL)  
• Electrocardiography and echocardiography: not given | 5    |
| n = 41                          | Definitions: blood levels of hs-TnI above the 99th percentile upper reference limit or new abnormalities on electrocardiography and echocardiography |                                                        |                                                                                        |      |
| Wuhan, China Mortality: 4.3%    | 10/138 (7.2%)                                          | 22.2% ICU vs. 2.0% non-ICU patients with myocardial injury | • TnI levels (pg/mL): 11.0 (IQR 5.6–26.4) vs. 5.1 (IQR 2.1–9.8) in ICU and non-ICU patients (reference: <26.2 pg/mL)  
• Electrocardiography and echocardiography: not given | 9    |
| n = 138                         | Definitions: blood levels of TnI above the 99th percentile upper reference limit or new abnormalities on electrocardiography and echocardiography |                                                        |                                                                                        |      |
| Wuhan, China Mortality: 61.5%   | 12/52 (23.1%)                                          | 28.1% non-survivors vs. 15.0% survivors with myocardial injury | • hs-TnI levels (pg/mL): 161.0 (IQR 41.8–766.1) in all patients (reference: <28 pg/mL)  
• Electrocardiography and echocardiography: not given | 10   |
| n = 53                          | Definitions: blood levels of hs-TnI above the 99th percentile upper reference limit |                                                        |                                                                                        |      |
| Wuhan, China Mortality: 28.3%   | 24/145 (16.6%)                                         | 46.0% non-survivors vs. 11% survivors with myocardial injury | • hs-TnI levels (pg/mL): 22.2 (IQR 5.6–83.1) vs. 3 (IQR 1.1–5.5) in non-survivors and survivors (reference: <28 pg/mL)  
• Electrocardiography and echocardiography: not given | 11   |
| n = 191                         | Definitions: blood levels of hs-TnI above the 99th percentile upper reference limit or new abnormalities on electrocardiography and echocardiography |                                                        |                                                                                        |      |
| Wuhan, China Mortality: 57/97   | 82/416 (19.7%)                                         | Myocardial injury is an independent risk factor for mortality with COVID-19 (HR 4.26, 95% CI 1.92–9.49) | • hs-TnI levels (ng/mL): 0.19 (IQR 0.08–1.12) in myocardial injury patients (reference: <0.04 ng/mL)  
• NT-proBNP levels (pg/mL): 1689 (IQR 698–3327) in myocardial injury patients (reference: <900 pg/mL)  
• Electrocardiography: 14/14 patients with myocardial injury showed findings compatible with myocardial ischaemia  
• Echocardiography: not given  
• TnI levels (mg/mL): 0.10 (IQR 0.01–0.77) vs. 0.00 (IQR 0.00–0.01) in severe and non-severe patients (reference: <0.12 ng/mL)  
• NT-proBNP levels (ng/L): 1142.0 (IQR 388.3–5956.5) vs. 101.9 (IQR 34.0–363.8) in severe and non-severe patients (reference: <1800 ng/L)  
• Electrocardiography: 19.6% non-specific ST-T changes and 29.5% tachycardia in all patients  
• Echocardiography: all abnormalities can be explained by underlying conditions except for a small amount of pericardial effusion | 12   |
| (58.8%)a n = 416                | Definitions: blood levels of hs-TnI above the 99th percentile upper reference limit |                                                        |                                                                                        |      |
| Wuhan, China Mortality: 12.5%   | 42/112 (37.5%)b                                         | • Peak TnI and NT-proBNP levels present HR 8.9 (95% CI 1.9–40.6) and HR 1.2 (95% CI 1.1–1.3) for the risk of death  
• No dynamic change in TnI and NT-proBNP levels observed during hospitalization | • hs-TnI levels (pg/mL): 161.0 (IQR 41.8–766.1) in all patients (reference: <28 pg/mL)  
• Electrocardiography and echocardiography: not given | 13   |
| n = 112                         | Definitions: blood levels of TnI above the 99th percentile upper reference limit |                                                        |                                                                                        |      |

*Definitions: blood levels of hs-TnI above the 99th percentile upper reference limit or new abnormalities on electrocardiography and echocardiography.*

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Table 2 (Continued)

| Cohort            | Myocardial injury | Severity/prognosis                                                                 | Troponin and other evidence                                                                 | Ref. |
|-------------------|-------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------|
| Wuhan, China      | 22/150 (14.7%)    | Myocardial injury is an independent risk factor for mortality with COVID-19 (HR 26.91, 95% CI 4.09–177.23) | • TnI levels (ng/L): 68.5 (IQR 9.3–969.3) vs. 4.5 (IQR 2.7–10.0) in severe and non-severe patients (reference: <26.3 ng/L) | 14   |
| Mortality: 7.3%   |                   |                                                                                     | • NT-proBNP levels (ng/L): 1030 (IQR 339–2276) vs. 83 (IQR 28–232) in severe and non-severe patients (reference: <973 ng/L if <45 years; <1210 ng/L if 45–54 years; <1980 ng/L if 55–64 years; <2850 ng/L if 65–74 years; <5260 ng/L if ≥75 years) |      |
| n = 150           |                   |                                                                                     | • Tn levels (ng/L): not given (reference: not given)                                            |      |
| Wuhan, China      | 49/176 (27.8%)    | Myocardial injury is an independent risk factor for mortality with COVID-19 (OR 6.93, 95% CI 1.83–26.22) | • Tn levels (ng/mL): 0.235 (IQR 0.042–1.996) vs. 0.006 (IQR 0.006–0.011) in non-survivors and survivors (reference: <0.04 ng/mL) | 15   |
| Mortality: 34.1%  |                   |                                                                                     | • NT-proBNP levels (pg/mL): 1819 (IQR 759–5164) vs. 132 (IQR 58–237) in non-survivors and survivors (reference: <900 pg/mL) |      |
| n = 176           |                   |                                                                                     | • TnT levels (ng/mL): not given (reference: not given) | 16   |
| Wuhan, China      | 106/671 (15.8%)   | TnI >0.026 ng/mL (HR 4.56, 95% CI 1.28–16.28) and NT-proBNP >900 pg/mL (HR 3.12, 95% CI 1.25–7.80) are independent risk factors for mortality with COVID-19 | • NT-proBNP levels (pg/mL): 817.4 (IQR 336.0–1944.0) vs. 141.4 (IQR 39.3–303.6) in non-myocardial and myocardial injury patients (reference: not given) |      |
| Mortality: 9.2%   |                   |                                                                                     | • hs-Tn levels (mmol/L): 316 (IQR 57–5420) in all patients (reference: <40 mmol/L) | 17   |
| n = 671           |                   |                                                                                     | • NT-proBNP levels (pg/mL): 2450 (IQR 881–7992) in all patients (reference: <125 pg/mL if <75 years; <450 pg/mL if >75 years) |      |
| Wuhan, China      | 52/187 (27.8%)    | Dynamic increase of TnI and NT-proBNP levels observed during hospitalization in non-survivors | • TnI levels (ng/mL): 2.47 (IQR 0.13–92.40) in myocardial injury patients (reference: <0.04 ng/mL) | 18   |
| Mortality: 23.0%  |                   |                                                                                     | • TnI levels (ng/mL): not given (reference: not given) | 19   |
| n = 187           |                   |                                                                                     | • NT-proBNP levels (pg/mL): 930.5 (IQR 106–1996.8) in all patients (reference: <99 pg/mL) |      |
| Wuhan, China      | 11/15 (73.3%)     | 77.8% of hs-TnI levels in the last test increased compared with that in the first test |                                                                                                 | 20   |
| Mortality: 10.0%  |                   |                                                                                     | • TnI/T levels: not given (reference: TnI: <0.04 ng/mL; TnI/T: <28 pg/mL) |      |
| n = 25            |                   |                                                                                     | • NT-proBNP levels (pg/mL): 385.5 (IQR 106–1996.8) in all patients (reference: <99 pg/mL) |      |
| Wuhan, China      | 31/91 (34.1%)†    | Myocardial injury is common in non-survivors                                         |                                                                                                 | 21   |
| Mortality: 10.0%  |                   |                                                                                     | • TnI/T levels: not given (reference: not given) |      |
| n = 92            |                   |                                                                                     | • NT-proBNP levels (pg/mL): 1819 (IQR 759–5164) vs. 132 (IQR 58–237) in non-survivors and survivors (reference: <900 pg/mL) |      |
| Multi-centre in   | 86/384 (22.4%)    |                                                                                     |                                                                                                 | 22   |
| China             |                   |                                                                                     | • TnI levels (ng/L): <0.04 ng/mL; TnI/T: <28 pg/mL |      |
| Mortality: 8.0%   |                   |                                                                                     | • NT-proBNP levels (pg/mL): 817.4 (IQR 336.0–1944.0) vs. 141.4 (IQR 39.3–303.6) in non-myocardial and myocardial injury patients (reference: not given) |      |
| n = 476           |                   |                                                                                     | • TnI levels (ng/mL): <0.04 ng/mL; TnI/T: <28 pg/mL |      |
| New York, USA     | 801/3533 (22.6%)  | 36.2%, 24.4% and 19.9% patients with myocardial injury in critical, severe and moderate groups |                                                                                                 | 23   |
| Mortality:        |                   |                                                                                     | • TnI levels (ng/mL): not given (reference: not given) |      |
| 553/2634 (21.0%)† |                   |                                                                                     | • NT-proBNP levels (pg/mL): 385.5 (IQR 106–1996.8) in all patients (reference: <99 pg/mL) |      |
| (n = 5700)        |                   |                                                                                     | • TnI levels (ng/mL): not given (reference: not given) |      |

CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; hs-TnI, high-sensitivity troponin I; ICU, intensive care unit; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; OR, odds ratio; TnI/T, troponin I/T.

†Mortality is counted in patients with known outcome (discharged or deceased). Patients who remained hospitalized at the final follow-up date are not included.

†One of 42 COVID-19 patients with elevated biomarkers was diagnosed as myocardial infarction.

†Six of 31 COVID-19 patients with elevated biomarkers were diagnosed as myocardial infarction.

†Electrocardiogram was performed during the periods of cardiac biomarker elevation.

†Reference ranges were different in separate centres.
the decompensation of underlying cardiovascular conditions also strongly contributes to the acute cardiac dysfunction.13

Arrhythmia and cardiac arrest
An increased risk of arrhythmia has recently been reported in patients with SARS-CoV-2 infection.12 Electrophysiologically, COVID-19 patients are prone to the development of tachycardia. A study of 112 COVID-19 patients reported that 29.5% of patients presented with tachycardia, and other evidence for myocardial injury.13 The heart rate of COVID-19 patients appeared to be correlated with troponin levels, suggesting the link of tachycardia to myocardial injury in COVID-19. In addition to tachycardia, malignant arrhythmia and following cardiac arrest may occur in COVID-19 patients, specifically in those with myocardial injury,17 which might lead to sudden cardiac death, reportedly responsible for 11.1% of deaths.14 A French population-based study found that the out-of-hospital cardiac arrest incidence in the COVID-19 pandemic increased two times over that in the same weeks in the non-pandemic period,39 and a third of the increase was caused by suspected or confirmed COVID-19.

Mechanism underlying myocardial injury in COVID-19
Despite the high incidence of myocardial injury in COVID-19 patients, the exact mechanisms underlying the pathogenesis of cardiac injury and dysfunction remain largely unclear. Molecular and cellular evidence and clinical data have disclosed multifactorial events and pathways which likely trigger or accelerate the micro-and macro-process of myocardial injury. The viral infection may provoke multiple pathogenic factors, which may directly or indirectly cause the impairment of cardiovascular cells by SARS-CoV-2 infection, as illustrated in Figure 1.

SARS-CoV-2 host cell invasion through surface angiotensin-converting enzyme 2 receptor
Similar to SARS-CoV, SARS-CoV-2 invades host cells through viral spike protein (S protein) binding to the surface angiotensin-converting enzyme 2 (ACE2) receptor40 (Figure 2). Known as a negative regulator of the renin–angiotensin system (RAS), ACE2 plays a regulatory role in counter-balancing the bioactivity of ACE.41 It can also initiate outside-in signalling as a membrane protein.42

The specific cellular mechanism, by which SARS-CoV-2 damages cardiomyocytes, has not been clarified completely. SARS-CoV-2 shares a similar biological pathway with SARS-CoV. Both viruses rely on type II transmembrane serine proteases, another protein expressed on the cellular membrane, to cleave S protein and expose the receptor-binding domain to bind with ACE2. This S protein–ACE2 binding leads to the endocytosis of virus particles43 and may be followed by the down-regulation of ACE2 expression in cardiomyocytes,44,45 and the over-activation of RAS. The down-regulation of ACE2 associated with SARS-CoV infection is partly caused by the shedding of ACE2 ectodomain, mediated by tumour necrosis factor (TNF)-α-converting enzyme in coupling with the production of TNF-α, a well-known factor for pro-fibrosis and myocardial damage.46 The Ras–ERK–AP-1 pathway may be triggered, as well as the activation of the C-C motif chemokine ligand 2 (a pro-fibrosis factor).47

The above theories are supported by an autopsy report regarding SARS, showing the presence of SARS-CoV in the heart associated with marked down-regulation of ACE2 expression.45 The interstitial fibrosis was observed in the heart tissues of SARS and COVID-19 patients with myocardial injury, implying the involvement of following pro-fibrotic effect.22,45 However, although the identification of viral particles and viral genetic materials in the myocardium of COVID-19 cases has offered pathological evidence of viral myocarditis,22,48 further investigation is needed to determine expression of ACE2 and its interactions with the virus and host cell components, which may help clarify the impacts of changed cellular ACE2 levels on the myocardial injury driven by SARS-CoV-2 infection.

Hypoxia and ischaemic injury
Pulmonary inflammation and dysfunction caused by SARS-CoV-2 infection limits the oxygen–blood exchange, and triggers hypoxemia, hypotension, and even septic shock.39 Consequently, insufficient oxygen supply may occur in vital organs, including the heart. Concomitantly, myocardial oxygen demand may be elevated by heightened temperature and high myocardial metabolic rate that augments the inflammatory burden and imbalance between oxygen supply and consumption.50 Along with COVID-19 progression, this imbalance is increasingly aggravated and worsened by the development of metabolic acidosis, fluid or electrolyte disorder, and dysfunction of the neuro-humoral system.51 Thus, myocardial injury in COVID-19 patients may be indirectly triggered or augmented, especially in those with pre-existing cardiovascular disorders and compromising myocardial reserve capacity, which may have already exhausted on the supply side.17

Abnormal coagulation and microcirculatory disturbance
In theory, SARS-CoV-2 may directly attack vascular endothelial cells, which also express high levels of ACE2,51 leading to abnormal coagulation and microcirculatory disturbance. Intramural microvascular blood flow may be altered, causing regional ischaemia, followed by focal myocardial injury and cardiac dysfunction.52 A recent study53 has shown that COVID-19 patients with DIC have a high incidence of myocardial injury. However, the detrimental effects of abnormal coagulation and microcirculatory disorders in myocardial injury need to be proved by further pathological evidence. Inflammation of small vessel walls and diffused microcirculatory thrombosis have been identified in liver and lung biopsy specimens from COVID-19 patients. However, so far, there has been a lack of convincing evidence in the heart.54,55

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**Figure 2** Schematic representation of molecular pathways underlying the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cellular invasion and injury. SARS-CoV-2 invasion is mediated by the S protein binding to its ligand angiotensin-converting enzyme 2 (ACE2), which is primed by type II transmembrane serine proteases (TMPRSS2) through cleaving S protein into S1 and S2 subunits to facilitate the exposure of receptor-binding domain (RBD) on S1 subunit. The binding of RBD to ACE2 is followed by receptor-mediated endocytosis. Activation of the renin–angiotensin system, up-regulation of the tumour necrosis factor (TNF)-α pathway and the Ras pathway following ACE2 attachment can injure cells/tissues that highly express ACE2. *These mechanisms are speculated based on SARS-CoV studies and the similarity of two viruses. AP-1, activator protein 1; CCL2, C-C motif chemokine ligand 2; ERK, extracellular signal-regulated kinase; TACE, tumour necrosis factor-α-converting enzyme.

**Cytokine storm**

Previous studies have confirmed that immune abnormalities contribute to many pathological changes in SARS-CoV and MERS-CoV infection.\[^7,56\] Specifically, the cytokine storm represents excessive and uncontrollable cytokine production in response to virus invasion and one of the main contributors to the pathogenic injury to the heart. The levels of serum pro-inflammatory cytokines [e.g., interleukin (IL)-1β, IL-6, interferon-γ] are markedly increased in COVID-19 patients and associated with disease progression.\[^5\] Interestingly, in the cytokine storm, Th2 anti-inflammatory cytokines, such as IL-4 and IL-10, are reportedly at high levels, and even related to COVID-19 severity.\[^33\] Asymptomatic patients exhibited lower levels of both pro- and anti-inflammatory cytokines than the symptomatic group, suggesting the pathogenic role of cytokines.\[^57\]

Among the inflammatory cytokines from anti-viral immune responses, IL-6 serves as a core component of the cytokine storm, expressing at significantly higher levels in COVID-19 patients with severe conditions and adverse prognosis, compared with those without.\[^11,26,33\] IL-6 not only amplifies the cytokine storm by stimulating the production of other pro-inflammatory cytokines but also promoting vascular leakage and interstitial oedema.\[^58\] Moreover, IL-6 weakens papillary muscle contraction and causes myocardial dysfunction.\[^59\] Increased levels of IL-6 occurred in many hospitalized COVID-19 patients, significantly associated with elevated high-sensitivity TnI levels.\[^60\] C-reactive protein, a popular inflammatory biomarker and indicator of the cardiovascular inflammation heavily regulated by IL-6, has been reported to be positively correlated with TnI levels in COVID-19 patients.\[^17\] These findings point to the IL-6 predominant cytokine storm’s potential contributing role in the development of myocardial injury, and warrants further study of IL-6 expression in cardiomyocytes.

Overall, the pathogenic changes in COVID-19-associated myocardial injury are multiple. The direct harmful effect of the viral infection on host cells, the renin–ACE axis disorder mediated by S protein–ACE2 receptor binding, the imbalance between myocardial oxygen supply and demand, dysfunctional microcirculation, and abnormal immune responses may all serve as adverse factors for the pathogenesis of myocardial injury in COVID-19. Of note, the above speculations are mostly based on clinical observation, and in-depth research may help further understanding of SARS-CoV-2-induced myocardial injury, and facilitate the development of preventive and/or therapeutic agents.

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Clinical profiles of COVID-19-associated myocardial injury

The COVID-19-associated myocardial injury occurs more frequently in the elderly with pre-existing cardiovascular comorbidities or risk factors, e.g. diabetes, hypertension, coronary heart disease, and chronic kidney disease, which are known independent risk factors for heart disease. Given that pre-existing CVD and in-hospital myocardial injury are both key determinants of COVID-19 fatality, it is not surprising that COVID-19 patients with the adverse conditions possess the highest mortality (69.4%), compared with patients without myocardial injury but with underlying CVD (13.3%) and patients with myocardial injury but without underlying CVD (37.5%), while the mortality in patients without myocardial injury or underlying CVD is the lowest (7.62%).

The general symptoms of COVID-19 patients are mostly atypical, similar to those observed in SARS, MERS, and even other respiratory infections, such as fever (87.9%), cough (67.7%), fatigue (38.1%), expectoration (33.4%). Confirmed cases with myocardial injury show more specific symptoms, such as chest tightness and pain. More than 13% of COVID-19 patients with myocardial injury have reported chest pain, while less than 1% of non-myocardial injury patients did the same. Notably, the majority of COVID-19 patients with myocardial injury do not show any difference in non-cardiac symptoms from those in ordinary COVID-19 patients.

The electrocardiographic findings of COVID-19-related myocardial injury sometimes resemble those seen in cardiac ischaemia. In a study of 14 patients who underwent an electrocardiogram examination during the period of cardiac biomarker elevation, there were electrocardiographic changes, such as T-wave depression and inversion, ST-segment depression, and Q waves, all compatible with myocardial ischaemia. Bangalore et al. reported 10 COVID-19 patients who were presumed to have acute myocardial infarction at the beginning, according to the ST-segment elevations on the electrocardiogram (40% diffuse and 60% focal). However, they were later diagnosed as myocardial injury since coronary angiography and echocardiography did not show abnormality.

With regard to the imaging features, echocardiography can morphologically evaluate the structural and functional changes in the myocardium injured by SARS-CoV-2 infection. Reduced left ventricular ejection fraction and abnormal wall motion shown on the echocardiogram have been reported in hospitalized COVID-19 patients with myocardial injury. However, these cardiac image changes may be, to a certain degree, attributable to pre-existing cardiac disorders. Besides that, the abnormalities on echocardiography were mainly a small amount of pericardial effusion. The sign of myocardial oedema and ventricular hypokinesis found by echocardiography or MRI suggests a critical state of COVID-19 patients. Computed tomography is also leveraged to explore the occurrence of myocardial injury in COVID-19 patients. Epicardial adipose tissue density evaluated by the chest computed tomography scan may serve as a valuable parameter of myocardial injury with heightened cytokine production and inflammatory activation.

Recent autopsy reports have demonstrated several anatomic features of COVID-19-induced myocardial injury. Liu et al. showed that a COVID-19 patient’s cardiac tissue was greyish-red and infiltrated with inflammatory cells, indicating the myocardial injury associated with SARS-CoV-2 infection. The autopsy also found a moderate amount of light-yellow pericardial effusion and mild epicardial oedema, further suggesting the occurrence of the pericardial inflammatory response in COVID-19 patients. Another pathologic case found focal myofibrillar lysis and lipid droplets in endomyocardial specimens of COVID-19 patients. Focal, mainly perivascular interstitial fibrosis, and large (>20μm), vacuolated, CD68-positive macrophages with coronavirus particles inside were also found in the myocardium. However, so far, there has been no convincing evidence of cardiac intramural microcirculation dysfunction or thrombosis in COVID-19. Future researches are required to clarify the histopathologic characteristics of COVID-19-related myocardial injury.

Management and therapeutic strategy for COVID-19 cardiac injury

Strategies for targeting cardiovascular complications

To date, treatment of COVID-19 has been mostly restricted to supportive care measures as few specific therapeutics have been available to treat this disease. Pre-existing poor health conditions make patients more vulnerable to infection-induced cardiovascular complications, thus increasing related mortality risk. Therefore, senior patients who have underlying cardiac conditions are highly vulnerable to COVID-19 cardiac injury, and they should be prioritized for clinical care.

Regarding diagnostic criteria, the abnormal levels of myocardial biomarkers, especially TnI/T, constitute the main criteria to identify COVID-19 patients with myocardial injury. However, TnI/T changes may be affected by other determinants, such as the infection status, hypoxia, and renal insufficiency, which are commonly observed with the development of COVID-19. The “rise-and-fall” pattern of TnI/T is also seen in patients with acute coronary syndrome (ACS). There may be a longer waiting period from the first symptom onset to receiving medical care during the COVID-19 pandemic than in the non-pandemic period. Hence, a comprehensive assessment of the heart function in COVID-19 patients should be performed using electrocardiography, imaging, and laboratory testing for proper clinical judgment in patients with abnormal TnI/T levels. However, even after comprehensive examinations, sometimes it remains hard to differentiate ACS from other TnI/T elevating conditions associated with COVID-19. Therefore, it is essential to promptly perform coronary angiography and continue necessary primary percutaneous coronary intervention (PCI) for patients with suspected ACS. The primary PCI procedures used for ACS patients is favourably suitable to COVID-19 patients.
Anti-viral therapies

Since the COVID-19 outbreak, several anti-virus agents have been proposed and are currently under clinical investigation. Among them, the most hopeful one is remdesivir. This broad-spectrum investigational anti-viral agent was initially developed for treating Ebola virus infection but failed to show satisfactory efficacy in clinical trials. In the first randomized controlled trial (RCT) regarding COVID-19, remdesivir showed little clinical benefit compared with placebo for serious COVID-19 patients. However, this trial was terminated early, so it is underpowered to draw any definite conclusion. The second RCT enrolling 1063 participants showed that remdesivir is superior to control treatment in shortening the time to recovery (11 days vs. 15 days, \( P < 0.001 \)) and alleviating respiratory tract infection in adults hospitalized with COVID-19. There is no significant difference in mortality between the groups receiving remdesivir and placebo. Nonetheless, remdesivir has offered new insight into the therapeutic approaches against the current global COVID-19 crisis.

Anti-inflammatory and immunoregulatory agents

The pivotal role of immunologic over-response in COVID-19 prompts anti-inflammatory therapy to be studied for treating COVID-19. Hydroxychloroquine and chloroquine are traditional anti-malarial drugs that can efficiently control the SARS-Cov-2 replication in vitro. The first study about hydroxychloroquine treatment in COVID-19 patients is a small open-label, non-randomized study, in which hydroxychloroquine administration was significantly associated with viral load reduction/disappearance. However, a double-masked non-randomized trial has yielded conflicting results, and increased prolongation of the QT interval was observed in patients who underwent hydroxychloroquine treatment. Hydroxychloroquine administration was not associated with a lowered risk of intubation or death in an observational study involving 1446 patients. Moreover, it could not prevent SARS-CoV-2 infection when used as post-exposure prophylaxis, reported by a RCT conducted in North America.

Corticosteroids have previously been used in the settings of SARS and MERS to control infection-associated ARDS. However, it has been debated whether corticosteroids exert protective or adverse effects, since studies of SARS and MERS cases have come to conflicting conclusions. The steroids may increase the incidence of in-hospital secondary infection and delay virus clearance, as reported in a COVID-19 study. However, a small dose of steroid treatment can help control fulminant myocarditis and reduce ARDS-related mortality. Based on the Recovery trial, one of the biggest studies of corticoids on COVID-19 to date, dexamethasone could be the first drug shown to reduce the death rates of COVID-19 patients. Compared with those receiving standard care, a low dose of dexamethasone for 10 days reduced mortality by one-third in patients on ventilators and by one-fifth in patients receiving supplemental oxygen in other ways. Therefore, short-duration administration of low-dose corticosteroids may practically serve as a therapeutic option for treating COVID-19.

Targeted anti-inflammatory therapies, such as IL-6 blockade, have also been viewed as a potential treatment option, given the pivotal role of cytokine storm in the pathogenesis of COVID-19 and its cardiovascular complications. The anti-IL-6 receptor monoclonal antibody, tocilizumab, has been reported to quickly control fever and improve respiratory function of 21 severe COVID-19 patients. However, an Italian RCT found that treatment with tocilizumab failed to reduce severe respiratory symptoms, intensive care visits, or death in patients with early-stage COVID-19. Thus, there appears to be controversy regarding the efficacy of anti-IL-6 therapy in the COVID-19 cohorts. More data from
patients in advanced stage and severe conditions are hopefully coming up from ongoing RCT.99

Regulators of angiotensin activities

The structural evidence of SARS-CoV-2 entering the cell via ACE2 has led to the hypothesis that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) may potentially induce the overexpression of ACE2, and subsequently increase susceptibility to SARS-CoV-2 infection and aggravate disease severity.90 However, ACEI/ARB appears to play a protective rather than a harmful role in COVID-19, given that the SARS-CoV-2 invasion may result in the activation of the RAS axis, which is partly responsible for severe organ injury of COVID-19.94 Potential mechanisms in detail have been summarized elsewhere.91 Growing evidence showed that COVID-19 patients under ACEI/ARB treatment had similar and even better clinical prognosis than those not.17,20,92,93 While several clinical trials are looking for compelling evidence proving the usefulness and safety of ACEI/ARB in COVID-19,94,99 it is not recommendable to alter the routine anti-hypertensive therapy in COVID-19 patients.

Conclusion

In the COVID-19 pandemic, patients with pre-existing medical conditions are vulnerable to myocardial injury as well as other cardiovascular complications. Individuals with elevated risk factors, such as advanced age, diabetes and obesity, are highly vulnerable to COVID-19-associated myocardial injury. Many direct and indirect pathogenic factors induced by the viral infection, such as ACE2-mediated SARS-CoV-2 infection of cardiomyocytes, hypoxia, microcirculatory disturbance, heightened coagulation and thrombogenesis, and cytokine storm, may contribute to the development of myocardial injury in COVID-19. It is important to closely monitor cardiovascular biomarkers, conduct early diagnosis, and take preventive measures of cardiac injury and dysfunction by COVID-19. It is also essential to continue medications for controlling pre-existing medical conditions. To date, the treatment of COVID-19 is largely restricted to supportive care measures. Cardiovascular considerations for the management of COVID-19 patients are of great importance and should continuously evolve in future researches.

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